



# PSYCHOSIS AND SCHIZOPHRENIA IN ADULTS

THE NICE GUIDELINE ON TREATMENT  
AND MANAGEMENT

UPDATED EDITION 2014

NATIONAL  
COLLABORATING  
CENTRE FOR  
MENTAL HEALTH

# **Psychosis and schizophrenia in adults**

## **Treatment and management**

This guideline should be read in conjunction with 'Service User Experience in Adult Mental Health', NICE Clinical Guidance 136

**National Clinical Guideline Number 178**

**National Collaborating Centre for Mental Health  
Commissioned by the  
National Institute for Health and Care Excellence**

# GUIDELINE DEVELOPMENT GROUP MEMBERS

**Elizabeth Kuipers (Chair, Guideline Development Group)**

Professor of Clinical Psychology, Institute of Psychiatry, King's College London

**Tim Kendall (Facilitator, Guideline Development Group)**

Director, National Collaborating Centre for Mental Health; Medical Director and Consultant Psychiatrist, Sheffield Health and Social Care NHS Foundation Trust

**Amina Yesufu Udechuku**

Systematic reviewer (from March 2012)

**Eric Slade**

Health economist (from January 2013)

**Max Birchwood**

Professor of Youth Mental Health, Division of Health and Wellbeing, Warwick Medical School, University of Warwick and Director of Research, Youthspace programme, Birmingham and Solihull Mental Health Foundation Trust

**Alison Brabban**

Consultant Clinical Psychologist, Tees, Esk & Wear Valleys NHS Foundation Trust; Honorary Senior Clinical Lecturer, Durham University; National Advisor for Severe Mental Illness (IAPT), Department of Health

**Lucy Rebecca Burt**

Research assistant (from October 2013)

**Nadir Cheema**

Health economist (until November 2012)

**Debbie Green**

Directorate Lead for Occupational Therapy and Social Inclusion, Adult Mental Health, Oxleas NHS Foundation Trust, London

**Bronwyn Harrison**

Research assistant (until October 2013)

**Zaffer Iqbal**

Head of Psychology and Consultant Clinical Psychologist, Navigo NHS Health & Social Care CiC

**Sonia Johnson**

Professor of Social and Community Psychiatry, Mental Health Sciences, University College London; Consultant Psychiatrist, Camden and Islington Early Intervention Service, Camden and Islington NHS Foundation Trust

**Tom Lochhead**

Mental Health Lead Professional for Social Work in Bath & North East Somerset

**Max Marshall**

Professor of Community Psychiatry, University of Manchester; Honorary Consultant, Lancashire Care NHS Foundation Trust; Medical Director Lancashire Care NHS Foundation Trust; Deputy Director/ Associate Director Mental Health Research Network England

**Evan Mayo-Wilson**

Senior systematic reviewer (until March 2012)

**Jonathan Mitchell**

Consultant Psychiatrist, Sheffield Health and Social Care NHS Foundation Trust

**Tony Morrison**

Professor of Clinical Psychology, Division of Psychology, University of Manchester

**Maryla Moulin**

Project manager

**David Shiers**

GP Advisor to the National Audit of Schizophrenia (the Royal College of Psychiatrists), London; Rethink Mental Illness Trustee (2010-2012)

**Sarah Stockton**

Senior information scientist

**Clare Taylor**

Senior editor

**Clive Travis**

Service User Representative

**Rachel Waddingham**

Service User Representative; London Hearing Voices Project Manager

**Peter Woodhams**

Carer Representative

**Norman Young**

Nurse Consultant, Cardiff and Vale UHB & Cardiff University

# TABLE OF CONTENTS

<b>1</b>	<b>Preface .....</b>	<b>8</b>
1.1	<i>National clinical guidelines.....</i>	9
1.2	<i>The national psychosis and schizophrenia guideline.....</i>	11
<b>2</b>	<b>Psychosis and schizophrenia in adults .....</b>	<b>14</b>
2.1	<i>The disorder.....</i>	14
2.2	<i>Assessment, engagement, consent and the therapeutic alliance.....</i>	26
2.3	<i>Language and stigma .....</i>	27
2.4	<i>Issues for families, carers and friends.....</i>	28
2.5	<i>Treatment and management of psychosis and schizophrenia in the NHS.....</i>	29
2.6	<i>Economic cost .....</i>	40
<b>3</b>	<b>Methods used to develop this guideline .....</b>	<b>43</b>
3.1	<i>Overview .....</i>	43
3.2	<i>The scope.....</i>	43
3.3	<i>The Guideline Development Group.....</i>	44
3.4	<i>Review questions .....</i>	45
3.5	<i>Clinical review methods .....</i>	47
3.6	<i>Health economics methods.....</i>	58
3.7	<i>Linking evidence to recommendations.....</i>	62
3.8	<i>Stakeholder contributions.....</i>	63
3.9	<i>Validation of the guideline .....</i>	64
<b>4</b>	<b>Carers' experience .....</b>	<b>65</b>
4.1	<i>Introduction.....</i>	65
4.2	<i>Carers' experience (qualitative review) .....</i>	66
4.3	<i>Interventions to improve carers' experience.....</i>	82
4.4	<i>Health economics evidence .....</i>	96
4.5	<i>Linking evidence to recommendations.....</i>	97
4.6	<i>Recommendations.....</i>	101
<b>5</b>	<b>Preventing psychosis and schizophrenia: treatment of at risk mental states .....</b>	<b>102</b>
5.1	<i>Introduction.....</i>	102
5.2	<i>Clinical review protocol for at risk mental states for psychosis and schizophrenia.....</i>	103
5.3	<i>Pharmacological interventions .....</i>	105
5.4	<i>Dietary interventions .....</i>	116
5.5	<i>Psychosocial interventions .....</i>	119

5.6	<i>Health economic evidence</i> .....	129
5.7	<i>Linking evidence to recommendations</i> .....	133
5.8	<i>Recommendations</i> .....	136
<b>6</b>	<b>Access and engagement</b> .....	<b>138</b>
6.1	<i>Introduction</i> .....	138
6.2	<i>Access and engagement to service-level interventions</i> .....	138
<b>7</b>	<b>Interventions to promote physical health in adults</b> .....	<b>157</b>
7.1	<i>Introduction</i> .....	157
7.2	<i>Behavioural interventions to promote physical activity and healthy eating</i> .....	157
7.3	<i>Interventions for smoking cessation and reduction</i> .....	172
<b>8</b>	<b>Peer-provided and self-management interventions</b> .....	<b>184</b>
8.1	<i>Introduction</i> .....	184
8.2	<i>Peer-provided interventions</i> .....	184
8.3	<i>Self-management interventions</i> .....	195
8.4	<i>Linking evidence to recommendations</i> .....	205
8.5	<i>Recommendations</i> .....	207
<b>9</b>	<b>Psychological therapy and psychosocial interventions</b> .....	<b>208</b>
9.1	<i>Introduction</i> .....	208
9.2	<i>Adherence therapy</i> .....	212
9.3	<i>Arts therapies</i> .....	216
9.4	<i>Cognitive behavioural therapy</i> .....	221
9.5	<i>Cognitive remediation</i> .....	242
9.6	<i>Counselling and supportive therapy</i> .....	250
9.7	<i>Family intervention</i> .....	256
9.8	<i>Psychodynamic and psychoanalytical therapies</i> .....	277
9.9	<i>Psychoeducation</i> .....	281
9.10	<i>Social skills training</i> .....	286
9.11	<i>Psychological management of trauma in psychosis and schizophrenia</i> .....	293
9.12	<i>**2009**Recommendations (across all treatments)</i> .....	300
<b>10</b>	<b>Pharmacological interventions in the treatment and management of schizophrenia</b> .....	<b>301</b>
10.1	<i>Introduction</i> .....	302
10.2	<i>Initial treatment with antipsychotic medication</i> .....	306
10.3	<i>Oral antipsychotics in the treatment of the acute episode</i> .....	311
10.4	<i>Promoting recovery in people with schizophrenia that are in remission – pharmacological relapse prevention</i> .....	320

10.5	<i>Promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment</i>	327
10.6	<i>Treatment with depot/ long-acting injectable antipsychotic medication</i>	347
10.7	<i>Side effects of antipsychotic medication</i>	352
10.8	<i>Effectiveness of antipsychotic medication</i>	357
10.9	<i>Health economics</i>	359
10.10	<i>Linking evidence to recommendations</i>	374
10.11	<i>Recommendations</i>	379
<b>11</b>	<b>Economic model - cost effectiveness of pharmacological interventions for people with schizophrenia</b>	<b>386</b>
11.1	<i>Introduction</i>	386
11.2	<i>Economic modelling methods</i>	387
11.3	<i>Results</i>	440
11.4	<i>Discussion of findings - limitations of the analysis</i>	449
11.5	<i>Conclusions</i>	455
<b>12</b>	<b>Teams and service-level interventions</b>	<b>457</b>
12.1	<i>Introduction</i>	457
12.2	<i>Interface between primary and secondary care</i>	458
12.3	<i>Non-acute Community mental healthcare</i>	468
12.4	<i>Alternatives to acute admission</i>	506
<b>13</b>	<b>Vocational rehabilitation</b>	<b>531</b>
13.1	<i>Introduction</i>	531
13.2	<i>Clinical evidence review – vocational rehabilitation interventions</i>	532
13.3	<i>Health economics evidence</i>	561
13.4	<i>Linking evidence to recommendations</i>	578
13.5	<i>Recommendations</i>	580
<b>14</b>	<b>Summary of recommendations</b>	<b>581</b>
14.1	<i>Care across all phases</i>	581
14.2	<i>Preventing psychosis</i>	584
14.3	<i>First episode psychosis</i>	585
14.4	<i>Subsequent acute episodes of psychosis or schizophrenia and referral in crisis</i>	591
14.5	<i>Promoting recovery and possible future care</i>	593
14.6	<i>Research recommendations</i>	598
<b>15</b>	<b>References</b>	<b>601</b>

## ACKNOWLEDGEMENTS

The Guideline Development Group (GDG) and the National Collaborating Centre for Mental Health (NCCMH) review team would like to thank the following people:

**Those who acted as advisors on specialist topics or have contributed to the process by meeting the Guideline Development Group:**

**Victoria Bird**, King's College London

**Brynmor Lloyd-Evans**, Mental Health Sciences Unit, University College London

**Alyssa Milton**, Mental Health Sciences Unit, University College London

**Daniel Tsoi**, University of Sheffield

**Sophia Winterbourne**, London School of Economics

**Those who conducted a review on behalf of the GDG:**

**Brynmor Lloyd-Evans**, Mental Health Sciences Unit, University College London

**Alyssa Milton**, Mental Health Sciences Unit, University College London

**Luke Sheridan Rains**, Mental Health Sciences Unit, University College London

**Research assistance**

Saima Ali

**Editorial assistance**

Nuala Ernest



# 1 PREFACE

This guideline was first published in December 2002 (NCCMH, 2003; NICE, 2002b) (referred to as the '2002 guideline') and updated in 2009 (NCCMH, 2010 [full guideline]; NICE, 2009d) (referred to as the '2009 guideline'). The 2009 guideline updated most areas of the 2002 guideline, except for some service-level interventions and the use of rapid tranquillisation. This second update (referred to as the '2014 guideline') reviews the areas of service-level interventions that were not updated in the 2009 guideline such as peer support and self-management interventions, vocational rehabilitation and teams and service-level interventions that encompass community-based interventions and alternatives to acute admission. In addition, the 2014 guideline provides a new review of carers' experience and physical healthcare. Given the change to the title (*Psychosis and Schizophrenia* rather than *Schizophrenia*), the 2014 guideline also incorporates a review on at risk mental states, and in the updated sections of the 2014 guideline, including the recommendations, the term 'psychosis and schizophrenia' is used rather than 'schizophrenia'. The chapter on experience of care in the 2009 guideline has been removed because it was superseded by *Service User Experience in Adult Mental Health* (NICE clinical guidance 136 (2012 [full guideline])). For a full version of the 2009 guideline see Appendix 27. See Appendix 1 for more details on the scope of the 2014 guideline. Sections of the guideline where the evidence has not been updated since 2009 are marked by asterisks and the date (\*\*2009\*\*\_\*\*2009\*\*). Sections where the evidence has not been updated since the 2002 are marked by asterisks and the date (\*\*2002\*\*\_\*\*2002\*\*).

This guideline has been developed to advise on the treatment and management of psychosis and schizophrenia in adults. The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, people with psychosis and schizophrenia, their carers and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for people with psychosis and schizophrenia while also emphasising the importance of the experience of care for people with psychosis and schizophrenia and their carers (see Appendix 1 for more details on the scope of the guideline).

Although the evidence base is rapidly expanding, there are a number of major gaps and future revisions of this guideline will incorporate new scientific evidence as it develops. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, and people with psychosis and schizophrenia and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

## **1.1 NATIONAL CLINICAL GUIDELINES**

### **1.1.1 What are clinical guidelines?**

Clinical guidelines are 'systematically developed statements that assist clinicians and service users in making decisions about appropriate treatment for specific conditions' (Mann, 1996). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. Where evidence is lacking, the guidelines incorporate statements and recommendations based upon the consensus statements developed by the Guideline Development Group (GDG).

Clinical guidelines are intended to improve the process and outcomes of healthcare in a number of different ways. They can:

- provide up-to-date evidence-based recommendations for the management of conditions and disorders by healthcare professionals
- be used as the basis to set standards to assess the practice of healthcare professionals
- form the basis for education and training of healthcare professionals
- assist service users and their carers in making informed decisions about their treatment and care
- improve communication between healthcare professionals, service users and their carers
- help identify priority areas for further research.

### **1.1.2 Uses and limitation of clinical guidelines**

Guidelines are not a substitute for professional knowledge and clinical judgement. They can be limited in their usefulness and applicability by a number of different factors: the availability of high-quality research evidence, the quality of the methodology used in the development of the guideline, the generalisability of research findings and the uniqueness of individuals.

Although the quality of research in this field is variable, the methodology used here reflects current international understanding on the appropriate practice for guideline development (Appraisal of Guidelines for Research and Evaluation Instrument [AGREE]; [www.agreetrust.org](http://www.agreetrust.org); AGREE Collaboration (2003)), ensuring the collection and selection of the best research evidence available and the systematic generation of treatment recommendations applicable to the majority of people with psychosis and schizophrenia. However, there will always be some people for whom and situations for which clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, in consultation with the person with psychosis and schizophrenia or their carer.

In addition to the clinical evidence, cost-effectiveness information, where available, is taken into account in the generation of statements and recommendations of the clinical guidelines. While national guidelines are concerned with clinical and cost effectiveness, issues of affordability and implementation costs are to be determined by the National Health Service (NHS).

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, and of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the person and provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered, otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care in order to support and encourage a good therapeutic relationship is at times as important as the specific treatments offered.

### **1.1.3 Why develop national guidelines?**

The National Institute for Health and Care Excellence (NICE) was established as a Special Health Authority for England and Wales in 1999, with a remit to provide a single source of authoritative and reliable guidance for service users, professionals and the public. NICE guidance aims to improve standards of care, diminish unacceptable variations in the provision and quality of care across the NHS, and ensure that the health service is person-centred. All guidance is developed in a transparent and collaborative manner, using the best available evidence and involving all relevant stakeholders.

NICE generates guidance in a number of different ways, three of which are relevant here. First, national guidance is produced by the Technology Appraisal Committee to give robust advice about a particular treatment, intervention, procedure or other health technology. Second, NICE commissions public health intervention guidance focused on types of activity (interventions) that help to reduce people's risk of developing a disease or condition, or help to promote or maintain a healthy lifestyle. Third, NICE commissions the production of national clinical guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE has established four National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare.

### **1.1.4 From national clinical guidelines to local protocols**

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving commissioners of healthcare, primary care and specialist mental health professionals, service users and carers should undertake the translation of the implementation plan into local protocols, taking into account both

the recommendations set out in this guideline and the priorities set in the National Service Framework for Mental Health (Department of Health, 1999) and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

### **1.1.5 Auditing the implementation of clinical guidelines**

This guideline identifies key areas of clinical practice and service delivery for local and national audit. Although the generation of audit standards is an important and necessary step in the implementation of this guidance, a more broadly-based implementation strategy will be developed. Nevertheless, it should be noted that the Care Quality Commission will monitor the extent to which commissioners and providers of health and social care have implemented these guidelines.

## **1.2 THE NATIONAL PSYCHOSIS AND SCHIZOPHRENIA GUIDELINE**

### **1.2.1 Who has developed this guideline?**

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London.

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included people with psychosis and schizophrenia and carers, and professionals from psychosis and schizophrenia psychiatry, clinical psychology, general practice, occupational therapy, nursing, psychiatric pharmacy, and the private and voluntary sectors.

Staff from the NCCMH provided leadership and support throughout the process of guideline development, undertaking systematic searches, information retrieval, appraisal and systematic review of the evidence. Members of the GDG received training in the process of guideline development from NCCMH staff, and the service users and carers received training and support from the NICE Patient and Public Involvement Programme. The NICE Guidelines Technical Adviser provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of eleven times throughout the process of guideline development. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisers where needed. The group oversaw the production and synthesis of research evidence before

presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

### **1.2.2 For whom is this guideline intended?**

This guideline will be relevant for adults with psychosis and schizophrenia and covers the care provided by primary, community, secondary, tertiary and other healthcare professionals who have direct contact with, and make decisions concerning the care of, adults with psychosis and schizophrenia.

The guideline will also be relevant to the work, but will not cover the practice, of those in:

- occupational health services
- social services
- the independent sector
- Other professional bodies/ group who have direct contact with people with psychosis or schizophrenia.

### **1.2.3 Specific aims of this guideline**

The guideline makes recommendations for the treatment and management of psychosis and schizophrenia. It aims to:

- improve access and engagement with treatment and services for people with psychosis and schizophrenia
- evaluate the role of specific psychological, psychosocial and pharmacological interventions in the treatment of psychosis and schizophrenia
- evaluate the role of psychological and psychosocial interventions in combination with pharmacological interventions in the treatment of psychosis and schizophrenia
- evaluate the role of specific service-level interventions for people with psychosis and schizophrenia
- integrate the above to provide best-practice advice on the care of individuals throughout the course of their psychosis and schizophrenia
- promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.

### **1.2.4 The structure of this guideline**

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide a summary of the clinical practice and research recommendations, and a general introduction to guidelines and to the methods used to develop them. For the methods used in 2009 relating to chapters 6, 9, 10 and 11 see Appendix 11. Chapter 4 to Chapter 13 provide the evidence that underpins the recommendations about the treatment and management of psychosis and schizophrenia.

Each evidence chapter begins with a statement about whether the chapter has been updated and a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted, and the structure of the chapters varies accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about both the interventions included and the studies considered for review. Clinical summaries are then used to summarise the evidence presented. Finally, recommendations related to each topic are presented at the end of each evidence review or at the end of the chapter, as appropriate. In the separate appendix files, full details about the included and excluded studies for the 2014 guideline can be found in Appendix 15 (for evidence reviewed in 2009 see Appendix 22). Where meta-analyses were conducted, the data for the 2014 guideline are presented using forest plots in Appendix 16 (for evidence reviewed in 2009 see Appendix 23) (see Text Box 1 for details).

**Text Box 1: Appendices in a separate file**

2014 Search strategies for the identification of clinical studies	Appendix 13
2014 Search strategies for the identification of health economics evidence	Appendix 14
2014 Study characteristics for quantitative studies	Appendix 15a
2014 Study characteristics for qualitative studies	Appendix 15b
2014 Clinical evidence forest plots	Appendix 16
2014 GRADE evidence profiles (clinical and health economic)	Appendix 17
2014 Health economic evidence- completed methodology checklists	Appendix 18
2014 Health economic evidence- evidence tables of published studies	Appendix 19
2009 Search strategies for clinical evidence	Appendix 20
2009 Clinical review and clinical questions	Appendix 21
2009 Study characteristics for clinical evidence	Appendix 22
2009 Clinical evidence forest plots and/ or data tables	Appendix 23
2009 Search strategies for the identification of health economics evidence	Appendix 24
2009 Search strategies for the identification for economic studies	Appendix 25
2009 Winbugs codes used for mixed treatment comparisons in the economic model of pharmacological treatments for relapse prevention	Appendix 26
2009 The full Schizophrenia in adults guideline	Appendix 27
2009 Health economics checklist	Appendix 28

In the event that amendments or minor updates need to be made to the guideline, please check the NCCMH website ([nccmh.org.uk](http://nccmh.org.uk)), where these will be listed and a corrected PDF file available to download.

## 2 PSYCHOSIS AND SCHIZOPHRENIA IN ADULTS

This guideline is concerned with the treatment and management of the non-specific diagnosis of psychosis and with the more specific diagnosis of schizophrenia in adults, as defined in the *International Classification of Diseases, 10th Revision* (ICD-10) (World Health Organization, 1992), in the community, in hospital and in prison. The term 'psychosis' covers a set of related conditions, of which the commonest is schizophrenia, and includes schizoaffective disorder, schizophreniform disorder, delusional disorder and the so-called non-affective psychoses. This guideline does not address the treatment and management of other psychotic disorders, such as bipolar disorder and unipolar psychotic depression, or psychosis and schizophrenia in children and young people, because they are covered by other NICE guidelines.

### 2.1 THE DISORDER

#### 2.1.1 Symptoms and presentation

Psychosis and the specific diagnosis of schizophrenia represent a major psychiatric disorder (or cluster of disorders) in which a person's perceptions, thoughts, mood and behaviour are significantly altered. Individuals who develop psychosis or schizophrenia will each have their own unique combination of symptoms and experiences, which will vary depending on their particular circumstances.

In the decade since the first NICE guideline on schizophrenia (2002b), there has been a considerable shift in understanding the complexity of psychosis and schizophrenia, with a greater appreciation of the role of affect in non-affective psychoses, and in the continua of processes that underlie the disorders. Current understanding is 'still limited by the substantial clinical, pathological and etiological heterogeneity of schizophrenia and its blurred boundaries with several other psychiatric disorders, leading to a 'fuzzy cluster' or overlapping syndromes, thereby reducing the content, discriminant and predictive validity of a unitary construct' (Keshavan et al., 2011) .

Typically, there will be a 'prodromal' period often characterised by some deterioration in personal functioning. Difficulties may include memory and attention problems, social withdrawal, unusual and uncharacteristic behaviour, disturbed communication and affect, unusual perceptual experiences, which are accompanied by bizarre ideas, poor personal hygiene, and reduced interest in day-to-day activities. During this prodromal period, people with psychosis often feel that their world has changed, but their interpretation of this change may not be shared by others. Relatives and friends usually notice this as changes 'in themselves'. The changes may affect the person's ability to study, to hold down employment, or maintain relationships; they may become increasingly isolated.

This prodromal period is typically followed by an acute phase marked by positive symptoms, such as hallucinations (hearing, seeing or feeling things that others do not), delusions (markedly unusual or bizarre ideas), behavioural disturbances such as agitation and distress, and disorders of thinking so that speech becomes muddled and hard to understand. If these acute problems resolve, usually after some treatment, the positive symptoms may disappear or reduce, but it is common for negative symptoms such as poor motivation, poor self-care and poor memory and attention to remain problematic. This may interfere with the person's ability to return to study, to work and to manage their day to day activities.

Affective dysfunction and comorbidities are now recognised to be highly prevalent in people with psychosis and schizophrenia; indeed those studies that have analysed the symptom structure of psychotic experience, all include a dimension of depression and related symptoms, even in 'non-affective' diagnoses (Russo et al., 2013). Over 90% of individuals with first episode psychosis report depression in the prodrome, during the acute episode, or in the year following recovery of positive symptoms (Upthegrove et al., 2010). Social anxiety disorder that is not attributable to paranoia is present in up to a third of individuals with psychosis and schizophrenia, with similar figures for post-traumatic stress disorder (PTSD). While figures for social anxiety disorder and PTSD remain constant across phases, depression tends to peak during the prodrome and in acute psychosis but declines to about one-third following recovery. It has been shown that there are several pathways to emotional dysfunction in psychosis, including the common background of social risk factors for both psychosis and depression and as a psychological reaction to the diagnosis itself (Birchwood, 2003).

People vary considerably in their pattern of symptoms and problems and in the resulting course of any remaining difficulties. While most people will recover from the initial acute phase, only 14 to 20% will recover fully. Others will improve but have recurrent episodes or relapses, the timing of which are related to stress, adversity, social isolation and poor take-up of treatments. Thus some people have disturbing experiences only briefly, whereas others will live with them for months or years. In the longer term (up to 15 years) over half of those diagnosed will have episodic rather than continuous difficulties. As Harrow and colleagues (2005) have observed, 'some of these intervals of recovery will appear spontaneously and may be tied to individual factors, such as resilience.'

### **2.1.2 At risk mental states**

In recent years there has been a growing emphasis on early detection and intervention in order to delay or possibly prevent the onset of psychosis and schizophrenia. This focus on very early intervention and prevention has stimulated an interest in identifying, and potentially intervening in, the so-called 'at risk mental states' (or prodrome) which may precede the onset of the disorder.



At risk or 'ultra-high risk' mental states, are characterised by help-seeking behaviour and the presence of attenuated (subclinical) positive psychotic symptoms, brief limited intermittent psychotic symptoms or a combination of genetic risk indicators, such as the presence of schizotypal disorder, with recent functional deterioration. Although the risk for schizophrenia emerging over a 12-month period appears to be increased (between one in five to one in ten may be expected to develop a schizophrenic disorder (Ruhrmann et al., 2010)), it remains the case that prediction of schizophrenia based on at risk or ultra-high risk mental states is modest given that the majority of those identified do not become psychotic. Furthermore, most people identified with at risk mental states have a mixture of other mental health problems (for example, depression, anxiety, substance-use disorders or emerging personality disorder) requiring a range of targeted interventions. In addition, the potential use of a clinical label that conveys a future risk of psychosis or schizophrenia raises ethical issues and may itself be perceived as stigmatising. It may be that at risk or ultra-high risk mental states are best viewed as a dimension rather than a diagnostic category, including at one extreme people with non-specific symptoms and at the other those on the cusp of psychosis. Finally, given the low rate of transition to psychosis, any interventions used must benefit (and not harm) the majority of people (false positives) who do not develop psychosis.

### **2.1.3 Impairment and disability**

Although the problems and experiences associated with psychosis and schizophrenia are often distressing, the effects of the disorder can be pervasive. A significant number of people continue to experience long-term impairments, and as a result psychosis and schizophrenia can have a considerable effect on people's personal, social and occupational lives. A European study of six countries found that over 80% of adults with this diagnosis had some persistent problems with social functioning, though not all of them were severe. The best predictor of poorer functioning in the long term was poor functioning in the first 3 years post-diagnosis (Wiersma et al., 2000), particularly for unemployment, which was linked to duration of untreated psychosis and increased negative symptoms (Turner et al., 2009). Current estimates of employment for people with schizophrenia are 5 to 15% with an average of 8% (Schizophrenia Commission, 2012), which is significantly less than the general population (of which 71 % are currently employed).

The disabilities experienced by people with psychosis and schizophrenia are not solely the result of recurrent episodes or continuing symptoms. Unpleasant side effects of treatment, social adversity and isolation, poverty and homelessness also play a part. These difficulties are not made any easier by the continuing prejudice, stigma and social exclusion associated with the diagnosis (Sartorius, 2002; Thornicroft, 2006).

Worldwide, it has been estimated that schizophrenia falls into the top fifteen medical disorders causing disability (Murray et al., 2013). Mortality among people with schizophrenia is approximately 50% above that of the general population. This is partly as a result of an increased incidence of suicide (an approximate lifetime risk of

5% (Hor & Taylor, 2010)) and violent death, and partly because of an increased risk of a wide range of physical health problems.

Cardiovascular events have been found to be the largest single contributor, with illnesses associated with obesity, metabolic aberrations, smoking, alcohol, lack of exercise, poor diet and diabetes, making significant contributions (von Hausswolff-Juhlin et al., 2009). The precise extent to which high mortality and disability rates are, at least in part, a result of some of the medications prescribed for schizophrenia is still not clear (Weinmann et al., 2009). Difficulties experienced by people with mental health problems in accessing general medical services in both primary and secondary care continue to contribute to reduced life expectancy (Lawrence & Kisely, 2010). Recent work indicates that young Caribbean and African men, and middle-aged women from diverse ethnic or cultural backgrounds, are at higher risk of suicide, and that this may be because of differences in symptom presentation and conventional risk-factor profiles across ethnic groups (Bhui & McKenzie, 2008).

#### **2.1.4 Prognosis, course and recovery**

Historically, many psychiatrists and other healthcare professionals have taken a pessimistic view of the prognosis for schizophrenia, regarding it as a severe, intractable and often deteriorating lifelong illness. This negative view has failed to find confirmation from long-term follow-up studies, which have demonstrated considerable variations in long-term outcome. While it is estimated that around three-quarters of people with schizophrenia will experience recurrent relapse and some continued disability (Brown et al., 2010), the findings of follow-up studies over periods of 20 to 40 years suggest that there is a moderately good long-term global outcome in over half of people with schizophrenia, with a smaller proportion having extended periods of remission of symptoms without further relapses (Banham & Gilbody, 2010; Harrison et al., 2001; Jobe & Harrow, 2005). It should also be noted that some people who never experience complete recovery from their experiences nonetheless manage to sustain an acceptable quality of life if given adequate support and help.

The early stages of psychosis and schizophrenia are often characterised by repeated exacerbation of symptoms such as hallucinations and delusions and disturbed behaviour. While a high proportion respond to initial treatment with antipsychotic medication, around 80% will relapse within 5 years of a treated first episode, which is partly explained by discontinuation of medication (Brown et al., 2010).

Research has suggested that delayed access to mental health services and treatment in early psychosis and schizophrenia – often referred to as the duration of untreated psychosis – is associated with slower or less complete recovery, and increased risk of relapse and poorer outcome in subsequent years (Bottlender et al., 2003; Harrigan et al., 2003; Robinson et al., 1999).

In the UK and other countries early intervention in psychosis teams have been introduced with an aim of reducing delay to treatment in order to try to improve

outcomes. In the longer term, the factors that influence the differential recovery from psychosis and schizophrenia are not well known. But recovery may happen at any time, even after many years (Harrison et al., 2001).

A number of social and economic factors appear to affect the course of psychosis and schizophrenia. For example, in developed countries it is well established that psychosis and schizophrenia is more common in lower socioeconomic groups. However, this appears to be partly reversed in some developing countries (Jablensky et al., 1992), suggesting that the relationship between incidence, recovery rates, and cultural and economic factors is more complex than a simple correspondence with socioeconomic deprivation (Warner, 1994). There is some evidence that clinical outcomes are worse in Europe than in East Asia, Latin America, North Africa and the Middle East (Haro et al., 2011).

The risk factors for developing psychosis and schizophrenia and the acceptability of interventions and the uptake of treatments have been shown to vary across ethnic groups. Although the focus in the UK has been on African and Caribbean populations, some evidence suggests other ethnic groups and migrants in general may be at risk; social risk factors may be expressed through an ethnic group, rather than being an intrinsic risk for that ethnic groups *per se*. However, the different pattern of service use, access to services and perceived benefits across ethnic groups is a cause of concern among service users.

The effects of psychosis and schizophrenia on a person's life experience and opportunities are considerable; service users and carers need help and support to deal with their future and to cope with any changes that may happen.

### **2.1.5 Diagnosis**

Although a full discussion of the diagnoses of psychosis and schizophrenia is outside the scope of this guideline, some specific issues are discussed here to provide context.

ICD-10 (World Health Organisation, 1992) describes symptom clusters necessary for the diagnosis of different subtypes of schizophrenia. For some subtypes, ICD-10 requires that clear psychotic symptoms be present for only 1 month, with any period of non-specific impairment or attenuated (prodromal) symptoms that may precede an acute episode not counted. In ICD-10, evidence of deteriorating and impaired functioning in addition to persistent psychotic symptoms is essential for a diagnosis. Isolated psychotic symptoms (typically auditory hallucinations) without functional impairment are surprisingly common in both the general population (van Os et al., 2009) and people with emotional disorders such as anxiety and depression (Varghese et al., 2011); such experiences should not be confused with a diagnosis of a psychotic disorder or schizophrenia.

The experience of a psychotic disorder challenges an individual's fundamental assumption that they can rely upon the reality of their thoughts and perceptions.

This is often both frightening and emotionally painful for both the service user and for those close to them. For this experience then to be classified as a disorder and to acquire a diagnostic label may either be helpful in facilitating understanding or may be experienced as yet a further assault upon one's identity and integrity.

Professionals need to be aware of both the positive and negative impacts of discussing a diagnosis (Pitt et al., 2009); positive aspects can include naming the problem and providing a means of access to appropriate help and support; negative aspects can include 'labelling' the person, stigma and discrimination and disempowerment. The toxicity of the label of 'schizophrenia' has led to calls to abandon the concept altogether (Bentall et al., 1988) or to rename the condition (Kingdon et al., 2007). This has led to some professionals and user/carer groups questioning the usefulness of diagnosis and instead preferring to emphasise a narrative or psychological formulation of an individual's experiences. There is some evidence that psychosocial explanations of psychosis are less associated with stigma, desire for social distance and perceptions of dangerousness and uncontrollability than biomedical explanations (such as a diagnosis of an illness) in the general public (Read et al., 2006), healthcare professionals (Lincoln et al., 2008) and service users (Wardle et al., In press).

The majority of people for whom a diagnosis of psychosis or schizophrenia is being considered will be in their first episode of illness, although the literature on duration of untreated psychosis would suggest some of these may have had psychotic experiences for many years (Marshall et al., 2005). The future course and diagnostic stability of an initial psychotic episode shows much variation, with a sizable proportion (approximately 20%) only having one episode (Rosen & Garety, 2005). In addition to a lack of predictive validity regarding course and outcome, there are also significant problems with the reliability of the diagnosis (Bentall, 1993). It is recognised that accurate diagnosis is particularly challenging in the early phases of psychosis, which has led early intervention for psychosis services to 'embrace diagnostic uncertainty' (Singh & Fisher, 2005).

For all of the above reasons, the less specific umbrella term 'psychosis' has, therefore, found increasing favour in some professionals and some user/carer groups.

### **2.1.6 Physical health**

The association between psychosis/schizophrenia and poor physical health is well established (Marder et al., 2003). Males with schizophrenia die 20 years earlier and females 15 years earlier than the general population (Wahlbeck et al., 2011). About a fifth of premature deaths arise from suicide and accidents but most are accounted for by physical disorders (Brown et al., 2010; Lawrence et al., 2013; Saha et al., 2007), which include cardiovascular disorders (for example, coronary heart disease, peripheral vascular disease and stroke), metabolic disorders such as diabetes mellitus, chronic obstructive pulmonary disease, certain cancers and infectious disorders such as HIV, hepatitis C and tuberculosis (Leucht et al., 2007). And although not life-threatening, difficulties such as sexual dysfunction, dental caries

(Friedlander & Marder, 2002), constipation and nocturnal enuresis (Barnes et al., 2012) can be distressing and socially isolating.

While much of the increased burden of poor physical health can be explained by the nature of psychosis and schizophrenia and side effects of treatment, this 'undoubtedly also results from the unsatisfactory organization of health services, from the attitudes of medical doctors, and the social stigma ascribed to the schizophrenic patients' (Leucht et al., 2007). Despite having two to three times the likelihood of developing diabetes mellitus compared with the general population, this condition often goes unrecognised in people with schizophrenia. In a study from the Maudsley hospital in London, a chart review indicated that 39 (6.1%) of 606 inpatients had diabetes or impaired glucose tolerance; when undiagnosed individuals were formally tested for diabetes by a fasting blood glucose measurement, a further 16% were discovered to have either diabetes or impaired fasting glucose (Taylor et al., 2005). A European study screening people with schizophrenia who were not known to have diabetes, discovered 10% had type 2 diabetes and 38% were at high risk of type 2 diabetes; this population's average age was only 38 years (Manu et al., 2012).

A recent Scottish study of 314 general practices compared the nature and extent of physical health comorbidities between 9,677 people with psychosis and schizophrenia and 1,414,701 controls (Smith et al., 2013). Based on the presence of a possible recorded diagnosis for 32 index physical conditions, the study found that people with schizophrenia were more likely to experience multiple physical comorbidities: higher rates of viral hepatitis, constipation and Parkinson's disorder but lower than expected rates of CVD. The authors concluded there was a systematic under-recognition and under treatment of CVD in people with schizophrenia in primary care, which might contribute to the substantial cardiovascular-related morbidity and premature mortality observed in this group.

A similar picture of late recognition and under-treatment is apparent for cancer, although intriguingly a recent study from Sweden revealed decreased incidences of certain cancers in people with schizophrenia and their unaffected relatives (Ji et al., 2013). The authors suggested that familiar/genetic factors contributing to schizophrenia may protect against the development of cancer; this protective effect did not hold for breast, cervical and endometrial cancers, where rates were higher in women with schizophrenia. Nevertheless, even with these protective factors towards certain cancers, people with schizophrenia are more likely to have metastases at diagnosis and less likely to receive specialised interventions (Kisely et al., 2013), which explains why they are still more likely to die prematurely from cancer than the general population (Bushe et al., 2010).

### *The impact of cardiovascular diseases*

The reduction in cardiovascular morbidity and mortality seen in the general population over the last 2 decades has not been seen in people with severe mental illness in whom CVD remains the single biggest contributor to premature death

(Saha et al., 2007). Moreover, there is a widening mortality gap for people with schizophrenia mainly as a result of higher relative rates of CVD compared with the general population (Brown et al., 2010; Hennekens et al., 2005; Lawrence et al., 2003; Osborn et al., 2007a).

CVD may result from the body's response to persisting stress/distress, potential genetic vulnerabilities, lifestyle issues (for example, tobacco use, diet, sedentariness, poverty and exclusion) and psychiatric medication (De Hert et al., 2009b). The tendency for metabolic risks to cluster together is conceptualised within the metabolic syndrome, reliably predicting future CVD, diabetes and premature death; the presence of central obesity is a core factor, usually combined with evidence of impaired glucose handling, lipid abnormalities and hypertension (Alberti et al., 2005). This is a significant problem for those with established schizophrenia (De Hert et al., 2009b); for example, a Finnish cohort study revealed that by the age of 40 metabolic syndrome was four times more likely than in non-psychiatric populations (Saari et al., 2005).

### *Antipsychotic medication*

Antipsychotic medication may cause metabolic/endocrine abnormalities (for example, weight gain, diabetes, lipid abnormalities and galactorrhoea), neurological disorders (for example, tardive dyskinesia) and cardiac abnormalities (for example, lengthened QT interval on electrocardiography) (American Diabetes Association et al., 2004; Expert Group, 2004; Holt et al., 2005; Koro et al., 2002; Lieberman et al., 2005; Lindenmayer et al., 2003; Nasrallah, 2003; Nasrallah, 2008; Saari et al., 2004; Thakore, 2005). The effects of antipsychotics on CVD risk factors such as weight gain and diabetes are examined in the sections below.

### *Weight gain, metabolic disturbance and antipsychotic medicines*

The prevalence of obesity has increased dramatically in the general population over the last 30 years, and has escalated even more rapidly in people with schizophrenia (Homel et al., 2002). It seems likely that environmental changes have provoked these increases in both populations but schizophrenia may also have disease-specific effects, such as genetic susceptibility, that have additive or synergistic actions to increase weight further. However the most important factor related to weight gain in people with schizophrenia is the use of antipsychotics, which are among the most obesogenic drugs. Moreover a causal link between antipsychotics and weight gain appears certain (Foley & Morley, 2011; Kahn et al., 2008; Tarricone et al., 2010). This is important because weight gain may lead to insulin resistance and other adverse impacts such as dyslipidaemia, diabetes and hypertension. The true impact may have been obscured by a lack of critical evaluation of weight gain specifically in people never previously exposed to antipsychotics. Many of the antipsychotic trials used short follow-up times observing older people with established illness, many of whom may already have gained weight from previous antipsychotic exposure. In contrast the European First Episode Schizophrenia Trial (EUFEST) (Kahn et al., 2008), examining weight gain in a treatment-naïve group of people with a first episode, found that the percentage of those gaining more than 7% of body weight

during the first year of treatment was 86% for olanzapine, 65% for quetiapine, 53% for haloperidol and 37% for ziprasidone. Citing the findings of this study, Nasrallah concluded that neither 'first-generation' antipsychotics, such as haloperidol, nor drugs promoted as being metabolically benign 'second-generation' antipsychotics, such as ziprasidone, could be regarded as exceptions to the generalisation that any antipsychotic was capable of causing significant weight gain (Nasrallah, 2011). A more recent EUFEST study also revealed that pre-treatment rates of metabolic syndrome were no different from prevalence rates estimated in a general population of similar age (Fleischhacker et al., 2012).

Underlining the differential impact of antipsychotics on a treatment-naïve population, a recent systematic review concluded that antipsychotic-induced weight gain had been underestimated three- to four-fold in those with first episode psychosis (Alvarez-Jimenez et al., 2008). Indeed the majority of the weight gained will have done so within the first 3 years of treatment (Addington et al., 2006).

Because first episode psychosis often commences when a person is in their late teens and 20s (Kirkbride et al., 2006) the impact of antipsychotics may coincide with a critical development phase. Although limited comparative data hampers conclusions, younger people appear more vulnerable to side effects than older people (weight gain, extrapyramidal symptoms, metabolic problems, prolactin elevation and sedation (Kumra et al., 2008)). Risk of weight gain may also be more likely in those with a low baseline weight (De Hert et al., 2009a). Not only can early weight gain eventually lead to obesity-related metabolic and cardiac disorders, but it may also restrict healthy physical activities as basic as walking, and lead to a lack of self-worth and confidence to participate (Vancampfort et al., 2011). In addition, other adverse effects such as hyperprolactinaemia (causing menstrual disturbances, sexual dysfunction and galactorrhoea) (Fedorowicz & Fombonne, 2005) and movement disorders can result in poor medicine concordance, which in turn may lead to this vulnerable group of young people experiencing a cycle of relapse and disillusion with services (Hack & Chow, 2001).

### *Lifestyle factors*

#### **Tobacco use**

Smoking tobacco is more common in people with psychosis and schizophrenia than the general population, even when variation in socioeconomic status is allowed for (Brown et al., 1999; Osborn et al., 2006), with 59% already smoking at the onset of psychosis (six times more frequently than age-matched peers without psychosis (Myles et al., 2012)). Whereas average smoking rates in the UK have fallen in the general population from around 40% in 1980 to 20% currently (Fidler et al., 2011), rates for people with established schizophrenia remain around 70% (Brown et al., 2010), and this group may also be less likely to receive smoking cessation advice thereby missing out on effective prevention of a potent cause of premature death (Duffy et al., 2012; Himelhoch & Daumit, 2003). Paradoxically rates of lung cancer

appear uninfluenced (Gulbinat et al., 1992; Harris & Barraclough, 1998; Jeste et al., 1996; Osborn et al., 2007a).

### **Diet, nutrition and physical activity**

Weight can increase rapidly in the early treatment phase not only because of the use of antipsychotic medication, but also as a result of a diet that is frequently low in fruit and vegetables and high in fat and sugar, lack of physical activity and impaired motivation to change health behaviours.

Fewer than 30% of people with schizophrenia are regularly active compared with 62% of people without a serious mental illness (Lindamer et al., 2008), and fewer than 25% undergo the recommended 150 minutes per week of at least moderate-intensity aerobic activity (Faulkner et al., 2006). It may also be important to acknowledge the risks of sedentariness on cardiovascular risk; a recent study of healthy volunteers showed that minimal-intensity physical activity (standing and walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable (Duvivier et al., 2013).

### **2.1.7 Incidence and prevalence**

Psychosis is relatively common mental illness, with schizophrenia being the most common form of psychotic disorder. A review of the incidence of psychosis and schizophrenia in England between 1950 and 2009 (Kirkbride et al., 2012) found a pooled incidence of 31.7 per 100,000 for psychosis and of 15 per 100,000 for schizophrenia. Rates varied according to gender and age group, with rates generally reducing with age (although with a second peak in women starting in the mid to late 40s). Men under the age of 45 were found to have twice the rate of schizophrenia than women, but there was no difference in its incidence after this age. The rate of schizophrenia was found to be significantly higher in black Caribbean (RR: 5.6; 95%CI: 3.4, 9.2; I<sup>2</sup>=0.77) and black African (RR: 4.7; 95% CI: 3.3, 6.8; I<sup>2</sup>=0.47) migrants and their descendants, compared with the baseline population. The incidence of psychosis has been reported to vary from place to place with rates in south-east London (55 per 100,000 person years) being more than twice those in both Nottingham and Bristol (25 per 100,000 person years and 22 per 100,000 person years, respectively) (Morgan et al., 2006).

The National Survey of Psychiatric Morbidity in the UK found a population prevalence of probable psychotic disorder of 5 per 1000 in the age group 16 to 74 years (Singleton et al., 2003). Schizophrenia has a point prevalence averaging around 0.45% and a lifetime expectancy of 0.7%, although there is considerable variation in different areas and a higher risk in urban environments (van Os et al., 2010).



### 2.1.8 Possible causes

It is known that there are a number of genetic and environmental risk factors for developing psychosis and schizophrenia, but there remains uncertainty about how these factors fit together to cause the disorder (Tandon et al., 2008).

Concerning genetic risks, having a close relative with psychosis or schizophrenia is the biggest risk factor for developing a psychotic disorder (Gilmore, 2010). However, while genetic risk is substantial, it is not due to a single 'schizophrenia' gene, but to many genes, each of which makes a small contribution (Sullivan et al., 2003). Genetic risk may also involve rare but important events such as deletions or duplications of genes (The International Schizophrenia Consortium, 2008).

Genetic risks are not sufficient to explain why some people develop psychosis and schizophrenia while others do not – for example, most people with psychosis and schizophrenia do not have an affected relative. Therefore, there must also be environmental risks, both biological and psychosocial. Potential biological risks include: complications before or during birth (such as infections, poor nutrition while in the womb, maternal stress or birth trauma) (Meli et al., 2012); cannabis use, especially in adolescence (Arseneault et al., 2004; Moore et al., 2007); older paternal age at birth (Miller et al., 2011) and seasonality of birth (Davies et al., 2003); and exposure to the protozoan parasite *Toxoplasma gondii* (Torrey et al., 2012). Potential psychosocial risks include: urban birth and exposure to living in cities (Vassos et al., 2012); childhood and adult adversity, including poor rearing environments, sexual, physical and emotional abuse, neglect and bullying (Bebbington et al., 2004; van Dam et al., 2012; Varese et al., 2012; Wahlberg et al., 1997); and migration, especially when the migrants are from a developing country or a country where the majority of the population is black (Cantor-Graae & Selten, 2005).

Several theories attempt to explain how genetic risks might fit together with biological and psychosocial risks to cause psychotic disorders. None of these theories are proven. One well established theory is the neurodevelopmental hypothesis (Fatemi & Folsom, 2009), which proposes that some people have a vulnerability to developing psychosis and schizophrenia that arises due to the interaction of genetic and environmental risks around the time of birth. For example, some people might have genes that increase the chances of complications before or during birth and/or have other genes that make it difficult to replace or repair damaged nerve cells when a complication occurs. The theory proposes that such people will sometimes acquire subtle neurological injuries that are not immediately obvious during childhood. However, as the child enters adolescence, these subtle injuries somehow disrupt the normal changes in brain connectivity that occur in all teenagers. The end result is that the affected person becomes particularly sensitive to developing psychosis in the presence of some of the environmental risks (for example, cannabis use) described above. There is evidence to support the neurodevelopmental hypothesis, for example, some people who develop schizophrenia have unusual personality traits (schizotypy) (Nelson et al., 2013), minor developmental delays (Jaaskelainen et al., 2008; Welham et al., 2009) and subtle neurological signs (Neelam et al., 2011). On

the other hand, the theory is too broad to be easily proven; no specific neurological injury has been pinpointed (although brain scans of some people who develop schizophrenia show a range of abnormalities); and not all people who develop schizophrenia have the signs described above. Moreover the theory does not readily explain the contribution of several known psychosocial risks, such as urbanicity or migration.

An alternative theory is that everyone carries some degree of vulnerability to developing psychosis and schizophrenia and that the critical factor in many people is not genes or subtle neurological injuries, but the timing, nature and degree of exposure to environmental risks (van Os et al., 2009). Proponents of this theory point to numerous studies illustrating that risks like urban living, poverty and child abuse are highly predictive of later psychotic symptoms with or without a genetic risk being present (Read et al., 2005). Perhaps psychological trauma in the early stages of development can set up psychological vulnerabilities that can lead to psychosis in later life in the face of other environmental risks (van Os et al., 2010). In favour of this theory is the discovery that isolated psychotic symptoms are common in the general population, and that psychotic symptoms often emerge against a background of more common symptoms such as depression and anxiety (Evins et al., 2005; Freeman & Garety, 2003; Krabbendam & van Os, 2005; Wigman et al., 2012).

Another theory is often described as 'the dopamine hypothesis', which proposes that psychosis and schizophrenia might be caused by over activity in the dopamine neurotransmitter system in the mesolimbic system of the brain (Kapur & Mamo, 2003). The main evidence to support this theory is that effective drug treatment for psychosis and schizophrenia regulates the dopaminergic neurotransmitter system. However, a distinction must be made between the established pharmacological action of antipsychotic drugs (which block dopamine receptors), and the hypothesis that schizophrenia is caused by excessive activity of dopaminergic neurones, for which the evidence is not clear-cut. For example, it could be that antipsychotic drugs cause a general neurological suppression that reduces the intensity of symptoms (Moncrieff, 2009).

Theories have also been put forward to explain how psychological factors may lead to the development of psychotic symptoms. Psychological factors can be divided into problems with basic cognitive functions, such as learning, attention, memory or planning, and biases in emotional and reasoning processes. Problems in basic cognitive functions are related to research in brain structure and function, while problems with emotional and reasoning processes may be linked to social factors. Both types of psychological factor have been implicated in the development of symptoms of psychosis and schizophrenia (Garety et al., 2007; Garety et al., 2001; Gray et al., 1991; Green, 1992; Hemsley, 1993). Hence studies of psychological factors can provide a link between biological and environmental risk factors (van Os et al., 2010).

On balance it is unlikely that any of these theories fully captures the complexity of the potential gene-environment interaction that underpins the development of psychosis and schizophrenia; see (van Os et al., 2010) for a detailed review of the potential complexity of these interactions.

## **2.2 ASSESSMENT, ENGAGEMENT, CONSENT AND THE THERAPEUTIC ALLIANCE**

Assessment involves gathering information about current symptoms, the effects of these symptoms on the individual (and their families and carers) and strategies the person has developed to cope with them. Assessment provides an opportunity to thoroughly examine the biological, psychological and social factors that may have contributed to the onset of the illness, and also enquire about common coexisting problems such as substance misuse, anxiety, depression and physical health problems.

Assessments are carried out for a number of reasons primarily to establish a diagnosis, as a means of screening (for example, for risk), to measure severity and change and as the basis for a psychological formulation. Psychological formulations provide an explanation of why a problem has occurred and what is maintaining it; they also guide the intervention and predict potential difficulties that might arise. The significant factors within the formulation will be underpinned by the theoretical persuasion of the practitioner, including cognitive behavioural, systemic or psychodynamic. A formulation is a hypothesis, based on the information that is available at the time and will often be developed or change during the course of the intervention. Although set in the context of a theoretical model, the formulation is individualised based on the unique life experiences of each person. The individual with psychosis or schizophrenia may not share professionals' view of what the main problem is. Seeking out and assisting with what the individual regards as the main problem can provide a route towards establishing common ground, which may help to establish trust and collaboration and allow collaborative care planning over time.

The development of a constructive therapeutic relationship is crucial to assessing and understanding the nature of a person's problems and provides the foundation of any subsequent management plan. Engaging effectively with an individual with psychosis or schizophrenia may require persistence, flexibility, reliability, consistency and sensitivity to the individual's perspective in order to establish trust. Involving carers, relatives and friends of individuals with psychosis, and acknowledging their views and needs, is also important in the process of assessment and engagement, and in the long-term delivery of interventions (Kuipers & Bebbington, 1990; Worthington et al., 2013).

At times people with acute psychosis may be intensely distressed, fearful, suspicious and agitated or angry as psychotic symptoms can have a profound effect on a person's judgment and their capacity to understand their situation. They may present a risk to themselves or others that justifies compulsory treatment or detention. Issues of consent remain important throughout the care pathway and

professionals need to be fully aware of all appropriate legislation, particularly the Mental Health Act (HMSO; Sartorius, 2002) and the Mental Capacity Act (HMSO). All reasonable steps need to be taken to engage individuals in meaningful discussion about issues relating to consent, and discussion with individuals should include specific work around relapse signatures, crisis plans, advance statements and advance decisions. The above statutory framework does provide for individuals with schizophrenia to make a contemporaneous decision to refuse treatment, though this could potentially be overruled by detention under the Mental Health Act.

In 2011-12, 48,631 individuals in England were compulsorily detained in hospital under Mental Health Act provisions, showing a continuation of the increasing trend in recent years (Care Quality Commission, 2012). There was also a 10% rise in the number of inpatients made subject to community treatment orders (CTOs) to 4,220. The CQC report identified concerns regarding inappropriate coercion in the system. The awareness among individuals who have a psychotic disorder, their carers, professionals and the general population that compulsory detention and treatment is a possibility forms a key component in the mental health landscape, which is variously seen as coercive, oppressive, enabling or protective. Therefore it is essential that any individual detained under the Mental Health Act continues to be involved in a collaborative approach to their difficulties. Seeking common objectives is a vital part of this process and individuals subject to the provisions of the Mental Health Act need the highest quality of care from the most experienced and trained staff, including consultant psychiatrists.

## **2.3 LANGUAGE AND STIGMA**

Although treatment for psychosis and schizophrenia has improved since the 1950s and 1960s, some people with this diagnosis still encounter difficulties finding employment and may feel excluded from society. In an editorial for the *British Medical Journal*, Norman Sartorius claimed that 'stigma remains the main obstacle to a better life for the many hundreds of millions of people suffering from mental disorders' (Sartorius, 2002). In part because of media coverage of events associated with psychosis and schizophrenia, people with the condition live with the stigma of an illness often seen as dangerous and best dealt with away from the rest of society. In this regard, research has shown that while the number of psychiatrically unrelated homicides rose between 1957 and 1995, homicides by people sent for psychiatric treatment did not, suggesting that the public fear of violence arising from people with schizophrenia is misplaced (Taylor & Gunn, 1999).

Those with psychosis and schizophrenia may also feel stigmatised because of mental health legislation, including compulsory treatment in the community, which may exacerbate their feelings of exclusion. The side effects of the medication, such as hypersalivation, involuntary movements, sedation and severe weight gain, and the less than careful use of diagnostic labels, can all contribute to singling out people with schizophrenia, marking them as different. In addition, people with this condition may find that any physical health problems they have are not taken as seriously by healthcare professionals.

In the view of many service users, clinical language is not always used in a helpful way, and may contribute to the stigma of psychosis and schizophrenia. For example, calling someone a 'schizophrenic' or a 'psychotic' gives the impression that the person has been wholly taken over by an illness, such that no recognisable or civilised person remains. Many non-psychiatric health workers and many employers continue to approach people with psychotic disorders in this way. There is a move away from using the word 'schizophrenia' for people with psychotic symptoms because the label is so unhelpful, especially in early intervention in psychosis services.

It is important that professionals are careful and considerate, but also clear and thorough in their use of clinical language and in the explanations they provide, not only to service users and carers but also to other healthcare professionals. Services should also ensure that all clinicians are skilled in working with people from diverse linguistic and ethnic backgrounds, and have a process by which they can assess cultural influences and address cumulative inequalities through their routine clinical practice (Bhui et al., 2007). Addressing organisational aspects of cultural competence and capability is necessary alongside individual practice improvements.

Parents of people with psychosis and schizophrenia often feel to blame, either because they believe that they have 'passed on the genes' causing schizophrenia, or because they are 'bad parents'. However, the families of people with schizophrenia often play an essential part in the treatment and care of their relative, and with the right support and help can positively contribute to promoting recovery. The caring role can come at a high cost of depression and strain, and services need to remain sensitive to the separate needs of carers (see Section 2.4).

## **2.4 ISSUES FOR FAMILIES, CARERS AND FRIENDS**

This guideline uses the term 'carer' to apply to all people who provide or intends to provide unpaid care or support for the person, including family members, friends and advocates, although some family members may choose not to be carers.

Many people with psychosis and schizophrenia receive significant support from carers and it is important to understand, therefore, that the caring role brings with it many difficult challenges for which they may not be prepared. Carers may often be important in the process of assessment and engagement in treatment and also in the successful delivery of effective interventions and therapies for people with psychotic disorders. As a result developing and sustaining supportive relationships with carers may be instrumental for recovery from psychosis and schizophrenia.

Carers will need detailed information about psychosis and schizophrenia and, with consent<sup>1</sup>, will need guidance on their involvement in the person's treatment and

---

<sup>1</sup>See <http://www.carersandconfidentiality.org.uk> for an interactive guide for professionals.

care. In such roles carers have rights and entitlements and these are described by the NHS in England<sup>2</sup>. Carers can be engaged in the care planning process by practitioners drawing on good practice examples such as the ‘Triangle of Care’ (Kuipers & Bebbington, 1990; Worthington et al., 2013)

Caring for a person with psychosis or schizophrenia can be emotionally, psychologically and financially challenging, therefore carers will need help and support not only in their caring role but also for their own wellbeing because they may experience grief, fear, distress and isolation, and these feelings can have a significant impact on their quality of life. Without this support carers can feel neglected by health and social care services in terms of their own health and support needs and become frustrated by the lack of opportunities to contribute to the development of the care plan for the person for whom they care.

## **2.5 TREATMENT AND MANAGEMENT OF PSYCHOSIS AND SCHIZOPHRENIA IN THE NHS**

### **2.5.1 Introduction**

From the 1850s to the 1950s, the treatment and management of psychosis and schizophrenia generally took place in large asylums where many people remained confined for much of their lives. Subsequently, the development of the post-war welfare state, which made benefits and housing more readily available in the community, the introduction of antipsychotic drugs and increased concern with the human rights of people with mental health problems have supported a government policy of gradual closure of most asylums (Killaspy, 2006). Similar deinstitutionalisation processes have taken place at varying rates in the USA and most European countries, often aimed both at improving people’s quality of life and reducing costs.

### **2.5.2 Pharmacological treatment**

Today, within both hospital and community settings, antipsychotic drugs remain the primary treatment for psychosis and schizophrenia. There is well-established evidence for their efficacy in both the treatment of acute psychotic episodes and relapse prevention over time (Horst et al., 2005). However, despite this, considerable problems remain. A significant proportion of service users – up to 40% (Kelly et al., 2008; Sacco et al., 2009) – have a poor response to conventional antipsychotic drugs and continue to show moderate to severe psychotic symptoms (both positive and negative).

In addition, conventional or typical antipsychotic agents (more recently called ‘first-generation’ antipsychotics [FGAs]) are associated with a high incidence and broad range of side effects including lethargy, sedation, weight gain and sexual

---

<sup>2</sup><http://www.nhs.uk/CarersDirect/guide/rights/Pages/carers-rights.aspx>.

dysfunction. Movement disorders, such as parkinsonism, akathisia and dystonia (often referred to as acute extrapyramidal side effects [EPS]), are common and can be disabling and distressing. A serious long-term side effect is tardive dyskinesia, which develops in around 20% of people receiving FGAs (Weinberger et al., 2008); this is a late-onset EPS characterised by abnormal involuntary movements of the lips, jaw, tongue and facial muscles, and sometimes the limbs and trunk. Although a person who develops tardive dyskinesia is usually unaware of the movements, they are clearly noticed by others, and the condition has long been recognised as a severe social handicap (Williams et al., 2012b).

In response to the limited effectiveness and extensive side effects of FGAs, considerable effort has gone into developing pharmacological treatments for schizophrenia that are more effective and produce fewer or less disabling side effects. The main advantage of these so-called second-generation ('atypical') antipsychotics (SGAs) appears to be that they have a lower liability for acute EPS and tardive dyskinesia. However, in practice this must be balanced against other side effects, such as weight gain and other metabolic problems that may increase the risk of type-2 diabetes and CVD (Lindenmayer et al., 2003; Mackin et al., 2007a; Marder et al., 1996; Nasrallah, 2003; Nasrallah, 2008; Suvisaari et al., 2007). There have been several recent suggestions that the distinction between FGAs and SGAs is artificial (Kendall, 2011; Leucht et al., 2013).

Raised serum prolactin is also an important adverse effect of antipsychotic medication, which can lead to problems such as menstrual abnormalities, galactorrhea and sexual dysfunction, and in the longer term to reduced bone mineral density (Haddad & Wieck, 2004; Meaney et al., 2004).

In people with schizophrenia who have not responded well to other antipsychotics, only one antipsychotic drug, clozapine, has a specific licence for the treatment of this group of people.

There is emerging evidence that some people can cope well in the long term without antipsychotic medication (Harrow et al., 2012), and some suggestions that both neurocognitive and social functioning may be improved without such medication (Faber et al., 2012; Wunderink et al., 2013); in addition, there is preliminary evidence that psychological interventions can be beneficial without antipsychotic medication (Morrison et al., 2012b). Such considerations have led some to question the default reliance on medication as first-line treatment for people with schizophrenia (Morrison et al., 2012a). Nevertheless, it is widely accepted that antipsychotics remain an essential component and not the mainstay of treatment (Kendall 2011).

### **2.5.3 Psychological and psychosocial interventions**

Before the introduction of neuroleptic medication for schizophrenia in the 1950s and 1960s, analytical psychotherapies based on the work of Frieda Fromm-Reichmann (1950) and Harry Stack Sullivan (1947) and others were widely practiced. The concept of rehabilitation grew during this period influenced by the pioneering work

of Manfred Bleuler in the Bergholzi clinic in Zurich where patients were engaged in meaningful vocational and occupational endeavour in the context of an 'open door' policy (Bleuler, 1978). In the early 1980s, the publication of the seminal 'Chestnut Lodge' evaluation of exploratory and investigative psychotherapies (McGlashan, 1984) had a major impact: the trial demonstrated no impact of psychotherapy on the core psychotic symptoms contributing to a decline in their use in routine practice with neuroleptics taking their place as the mainstay of treatment.

However, as deinstitutionalisation gained ground in the 1970s, psychological and social research into factors that might contribute to relapse in people with psychosis or schizophrenia living in community settings, such as stressful life events and communication difficulties in families (high 'expressed emotion'), stimulated the development of family intervention to prevent relapse (Leff et al., 1982; Lobban & Barrowclough, 2009). Family intervention often included education for family members about schizophrenia (sometimes called 'psychoeducation') and, in time, research was conducted on the benefits of psychoeducation alone (Birchwood et al., 1992).

Interest in psychological and broader psychosocial interventions for the treatment of psychosis and schizophrenia was also precipitated in the 1980s by the increasing recognition of the limitations, side effects and health risks associated with antipsychotic medication and low rates of adherence (Akbarpour et al., 2010) and growing evidence for the impact of cumulative neuroleptic exposure on cortical grey matter loss (Baker et al., 2006).

Over the last decade, there has been a revolution in understanding the role that ecological and psychological processes have on the risk for psychosis and on resilience (Bloch et al., 2010). This includes, for example, the impact of urban upbringing and residence in unstable, fragmented neighbourhoods (Chen et al., 2013) and the impact that low self-esteem can have on the way in which individuals with psychotic experience appraise its meaning.

Demand for psychological therapies in general has also grown, culminating in the Department of Health's Improving Access to Psychological Therapies (IAPT) initiative; indeed, in the mental health strategy, *No Health Without Mental Health* (Prince et al., 2007), funding has been made available to extend IAPT to those with severe mental illness, particularly psychosis and schizophrenia.

### *Cognitive-developmental processes in psychosis*

The familiar notion that the onset of psychosis coincides with the 'first psychotic episode' is now understood to be something of a misnomer; it is, in reality, the 'end of the beginning'. With few exceptions, the formal onset of psychosis is preceded by many months of untreated psychosis and before that, many years of changes stretching back into late childhood. Important prospective studies, particularly the 'Dunedin Study' (Dalack & Meador-Woodruff, 1999), have shown that subtle psychotic-like experiences at age 11 strongly predict the later emergence of



psychosis; however many individuals manage to escape this outcome. Population studies such as the NEMESIS project (de Leon et al., 2005) and the UK AESOP study (Chen et al., 2013) have shown that a number of 'environmental' factors predict those who are more likely to show persistence and worsening of symptoms, including: cannabis exposure in adolescence, social deprivation, absence of a parent and the experience of childhood abuse or neglect. Affective dysregulation has been shown to be a dimension that is both highly comorbid with psychosis (now argued to be a dimension of psychosis) and a strong feature in its early development (Evins et al., 2005); the presence of affective dysfunction in adolescence, particularly depression and social anxiety, has been shown to be a predictor of transition from psychotic experience to psychotic disorder (Bloch et al., 2010).

Social disability is one of the hallmarks of psychosis and those with adolescent onset tend to fare worse in this regard. Prospective studies of social disability and recovery have shown that early functional and vocational recovery, rather than symptoms of psychosis, play a pivotal role in preventing the development of chronic negative symptoms and disability, underlining the need for interventions that specifically address early psychosocial recovery (Fatemi et al., 2005).

These cognitive-developmental processes have informed influential cognitive models of psychosis (Gallagher et al., 2007) and specific symptoms of psychosis such as auditory hallucinations (Gelkopf et al., 2012; George et al., 2008) and affective processes (George et al., 2000). These models have informed wider foci of interventions in psychosis in addition to psychotic symptoms, embracing the family, developmental trauma and their adult sequelae, affective dysfunction, substance misuse and peer social engagement.

### *Aims of psychological and psychosocial interventions*

The aims of psychological and psychosocial interventions in psychosis and schizophrenia are therefore numerous. These should include interventions to improve symptoms but also those that address vulnerability, which are embedded in developmental processes. The aims, therefore, include: reduction of distress associated with psychosis symptoms (Hartman et al., 1991); promoting social and educational recovery; reducing depression and social anxiety (Hong et al., 2011); and relapse prevention. Reducing vulnerability and promoting resilience will require reducing cannabis misuse, promoting social stability and family support, and dealing with the sequelae of abuse and neglect including attachment formation.

## **2.5.4 Management of at risk mental states and early psychotic symptoms**

Reliable and valid criteria are now available to identify help-seeking individuals in diverse settings who are at high risk of imminently developing schizophrenia and related psychoses. Yung and colleagues (Yung et al., 1996) developed operational criteria to identify three subgroups possessing an at risk mental state for psychosis. Two subgroups specify state risk factors, defined by the presence of either transient psychotic symptoms, also called brief limited intermittent psychotic symptoms, or

attenuated (subclinical) psychotic symptoms. The other subgroup comprises trait-plus-state risk factors, operationally defined by the presence of diminished functioning plus either a first-degree relative with a history of psychosis or a pre-existing schizotypal personality disorder. All subgroups are within a specified age range known to be at greatest risk for the onset of psychosis.

Effective interventions to prevent or delay transition to psychosis are needed because of the significant personal, social and financial costs associated with it. To date there have been six randomised controlled trials (RCTs) that have reported outcomes associated with antipsychotic medication, omega-3 polyunsaturated fatty acids and/or psychological interventions, each using similar operational definitions of at risk mental states. These studies have been conducted in Australia (McGorry et al., 2002; Yung et al., 2011), North America (Addington et al., 2011; McGlashan et al., 2006); the UK (Morrison et al., 2007; Morrison et al., 2004) and Austria (Amminger et al., 2010).

It is generally agreed that research regarding interventions for at risk mental states and subthreshold psychotic experiences is in a state of clinical equipoise. Existing recommendations promote a clinical staging approach that utilises benign interventions (such as monitoring mental states, case management, social support and psychosocial interventions) before considering those with more significant side effects, such as antipsychotic medication, or restrictive approaches involving hospitalisation (International Early Psychosis Association Writing Group, 2005; McGorry et al., 2006). However, due to local resources and service configurations, clinicians' attitudes and awareness of such recommendations, current clinical practice is likely to be highly variable, which is evident in the recent large international naturalistic cohort studies (Cannon et al., 2008; Ruhrmann et al., 2010).

### **2.5.5 Service-level interventions**

Service-level interventions for people with psychosis and schizophrenia are delivered both in hospital and in community settings. The 'balanced care' model of mental health service provision (Thornicroft & Tansella, 2012) emphasises the importance of achieving an equilibrium among all service components including outpatient services and community mental health teams, acute inpatient services, community residential care and services for supporting employment.

Despite the policy of shifting care to the community, expenditure on inpatient care remains substantial: secure units, community mental health teams and acute wards are the top three sources of mental health expenditure in the NHS (Nayor & Bell, 2010). As the large asylums closed, government policy promoted the opening of acute psychiatric units within general hospitals. Some such units remain, but recently the separation of mental health provider trusts from physical health services, together with disappointment with the extent to which mental healthcare in the general hospital has reduced stigma, has resulted in a trend towards small freestanding mental health inpatient units, usually within or close to the catchment areas they serve (Totman et al., 2010). Both service users and clinicians have argued

that general acute admission wards are often unsafe environments with limited provision of therapeutic interventions and activities (Holloway & Lloyd, 2011). In response, there has been a series of initiatives aimed at improving the quality and effectiveness of inpatient care, including the Accreditation for Acute Inpatient Mental Health Services (AIMS) programme initiated by the Royal College of Psychiatrists (Cresswell & Lelliott, 2009) and STAR WARDS (Simpson & Janner, 2010).

Beyond the acute admission ward, there has been interest for many decades in whether residential crisis houses outside hospital can provide effective and acceptable alternatives to hospital admission for some people who have severe mental illness. Service users and voluntary sector organisations have strongly advocated them. They are available in a minority of trusts and are often closely connected to crisis resolution and home treatment teams (Johnson et al., 2010). While numbers of acute beds have fallen, secure bed use for longer term admission of people deemed too dangerous for local psychiatric units has increased (Walker et al., 2012). This trend, together with a rise in supported housing and in detentions under the Mental Health Act, has led some to argue that a reinstitutionalisation process is in progress (Priebe et al., 2005).

The lynchpin of community mental healthcare for people with a psychotic disorder in the past 2 decades has been the multidisciplinary community mental health team, providing assessment and long-term follow-up. Mandated by the NHS Plan (2000), a strikingly extensive national initiative has been the introduction in every catchment area in England of three types of specialist community mental health teams: (1) crisis resolution and home treatment teams provide urgent assessment when hospital admission is contemplated and, where feasible, offer intensive home treatment as an alternative (Johnson et al., 2008); (2) assertive outreach (assertive community treatment) teams work intensively with people who are most difficult to engage (Wright et al., 2003); and (3) early intervention in psychosis services seek to reduce treatment delays at the onset of psychosis and to promote recovery and reduce relapse following a first episode of psychosis (Lester et al., 2009a). With a new government in 2010 and a shift towards focusing on outcomes rather than requiring certain service configurations, these new team types are no longer mandatory, but they remain important components of service systems in most local areas. In some regions, generic community mental health teams are now giving way to further types of specialist service, including primary care liaison teams and specialist teams for psychosis. In recent innovations, there has been a further focus on the development of integrated pathways through services: for example, in some catchment areas integrated acute care pathways closely integrate inpatient wards, crisis teams, crisis houses and acute day services, with a single management structure and sometimes staff rotation between services. Rehabilitation services, often consisting of inpatient, residential and community team components, are a longstanding resource for people with psychosis and schizophrenia in many areas, focusing on people with treatment-resistant symptoms and severe difficulties in functioning (Killaspy et al., 2013).

A great variety of services aim to meet the social needs of people with psychosis and schizophrenia. Recent emphasis has been on developing services that support people in achieving their own self-defined recovery goals. As the National Institute for Mental Health in England (NIMHE) stated: 'Recovery is what people experience themselves as they become empowered to manage their lives in a manner that allows them to achieve a fulfilling, meaningful life and a contributing positive sense of belonging in their communities' (National Institute for Mental Health in England, 2005). The social disadvantages experienced by people with severe mental illness, including stigma, social exclusion and poverty, are still great, therefore high levels of need in domains such as accommodation, work, occupational, educational and social activities, and social support remain unaddressed (Thornicroft et al., 2004). A complex range of supported accommodation, varying in quality, support level and approach, is delivered primarily by the voluntary and private sectors (Macpherson et al., 2012). Employment rates among people with severe mental illness are notably low in the UK, and a range of services, including individual placement and support schemes (Rinaldi et al., 2010) and social firms (which seek to create jobs for people who are disadvantaged in the labour market) have sought to address this. Social support and non-vocational activities have traditionally been the province of local authority day centres. These have sometimes been criticised as excessively institutional, and have been supplemented or replaced by a wider range of initiatives aimed at improving access to meaningful activities, enhancing personal relationships, reducing stigma and discrimination, and lessening the negative effects of social isolation. Many such innovative services are provided by the voluntary sector, but relatively little evidence on activities and outcomes is available as yet. See Section 2.5.6 for further discussion about employment for people with psychosis and schizophrenia.

### **2.5.6 Employment**

When people have a job that gives them purpose, structure and a valued role in society this impacts positively on their self-esteem, community inclusion and opportunities (Ross, 2008) as well as having a financial reward, although there are many positive benefits to unpaid work. Conversely, unemployment limits life chances and has a detrimental impact on physical health, social networks and choice (Advisory Conciliation and Arbitration Service, 2009).

Rates of unemployment for people with severe mental illness are approximately six to seven times higher than people with no mental disorder (Organisation for Economic Co-operation and Development, 2011). Different studies put the employment rate of people with severe mental illness in a range of between 15% (Evans & Repper, 2000) to 20% (Schneider et al., 2007), and they are the largest group claiming incapacity benefit (Ross, 2008).

For people with a severe mental illness, the best predictor for a positive outcome towards an employment goal is the service user wanting to have a work role (Ross, 2008) and a work history (Michon et al., 2005), rather than the diagnosis or

symptoms. Having unmet needs and not receiving incapacity benefit or income support was associated with wanting to work full-time (as opposed to part time) rather than self-esteem, quality of life, severity of symptoms or level of functioning (Rice et al., 2009).

The stress-vulnerability model can lead to the view that work could be detrimental to people with psychosis and schizophrenia because it could be stressful (Zubin & Spring, 1977). But having little structure or role in society, which can lead to social isolation and poverty, are widely recognised as stressors (Marrone & Golowka, 1999) and contributors to poor physical and mental health (Boardman et al., 2003). If health and social care professionals assume that service users do not want to work and suggest that work may be an unreasonable aspiration or too stressful, this will limit the views of the service user. Low expectations of mental health staff can be a major barrier to service users finding employment (Office of the Deputy Prime Minister, 2004). There is evidence that up to 97.5% of service users may want some type of work role, be that volunteering or paid employment, but when asked if they had any help with seeking work, 53% had not received any support with this goal (Seebohm & Secker, 2005).

Stigma and discrimination is experienced by people with psychosis and schizophrenia from employers, with 75% of employers stating that it would be difficult to employ a person with a psychotic disorder (Office of the Deputy Prime Minister, 2004). Some employers believe that workers with mental health problems cannot be trusted and cannot work with the public and that work would be negative to their mental health. Larger employers are more likely to employ people with psychosis and schizophrenia, perhaps because they have wider support structures (Biggs et al., 2010). Service users identified the attitude of employers as the biggest barrier to work (Seebohm & Secker, 2005). However, the attitude of employment agencies has improved and they were able to identify the advantages of employment for service users (Biggs et al., 2010).

Other barriers to employment identified by service users with mental health problems are the benefits system and having a lack of work experience, skills and qualifications (Seebohm & Secker, 2005). One key determinant that can limit employment outcomes is the level of educational attainment. Experiencing disruption to education as a direct result of mental health problems can impact on access to the labour market and can make it difficult to attain and sustain a work role (Organisation for Economic Co-operation and Development, 2011; Schneider et al., 2009). Even for healthy young people there is evidence for long-term negative effects on their work prospects when, having completed their education, they are unable to access the labour market during a recession; this can lead to subsequent anxiety about job security because past unemployment will influence future expectations and limit lifetime earnings (Bell & Blanchflower, 2011). Therefore, when a young person's future is compounded further by poor mental health, they require exceptional support and guidance to achieve their occupational aspirations and

mental health workers need to be active in challenging the barriers that may be inherent within the system for service users to achieve their full potential.

### **2.5.7 Inequalities**

The Equality Act identifies the following characteristics that require protection against discrimination in relation to service provision: age, race, religion or belief, gender, sexual orientation, transgender identity, disability and pregnancy and maternity. Marriage or civil partnership relates only to employment. It is important for service providers and mental health workers to be aware of the different needs and outcomes for people with protected characteristics, and how these may affect the way that services and interventions are designed, accessed, delivered and evaluated. As a result of this information, services need to take equality into account in working with individuals or population groups, so that they can demonstrate that people within these characteristics are not disadvantaged in their care and subsequent outcomes and address health inequalities.

Many of the protected characteristics, such as race, age, perinatal mental health and gender, have been covered widely in the literature in relation to psychosis and schizophrenia. The evidence base is non-existent in relation to the population that have protected characteristics relating to sexual orientation, gender reassignment and disability. However, current evidence demonstrates lesbian, gay and bisexual people have a higher prevalence of self-harm, suicidal ideation, substance misuse (Hunt & Fish, 2008) (Stonewall, 2012) and are frequent victims of bullying and hate crime from family members and within society (Dick, 2008) and subsequent psychological trauma (Herek et al., 1999).

### **2.5.8 Primary and secondary care interface**

The last decade has seen much change in how the care of people with psychosis and schizophrenia living in the community is organised between primary and secondary care. Not only has secondary care provision undergone major alteration but there have also been significant changes in primary care provision. A recent 12-month investigation of 1,150 primary care records of people with severe mental illness – the most common diagnoses being schizophrenia (56%) and bipolar disorder (37%) – from 64 practices in England (Reilly et al., 2012) found that per annum about two thirds were seen by a combination of primary and specialist services and a third were seen just in primary care. These findings superficially appeared similar to findings from the largest previous survey (Kendrick et al., 1994). However this new study (Reilly et al., 2012) revealed a marked reduction in this population's annual general practitioner (GP) consultation rates averaging only 3 (range 2–6) per annum, far lower than the rates of 13 to 14 per annum reported in the mid-1990s (Nazareth & King, 1992), and only slightly higher than the annual consultation rate of the general population at 2.8 (range 2.5–3.2) in 2008 (Hippisley-Cox & Vinogradova, 2009). Moreover practice nurses, key providers of cardiovascular risk screening and health education in primary care, consulted with this population on average only once a year compared with the general practice population rate of 1.8 consultations per year; nor was health education a common feature of these consultations, the authors

concluding that practice nurses appear to be an underutilised resource (Reilly et al., 2012). This diminution in contact with a primary care practitioner is perhaps surprising given that in 2006 the Quality and Outcomes Framework (NHS Employers and British Medical Association 2011/12) instituted a pay for performance scheme designed to encourage health promotion and disease management programmes, paying primary care to measure four physical health indicators for people with severe mental illness on the primary care mental illness register: BMI (MH12), blood pressure (MH13), total to HDL cholesterol ratio (MH14) and blood glucose (MH15).

Patients view primary care as providing an important coordinating role for their mental and physical healthcare; they particularly value a stable continuity of doctor-patient relationship in primary care (Lester et al., 2005). In contrast GPs report feeling that the holistic care of people with severe mental illness is beyond their remit (Lester et al., 2005); some may hold negative opinions about providing care for this population (Curtis et al., 2012; Lawrie et al., 1998); and the majority regard themselves as simply involved in the monitoring and treatment of physical illness and prescribing for mental illness (Bindman et al., 1997; Kendrick et al., 1994).

### *Detection and referral of psychosis*

The pathway to effective assessment and treatment for someone with a newly presenting psychotic illness is an important aspect of the primary-secondary interface. Rarity of presentation of psychotic disorders in primary care can impede early detection, highlighted by a Swiss study that found that GPs suspect an emerging psychosis in only 1.4 patients per year (Simon et al., 2005). Yet GP involvement is linked with fewer legal detentions and can reduce distress (Burnett et al., 1999; Cole et al., 1995). However, few GPs receive postgraduate mental health training, and even when they do a well-powered study of a GP educational intervention about early presentations of psychosis failed to reduce treatment delay, although the training may have facilitated access to specialist early intervention teams (Lester et al., 2009b). When asked, GPs prefer greater collaboration with specialist services and low-threshold referral services rather than educational programmes (Simon et al., 2005).

### *Coordination of physical healthcare*

The other major interface issue concerns the management of physical health. A Scottish primary care study confirmed the high rates of multiple comorbid physical health problems experienced by people with schizophrenia, and that the likelihood of comorbidity was almost doubled for those living in the most deprived areas (Langan et al., 2013). There is evidence from studies in the general population that the extent of comorbidity is greater in younger age groups, even though there is increasing morbidity with age (van den Akker et al., 1998). This is particularly pertinent for people experiencing schizophrenia, where young onset and social disadvantage are both likely.

Cardiovascular disease (CVD) is the single commonest cause of premature mortality in people with psychosis and schizophrenia and yet, despite numerous published screening recommendations in this guideline and other reports (Buckley et al., 2005; Mackin et al., 2007b; Morrato et al., 2009; Nasrallah et al., 2006), there continues to be systematic under-recognition and under-treatment in primary care (Smith et al., 2013). Recognition and treatment of CVD risk was one of the themes investigated by the recent National Audit of Schizophrenia (Royal College of Psychiatrists, 2012) using standards derived from the 2009 guideline (NICE, 2009d). In the largest audit of its kind yet undertaken, 94% of the trusts and health boards across England and Wales took part, returning data between February and June 2011 on 5,091 patients with an average age of 45 years. This case record audit reviewed the care of people with a diagnosis of either schizophrenia or schizoaffective disorder in contact with community-based mental health services in the previous 12 months. Only 29% had record of a comprehensive assessment of cardiovascular risk, including weight (or BMI), smoking status, blood glucose, blood lipid levels and blood pressure; 43% appeared not to have been weighed and 52% had information about family history of CVD, diabetes, hypertension or hyperlipidaemia during the previous 12 months. Of those with an established comorbidity of either CVD or diabetes mellitus, fewer than half had record of a comprehensive assessment of cardiovascular risk. Even where monitoring had identified a problem, an intervention did not necessarily occur – for instance only 20.1% of those identified to have a lipid abnormality appear to have been offered an intervention.

Perhaps because poor physical health may take several years to fully develop in people with psychosis and schizophrenia, there has been a tendency for most guidance and recommendations to focus on treating the endpoints of disease. Yet modifiable cardiovascular risk appears within weeks of commencing treatment (Foley & Morley, 2011). New models are, however, emerging. For instance, the potential for nurse-led approaches to cardiovascular risk screening has attracted interest. A recent study designed to complement the configuration of UK primary and secondary care services placed a general nurse, experienced in cardiovascular risk assessment but without previous mental health experience, within four community mental health teams; the nurse-led intervention was superior, resulting in an absolute increase of approximately 30% more people with serious mental illness receiving screening for each CVD risk factor than in control arm of the study (Osborn et al., 2010a). Another model, recently introduced in New South Wales is encouraging a systematic approach by specialist services for people with first episode psychosis based on an agreed clinical algorithm focusing on key cardiovascular risks – notably weight gain, smoking, lipid and glucose abnormalities, hypertension, awareness of family history of CVD or diabetes (Curtis et al., 2012). This resource has recently been adapted for use in the UK by the Royal College of General Practitioners and the Royal College of Psychiatrists as part of the National Audit of Schizophrenia initiative; the Positive Cardiometabolic Health Resource (Lester UK adaptation, 2012) encourages a collaborative framework between primary and specialist care for dealing with the cardiometabolic risks linked to prescribing antipsychotic medicines.



While such examples of innovation and collaboration between professionals from primary and specialist care are encouraging, there remains little systematic evaluation of ways to better address multiple physical health morbidities in people with psychosis and schizophrenia.

## 2.6 ECONOMIC COST

Schizophrenia is one of the main contributors to global disease burden (Collins et al., 2011), having a significant impact on individuals and placing heavy responsibility on their carers, as well as potentially large demands on the healthcare system. In the most recent 'Global Burden of Disease' analysis by Murray and colleagues (2012) schizophrenia appeared among the top 20 causes of disability in many regions and was ranked as the 16th leading cause of disability among all diseases worldwide. When the burden of premature mortality and non-fatal health outcomes were combined and expressed in disability adjusted life years (DALYs), schizophrenia was the 43rd leading cause of worldwide burden among all diseases and from 1990 to 2010 there was a 43.6% increase in DALYs attributable to schizophrenia worldwide. Similarly, in the UK sub-analysis of the 'Global Burden of Disease' study Murray and colleagues (2013) found schizophrenia to be one of the leading causes of years lived with disability (YLDs) with approximately 15% increase in YLDs and 14% increase in DALYs from 1990 to 2010.

In England schizophrenia is estimated to cost £7.9 billion (in 2011/2012 prices) (Mangalore & Knapp, 2007). Of this, roughly £2.4 billion (about 30% of the total cost) comprise direct costs of treatment and care falling on the public purse, while the remaining £5.6 billion (70% of the total cost) constitute indirect costs to society. The cost of lost productivity of people with schizophrenia owing to unemployment, absence from work and premature mortality reach £4.0 billion, while the cost of lost productivity of carers is £38.0 million. The cost of informal care and private expenditures borne by families, account for approximately £729.4 million. In addition, £1.2 million of the total cost can be attributed to criminal justice system services, £676.0 million to benefit payments and another £16.6 million to the administration of these payments. Based on the above estimates, the average annual cost of a person with schizophrenia in England is approximately £65,000.

Davies and Drummond (1994) estimated that the lifetime total direct and indirect costs of a person with schizophrenia ranged from £8,000 (for a person with a single episode of schizophrenia) to £535,000 (for a person with multiple episodes lasting more than 2.5 years, requiring long-term care either in hospital or intensive community programmes) in 1990/1991 prices. Guest and Cookson (1999) estimated the average costs of a newly diagnosed person with schizophrenia at around £115,000 over the first 5 years following diagnosis, or approximately £23,000 annually (1997 prices). Of these, 49% were indirect costs owing to lost productivity.

Schizophrenia has been shown to place a substantial economic burden to the healthcare system and society worldwide: Wu and colleagues (2005) reported a total

cost of schizophrenia in the US of US\$62.7 billion (2002 prices). More than 50% of this cost was attributed to productivity losses, caused by unemployment, reduced workplace productivity, premature mortality from suicide and family caregiving; another 36% was associated with direct healthcare service use and the remaining 12% was incurred by other non-healthcare services. In Canada, Goeree and colleagues (2005) estimated the total cost of schizophrenia at approximately CA\$2.02 billion (2002 prices). Again, productivity losses were by far the main component of this cost (70% of the total cost). In Australia, the total societal cost associated with schizophrenia reached AU\$1.44 billion in 1997/1998 prices, with roughly 60% relating to indirect costs (Carr et al., 2003). Finally, several national studies conducted in Europe in the 1990s showed that schizophrenia was associated with significant and long-lasting health, social and financial implications, not only for people with schizophrenia but also for their families, other caregivers and the wider society (Knapp et al., 2004).

The use of hospital inpatient care by people with psychosis and schizophrenia is substantial. In the financial year 2011–2012, 29,172 admissions were reported for schizophrenia and related disorders in England, resulting in over 2.8 million inpatient bed days. Moreover, there were approximately 56,000 outpatient attendances and 2,700 teleconsultations related to the management of schizophrenia and other psychotic disorders (The Health and Social Care Information Centre, 2012). Inpatient care is by far the most costly healthcare component in the overall treatment of schizophrenia. Kavanagh and colleagues (1995) found that care in short- or long-stay psychiatric hospitals accounted for 51% of the total public expenditure on care for people with schizophrenia. Lang and colleagues (1997) reported that provision of inpatient care for people with schizophrenia amounted to 59% of the total cost of health and social care for this population. Similarly Knapp and colleagues (2002) suggested that inpatient care accounted for 56.5% of the total treatment and care costs of schizophrenia, compared with 2.5% for outpatient care and 14.7% for day care. Unemployment is a considerable burden for people with schizophrenia. A rate of employment among people with schizophrenia is reported to be between 15 (Evans & Repper, 2000) and 20% (Schneider et al., 2007) in the UK. Stigmatisation is one of the main barriers to employment for this population. Generally the rates of employment are higher for newly diagnosed people compared with those with established schizophrenia; however, the majority of people presenting to services for the first time are already unemployed (Marwaha & Johnson, 2004). According to Guest and Cookson (1999), between 15 and 30% of people with schizophrenia are unable to work at diagnosis, rising to 67% following a second episode. Overall, the estimates of total indirect costs of people with schizophrenia in the UK range from £412 million for newly diagnosed people over the first 5 years following diagnosis (Guest & Cookson, 1999) to £1.7 billion annually for people with chronic schizophrenia (Davies & Drummond, 1994).

Family members and friends often provide care and support to those with schizophrenia, which places significant burdens on them that impact upon their health, leisure time, employment and financial status. Guest and Cookson (1999)

estimated that, in the UK, 1.2 to 2.5% of carers gave up work to care for dependants with schizophrenia.

Measuring the total cost of informal care provided by family members and friends is difficult but it is important to highlight that it is a significant amount. Data on costs of informal care for people with schizophrenia are not available. Based on figures provided by the Office for National Statistics, the Sainsbury Centre for Mental Health (2003) estimated that in 2002/2003 the aggregate value of informal care provided by family members and friends in the UK to those with mental health problems was £3.9 billion.

It is therefore evident that efficient use of available healthcare resources is required to maximise the health benefit for people with schizophrenia and, at the same time, reduce the emotional distress and financial implications to society.

# 3 METHODS USED TO DEVELOP THIS GUIDELINE

## 3.1 OVERVIEW

The development of this guideline followed *The Guidelines Manual* (NICE, 2012b). A team of health care professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the development of a person-centred, evidence-based guideline. There are seven basic steps in the process of developing a guideline:

1. Define the scope, which lays out exactly what will be included (and excluded) in the guidance.
2. Define review questions that cover all areas specified in the scope.
3. Develop a review protocol for the systematic review, specifying the search strategy and method of evidence synthesis for each review question.
4. Synthesise data retrieved, guided by the review protocols.
5. Produce evidence profiles and summaries using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
6. Consider the implications of the research findings for clinical practice and reach consensus decisions on areas where evidence is not found.
7. Answer review questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence for the clinical and cost effectiveness of the interventions and services used in the treatment and management of people with psychosis and schizophrenia in adults. Where evidence was not found or was inconclusive, the GDG discussed and attempted to reach consensus on what should be recommended, factoring in any relevant issues. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

## 3.2 THE SCOPE

Topics are referred by the Secretary of State and the letter of referral defines the remit, which defines the main areas to be covered (see *The Guidelines Manual* (NICE, 2012b) for further information). The NCCMH developed a scope for the guideline based on the remit (see Appendix 1). The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- identify the key aspects of care that must be included

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the National Collaborating Centre, and the remit from the Department of Health/Welsh Assembly Government
- inform the development of the review questions and search strategy
- inform professionals and the public about expected content of the guideline
- Keep the guideline to a reasonable size to ensure that its development can be carried out within the allocated period.

An initial draft of the scope was sent to registered stakeholders who had agreed to attend a scoping workshop. The workshop was used to:

- obtain feedback on the selected key clinical issues
- identify which population subgroups should be specified (if any)
- seek views on the composition of the GDG
- Encourage applications for GDG membership.

The draft scope was subject to consultation with registered stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website ([www.nice.org.uk](http://www.nice.org.uk)). Comments were invited from stakeholder organisations. The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by NICE.

### **3.3 THE GUIDELINE DEVELOPMENT GROUP**

During the consultation phase, members of the GDG were appointed by an open recruitment process. GDG membership consisted of: professionals in psychiatry, clinical psychology, nursing, social work, and general practice; academic experts in psychiatry and psychology; and service users, carers and representatives from service user and carer organisations. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economic literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

#### **3.3.1 Guideline Development Group meetings**

Eleven GDG meetings were held between Tuesday 28 February 2012 and Tuesday 15 October 2013. During each day-long GDG meeting, in a plenary session, review questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest (see Appendix 2), and service user and carer concerns were routinely discussed as a standing agenda item.

#### **3.3.2 Service users and carers**

Individuals with direct experience of services gave an integral service-user and carer focus to the GDG and the guideline. The GDG included two service users and a carer representative of a national service user group. They contributed as full GDG

members to writing the review questions, providing advice on outcomes most relevant to service users and carers, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service user research to the attention of the GDG. In drafting the guideline, there was regular communication with the NCCMH team to develop the chapter on carer experience and they contributed to writing the guideline's introduction and identified recommendations from the service user and carer perspective.

### **3.3.3 Special advisors**

Special advisors, who had specific expertise in one or more aspects of treatment and management relevant to the guideline, assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 4a lists those who agreed to act as special advisors.

### **3.3.4 National and international experts**

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to identify unpublished or soon-to-be published studies, to ensure that up-to-date evidence was included in the development of the guideline. They informed the GDG about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 5 lists researchers who were contacted.

## **3.4 REVIEW QUESTIONS**

Review (clinical) questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. Before the first GDG meeting, draft review questions were prepared by NCCMH staff based on the scope (and an overview of existing guidelines), and discussed with the guideline Chair. The draft review questions were then discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. The final list of review questions and their protocols can be found in Appendix 6.

For questions about interventions, the PICO (Population, Intervention, Comparison and Outcome) framework was used to structure each question (see Table 1).

**Table 1: Features of a well-formulated question on the effectiveness of an intervention – PICO**

<b>Population:</b>	Which population of service users are we interested in? How can they be best described? Are there subgroups that need to be considered?
<b>Intervention:</b>	Which intervention, treatment or approach should be used?
<b>Comparison:</b>	What is/are the main alternative/s to compare with the intervention?
<b>Outcome:</b>	What is really important for the service user? Which outcomes should be considered: intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning and other measures such as quality of life; general health status?

In some situations, the prognosis of a particular condition is of fundamental importance, over and above its general significance in relation to specific interventions. Areas where this is particularly likely to occur relate to assessment of risk, for example in terms of behaviour modification or screening and early intervention. In addition, review questions related to issues of service delivery are occasionally specified in the remit from the Department of Health/Welsh Assembly Government. In these cases, appropriate review questions were developed to be clear and concise.

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of review question of relevance to NICE guidelines. These are listed in Table 2. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

However, in all cases, a well-conducted systematic review (of the appropriate type of primary study) is likely to always yield a better answer than a single study.

For reviews of interventions, if no existing systematic reviews address the review question, then in the first instance only RCTs will usually be included. The range of included studies will be expanded to controlled before-after studies and interrupted time-series if the RCT evidence is inadequate to address the review question.

**Table 2: Best study design to answer each type of question**

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial (RCT); other studies that may be considered in the absence of RCTs are the following: internally/externally controlled before and after trial, interrupted time-series
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in an RCT or inception cohort study
Rates (of disease, service user experience, rare side effects)	Prospective cohort, registry, cross-sectional study
Experience of care	Qualitative research (for example, grounded theory, ethnographic research)

## 3.5 CLINICAL REVIEW METHODS

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific review questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible and, if evidence is not available, informal consensus methods are used to try and reach general agreement between GDG members (see Section 3.5.6) and the need for future research is specified.

### 3.5.1 The search process

#### *Scoping searches*

A broad preliminary search of the literature was undertaken in August 2011 to obtain an overview of the issues likely to be covered by the scope, and to help define key areas. Searches were restricted to clinical guidelines, Health Technology Assessment (HTA) reports, key systematic reviews and RCTs. A list of databases and websites searched can be found in Appendix 13.

#### *Systematic literature searches*

After the scope was finalised, a systematic search strategy was developed to locate as much relevant evidence as possible. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise a broad approach to searching to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to certain study designs if specified in the review protocol, and conducted in the following databases:

- Australian Education Index (AEI)
- Applied Social Services Index and Abstracts (ASSIA)
- British Education Index (BEI)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)



- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- CENTRAL
- Education Resources in Curriculum (ERIC)
- Embase
- HTA database (technology assessments)
- International Bibliography of Social Science (IBSS)
- MEDLINE/MEDLINE In-Process
- Psychological Information Database (PsycINFO)
- Social Services Abstracts (SSA)
- Sociological Abstracts.

The search strategies were initially developed for MEDLINE before being translated for use in other databases/interfaces. Strategies were built up through a number of trial searches and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered. The search terms for each search are set out in full in Appendix 13.

### *Reference management*

Citations from each search were downloaded into reference management software and duplicates removed. Records were then screened against the eligibility criteria of the reviews before being appraised for methodological quality (see below). The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

### *Search filters*

To aid retrieval of relevant and sound studies, filters were used to limit a number of searches to systematic reviews, RCTs and qualitative studies. The search filters for systematic reviews and RCTs are adaptations of filters designed by the CRD and the Health Information Research Unit of McMaster University, Ontario. The qualitative research filter was developed in-house. Each filter comprises index terms relating to the study type(s) and associated text-words for the methodological description of the design(s).

### *Date and language restrictions*

Systematic database searches were initially conducted in June 2012 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in June 2013 to October 2013 ahead of the guideline consultation. After this point, studies were only included if they were judged by the GDG to be exceptional (for example, if the evidence was likely to change a recommendation).

Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to a review question.

Date restrictions were not applied, except for updates of systematic reviews which were limited to the date the last searches were conducted. Searches for systematic reviews and qualitative research were also restricted to a shorter time frame as older research was thought to be less useful.

### *Other search methods*

Other search methods involved: (a) scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies) for more published reports and citations of unpublished research; (b) sending lists of studies meeting the inclusion criteria to subject experts (identified through searches and the GDG) and asking them to check the lists for completeness, and to provide information of any published or unpublished research for consideration (see Appendix 5); (c) checking the tables of contents of key journals for studies that might have been missed by the database and reference list searches; (d) tracking key papers in the Science Citation Index (prospectively) over time for further useful references; (e) conducting searches in ClinicalTrials.gov for unpublished trial reports; (f) contacting included study authors for unpublished or incomplete datasets. Searches conducted for existing NICE guidelines were updated where necessary. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as appropriate.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 13.

### *Study selection and assessment of methodological quality*

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. More specific eligibility criteria were developed for each review question and are described in the relevant clinical evidence chapters. Eligible systematic reviews and primary-level studies were critically appraised for methodological quality (risk of bias) using a checklist (see *The Guidelines Manual* (NICE, 2012b) for templates). The eligibility of each study was confirmed by at least one member of the GDG.

For some review questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the GDG took into account the following factors when assessing the evidence:

- participant factors (for example, gender, age and ethnicity)
- provider factors (for example, model fidelity, the conditions under which the intervention was performed and the availability of experienced staff to undertake the procedure)
- cultural factors (for example, differences in standard care and differences in the welfare system).

It was the responsibility of the GDG to decide which prioritisation factors were relevant to each review question in light of the UK context.

### *Unpublished evidence*

Stakeholders, authors and principle investigators were approached for unpublished evidence (see Appendix 5). The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess risk of bias. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline. Therefore, in most circumstances the GDG did not accept evidence submitted 'in confidence'. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

### *Experience of care*

Reviews were sought of qualitative studies that used relevant first-hand experiences of carers. The experience of service users with mental health problems has been reviewed in *Service User Experience in Adult Mental Health* (NCCMH, 2012 [full guideline]). Therefore, for this guideline, only a review of the carer experience of care was conducted. A particular outcome was not specified by the GDG. Instead, the review was concerned with narrative data that highlighted the experience of care. Where the search did not generate an adequate body of literature, a further search for primary qualitative studies was undertaken.

## **3.5.2 Data extraction**

### *Quantitative analysis*

Study characteristics, aspects of methodological quality, and outcome data were extracted from all eligible studies, using Review Manager 5.1 (The Cochrane Collaboration, 2011) and an Excel-based form (see Appendix 7).

In most circumstances, for a given outcome (continuous and dichotomous), where more than 50% of the number randomised to any group were missing or incomplete, the study results were excluded from the analysis (except for the outcome 'leaving the study early', in which case, the denominator was the number randomised). Where there were limited data for a particular review, the 50% rule was not applied. In these circumstances the evidence was downgraded (see section 3.5.4).

Where possible, outcome data from an intention-to-treat analysis (ITT) (that is, a 'once-randomised-always-analyse' basis) were used. Where ITT had not been used or there were missing data, the effect size for dichotomous outcomes were recalculated using best-case and worse-case scenarios. Where conclusions varied between scenarios, the evidence was downgraded (see section 3.5.4).

Where some of the studies failed to report standard deviations (for a continuous outcome), and where an estimate of the variance could not be computed from other reported data or obtained from the study author, the following approach was taken.<sup>3</sup> When the number of studies with missing standard deviations was less than one-third and when the total number of studies was at least ten, the pooled standard deviation was imputed (calculated from all the other studies in the same meta-analysis that used the same version of the outcome measure). In this case, the appropriateness of the imputation was made by comparing the standardised mean differences (SMDs) of those trials that had reported standard deviations against the hypothetical SMDs of the same trials based on the imputed standard deviations. If they converged, the meta-analytical results were considered to be reliable.

When the conditions above could not be met, standard deviations were taken from another related systematic review (if available). In this case, the results were considered to be less reliable.

The meta-analysis of survival data, such as time to any mood episode, was based on log hazard ratios and standard errors. Since individual participant data were not available in included studies, hazard ratios and standard errors calculated from a Cox proportional hazard model were extracted. Where necessary, standard errors were calculated from confidence intervals (CIs) or *p* value according to standard formulae (see the Cochrane Reviewers' Handbook 5.1.0 (Higgins & Green)). Data were summarised using the generic inverse variance method using Review Manager.

Consultation with another reviewer or members of the GDG was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer was checked by the second reviewer. Disagreements were resolved through discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Berlin, 2001; Jadad et al., 1996).

### *Qualitative analysis*

After transcripts/reviews or primary studies of carer experience were identified (see 3.5.1), each was read and re-read and sections of the text were collected under different headings. Under the broad headings, specific emergent themes were identified and coded by two researchers working independently. Overlapping themes and themes with the highest frequency count across all testimonies were

---

<sup>3</sup>Based on the approach suggested by Furukawa and colleagues (2006).

extracted and regrouped. The findings from this qualitative analysis can be found in Chapter 4.

The quality of the included studies was assessed using the NICE quality checklist for qualitative literature (see *The Guidelines Manual* (NICE, 2012b) for templates). The domains of this checklist (including the theoretical approach, study design, validity and data analysis) aim to provide a transparent description of methods in order to assess the reliability and transferability of the findings of primary studies to their setting. As there is currently no accepted gold standard of assessing study quality, studies were not excluded or weighted on the basis of quality.

### 3.5.3 Evidence synthesis

The method used to synthesize evidence depended on the review question and availability and type of evidence (see Appendix 6 for full details). Briefly, for questions about the psychometric properties of instruments, reliability, validity and clinical utility were synthesized narratively based on accepted criteria. For questions about test accuracy, bivariate test accuracy meta-analysis was conducted where appropriate. For questions about the effectiveness of interventions, standard meta-analysis or network meta-analysis was used where appropriate, otherwise narrative methods were used with clinical advice from the GDG. In the absence of high-quality research, an informal consensus process was used (see 3.5.7).

### 3.5.4 Grading the quality of evidence

For questions about the effectiveness of interventions, the GRADE approach<sup>4</sup> was used to grade the quality of evidence for each outcome (Guyatt et al., 2011). For questions about the experience of care and the organisation and delivery of care, methodology checklists (see section 3.5.1) were used to assess the risk of bias, and this information was taken into account when interpreting the evidence. The technical team produced GRADE evidence profiles (see below) using GRADE profiler (GRADEpro) software (Version 3.6), following advice set out in the GRADE handbook (Schünemann et al., 2009). Those doing GRADE ratings were trained, and calibration exercises were used to improve reliability (Mustafa et al., 2013).

#### *Evidence profiles*

A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis for each 'critical' and 'important' outcome (see Table 3 for an example of an evidence profile). The GRADE approach is based on a sequential assessment of the quality of evidence, followed by judgment about the balance between desirable and undesirable effects, and subsequent decision about the strength of a recommendation.

Within the GRADE approach to grading the quality of evidence, the following is used as a starting point:

---

<sup>4</sup> For further information about GRADE, see [www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)

- RCTs without important limitations provide high quality evidence
- observational studies without special strengths or important limitations provide low quality evidence.

For each outcome, quality may be reduced depending on five factors: methodological limitations, inconsistency, indirectness, imprecision and publication bias. For the purposes of the guideline, each factor was evaluated using criteria provided in Table 4.

For observational studies without any reasons for down-grading, the quality may be up-graded if there is a large effect, all plausible confounding would reduce the demonstrated effect (or increase the effect if no effect was observed), or there is evidence of a dose-response gradient (details would be provided under the 'other' column).

Each evidence profile includes a summary of findings: number of participants included in each group, an estimate of the magnitude of the effect, and the overall quality of the evidence for each outcome. Under the GRADE approach, the overall quality for each outcome is categorised into one of four groups (high, moderate, low, very low).

**Table 3: Example of a GRADE evidence profile**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control group	Relative (95% CI)	Absolute		
Outcome 1 (measured with: any valid method; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	47	43	-	SMD 0.20 lower (0.61 lower to 0.21 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Outcome 2 (measured with: any valid rating scale; Better indicated by lower values)												
4	randomised trials	serious <sup>2</sup>	no serious inconsistency	no serious indirectness	serious <sup>1</sup>	none	109	112	-	SMD 0.42 lower (0.69 to 0.16 lower)	⊕⊕○○ LOW	CRITICAL
Outcome 3 (measured with: any valid rating scale; Better indicated by lower values)												
26	randomised trials	no serious risk of bias	serious <sup>3</sup>	no serious indirectness	no serious imprecision	none	521/5597 (9.3%)	798/3339 (23.9%)	RR 0.43 (0.36 to 0.51)	136 fewer per 1000 (from 117 fewer to 153 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Outcome 4 (measured with: any valid rating scale; Better indicated by lower values)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	503	485	-	SMD 0.34 lower (0.67 to 0.01 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

<sup>1</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

<sup>2</sup> Risk of bias across domains was generally high or unclear.

<sup>3</sup> There is evidence of moderate heterogeneity of study effect sizes.

**Table 4: Factors that decrease quality of evidence**

Factor	Description	Criteria
Limitations	Methodological quality/ risk of bias.	Serious risks across most studies (that reported a particular outcome). The evaluation of risk of bias was made for each study using NICE methodology checklists (see Section 3.5.1).
Inconsistency	Unexplained heterogeneity of results.	Moderate or greater heterogeneity (see (Schünemann et al., 2009) for further information about how this was evaluated)
Indirectness	How closely the outcome measures, interventions and participants match those of interest.	If the comparison was indirect, or if the question being addressed by the GDG was substantially different from the available evidence regarding the population, intervention, comparator, or an outcome.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect.	If either of the following two situations were met: <ul style="list-style-type: none"><li>• the optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) was not achieved</li><li>• the 95% confidence interval around the pooled or best estimate of effect included both 1) no effect and 2) appreciable benefit or appreciable harm</li></ul>
Publication bias	Systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.	Evidence of selective publication. This may be detected during the search for evidence, or through statistical analysis of the available evidence.

### 3.5.5 Presenting evidence to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager Version 5.2 and GRADE summary of findings tables (see below) were presented to the GDG.

Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were included in the study characteristics table. The range of effect estimates were included in the GRADE profile, and where appropriate, described narratively.

#### *Summary of findings tables*

Summary of findings tables generated from GRADEpro were used to summarise the evidence for each outcome and the quality of that evidence (Table 5). The tables provide illustrative comparative risks, especially useful when the baseline risk varies for different groups within the population.



**Table 5: Example of a GRADE summary of findings table**

Patient or population: Settings: Intervention: Comparison:						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Any control group	Intervention group				
<b>Outcome 1</b> any valid rating scale		The mean outcome in the intervention group was <b>0.20 standard deviations lower</b> (0.61 lower to 0.21 higher)		90 (2 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
<b>Outcome 2</b> any valid rating scale		The mean outcome in the intervention group was <b>0.42 standard deviations lower</b> (0.69 to 0.16 lower)		221 (4 studies)	⊕⊕⊖⊖ low <sup>1,2</sup>	
<b>Outcome 3</b> any valid rating scale	239 per 1000	<b>103 per 1000</b> (86 to 122)	<b>RR 0.43</b> (0.36 to 0.51)	8936 (26 studies)	⊕⊕⊕⊖ moderate <sup>3</sup>	
<b>Outcome 4</b> any valid rating scale		The mean outcome in the intervention group was <b>0.34 standard deviations lower</b> (0.67 to 0.01 lower)		988 (5 studies)	⊕⊕⊕⊕ high	
*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						
Note. CI = Confidence interval. <sup>1</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. <sup>2</sup> Risk of bias across domains was generally high or unclear. <sup>3</sup> There is evidence of moderate heterogeneity of study effect sizes.						

### 3.5.6 Extrapolation

When answering review questions, if there is no direct evidence from a primary dataset<sup>5</sup> based on the initial search for evidence it may be appropriate to extrapolate from another dataset. In this situation, the following principles were used to determine when to extrapolate:

- a primary dataset is absent, of low quality or is judged to be not relevant to the review question under consideration
- a review question is deemed by the GDG to be important, such that in the absence of direct evidence, other data sources should be considered
- non-primary data source(s) is in the view of the GDG available, which may inform the review question.

When the decision to extrapolate was made, the following principles were used to inform the choice of the non-primary dataset:

- the populations (usually in relation to the specified diagnosis or problem which characterises the population) under consideration share some common characteristic but differ in other ways, such as age, gender or in the nature of the disorder (for example, a common behavioural problem; acute versus chronic presentations of the same disorder); and
- the interventions under consideration in the view of the GDG have one or more of the following characteristics:
  - share a common mode of action (for example, the pharmacodynamics of drug; a common psychological model of change - operant conditioning)
  - be feasible to deliver in both populations (for example, in terms of the required skills or the demands of the health care system)
  - share common side effects/harms in both populations; and
- the context or comparator involved in the evaluation of the different datasets shares some common elements which support extrapolation; and
- the outcomes involved in the evaluation of the different datasets shares some common elements which support extrapolation (for example, improved mood or a reduction in challenging behaviour).

When the choice of the non-primary dataset was made, the following principles were used to guide the application of extrapolation:

- the GDG should first consider the need for extrapolation through a review of the relevant primary dataset and be guided in these decisions by the principles for the use of extrapolation
- in all areas of extrapolation datasets should be assessed against the principles for determining the choice of datasets. In general the criteria in the four principles set out above for determining the choice should be met
- in deciding on the use of extrapolation, the GDG will have to determine if the extrapolation can be held to be reasonable, including ensuring that:

---

<sup>5</sup>A primary dataset is defined as a dataset which contains evidence on the population and intervention under review

- the reasoning behind the decision can be justified by the clinical need for a recommendation to be made
- the absence of other more direct evidence, and by the relevance of the potential dataset to the review question can be established
- the reasoning and the method adopted is clearly set out in the relevant section of the guideline.

### **3.5.7 Method used to answer a review question in the absence of appropriately designed, high-quality research**

In the absence of appropriately designed, high-quality research (including indirect evidence where it would be appropriate to use extrapolation), an informal consensus process was adopted. The process involved a group discussion of what is known about the issues. The views of GDG were synthesised narratively by a member of the review team, and circulated after the meeting. Feedback was used to revise the text, which was then included in the appropriate evidence review chapter.

## **3.6 HEALTH ECONOMICS METHODS**

The aim of the health economics was to contribute to the guideline's development by providing evidence on the cost effectiveness of interventions for adults with psychosis and schizophrenia covered in the guideline. This was achieved by:

- systematic literature review of existing economic evidence
- decision-analytic economic modelling.

Systematic reviews of economic literature were conducted in all areas covered in the guideline. Economic modelling was undertaken in areas with likely major resource implications, where the current extent of uncertainty over cost effectiveness was significant and economic analysis was expected to reduce this uncertainty, in accordance with *The Guidelines Manual* (NICE, 2012b). Prioritisation of areas for economic modelling was a joint decision between the Health Economist and the GDG. The rationale for prioritising review questions for economic modelling was set out in an economic plan agreed between NICE, the GDG, the Health Economist and the other members of the technical team. For the 2014 guideline, the cost effectiveness of vocational rehabilitation for people with psychosis and schizophrenia was selected as a key issue that was addressed by economic modelling.

In addition, literature on the health-related quality of life of people with psychosis and schizophrenia was systematically searched to identify studies reporting appropriate utility scores that could be utilised in a cost-utility analysis.

The rest of this section describes the methods adopted in the systematic literature review of economic studies. Methods employed in economic modelling are described in the respective sections of the guideline.

### 3.6.1 Search strategy for economic evidence

#### *Scoping searches*

A broad preliminary search of the literature was undertaken in August 2011 to obtain an overview of the issues likely to be covered by the scope, and help define key areas. Searches were restricted to economic studies and HTA reports, and conducted in the following databases:

- Embase
- MEDLINE/MEDLINE In-Process
- HTA database (technology assessments)
- NHS Economic Evaluation Database (NHS EED)

Any relevant economic evidence arising from the clinical scoping searches was also made available to the health economist during the same period.

#### *Systematic literature searches*

After the scope was finalised, a systematic search strategy was developed to locate all the relevant evidence. Searches were restricted to economic studies and health technology assessment reports, and conducted in the following databases:

- Embase
- HTA database (technology assessments)
- MEDLINE/MEDLINE In-Process
- NHS EED
- PsycINFO

Any relevant economic evidence arising from the clinical searches was also made available to the health economist during the same period.

The search strategies were initially developed for MEDLINE before being translated for use in other databases/interfaces. Strategies were built up through a number of trial searches, and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered. In order to assure comprehensive coverage, search terms for the population were kept purposely broad to help counter dissimilarities in database indexing practices and thesaurus terms, and imprecise reporting of study populations by authors in the titles and abstracts of records.

For standard mainstream bibliographic databases (Embase, MEDLINE and PsycINFO) search terms were combined with a search filter for health economic studies. For searches generated in topic-specific databases (HTA, NHS EED) search terms were used without a filter. The search terms are set out in full in Appendix 14.

### *Reference management*

Citations from each search were downloaded into reference management software and duplicates removed. Records were then screened against the inclusion criteria of the reviews before being quality appraised. The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

### *Search filters*

The search filter for health economics is an adaptation of a pre-tested strategy designed by CRD (2007). The search filter is designed to retrieve records of economic evidence (including full and partial economic evaluations) from the vast amount of literature indexed to major medical databases such as MEDLINE. The filter, which comprises a combination of controlled vocabulary and free-text retrieval methods, maximises sensitivity (or recall) to ensure that as many potentially relevant records as possible are retrieved from a search. A full description of the filter is provided in Appendix 14.

### *Date and language restrictions*

Systematic database searches were initially conducted in June 2012 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in June 2013 ahead of the guideline consultation. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to an area under review. In order to obtain data relevant to current healthcare settings and costs, all the searches were restricted to research published from 1996 onwards, except for an update search of an existing review from Chapter 5, which was limited from the date the last search was conducted.

### *Other search methods*

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies from the economic and clinical reviews) to identify further studies for consideration.

Full details of the search strategies and filter used for the systematic review of health economic evidence are provided in Appendix 14.

## **3.6.2 Inclusion criteria for economic studies**

The following inclusion criteria were applied to select studies identified by the economic searches for further consideration:

1. Only English language papers were considered.

2. Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.
3. Studies published from 2002 onwards were included. This date restriction was imposed to obtain data relevant to current healthcare settings and costs.
4. Selection criteria based on types of clinical conditions and service users as well as interventions assessed were identical to the clinical literature review.
5. Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable. Poster presentations, abstracts, dissertations, commentaries and discussion publications were excluded.
6. Full economic evaluations that compared two or more relevant interventions and considered both costs and consequences, as well as costing analyses comparing only costs between two or more interventions, were included in the review.
7. Economic studies were included if they used clinical effectiveness data from an RCT, a prospective cohort study, pre- and post-observational studies or a systematic review and meta-analysis of clinical studies. Studies that utilised clinical effectiveness parameters based mainly on expert opinion or assumptions were excluded from the review.
8. Studies were included only if the examined interventions and populations under consideration were clearly described.
9. Studies that adopted a very narrow perspective, ignoring major categories of costs relevant to the NHS, were excluded; for example studies that estimated exclusively hospitalisation costs were considered non-informative to the guideline development process. Also, studies that considered other types of costs, except direct healthcare costs, were excluded from this review.

### **3.6.3 Applicability and quality criteria for economic studies**

All economic papers eligible for inclusion were appraised for their applicability and quality using the methodology checklist for economic evaluations recommended by NICE (NICE, 2012b). The methodology checklist for economic evaluations was also applied to the economic models developed specifically for this guideline. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process, along with the results of the economic modelling conducted specifically for this guideline. The completed methodology checklists for all economic evaluations considered in the guideline are provided in Appendix 18.

### **3.6.4 Presentation of economic evidence**

The economic evidence considered in the guideline is provided in the respective evidence chapters, following presentation of the relevant clinical evidence. The references to included studies and the respective evidence tables with the study characteristics and results are provided in Appendix 19. Methods and results of

economic modelling undertaken alongside the guideline development process are presented in the relevant evidence chapters. Characteristics and results of all economic studies considered during the guideline development process (including modelling studies conducted for this guideline) are summarised in economic evidence profiles accompanying respective GRADE clinical evidence profiles in Appendix 17.

### **3.6.5 Results of the systematic search of economic literature**

The titles of all studies identified by the systematic search of the literature were screened for their relevance to the topic (that is, economic issues and information on health-related quality of life in people with psychosis and schizophrenia). References that were clearly not relevant were excluded first. The abstracts of all potentially relevant studies (90 references) were then assessed against the inclusion criteria for economic evaluations by the health economist. Full texts of the studies potentially meeting the inclusion criteria (including those for which eligibility was not clear from the abstract) were obtained. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Economic evaluations eligible for inclusion (47 references) were then appraised for their applicability and quality using the methodology checklist for economic evaluations. Finally, 21 economic studies identified by the systematic literature search, as well as two studies that were unpublished at the time of the guideline development and were identified through consultation with the GDG, met fully or partially the applicability and quality criteria for economic studies, and were thus considered at formulation of the guideline recommendations.

## **3.7 LINKING EVIDENCE TO RECOMMENDATIONS**

Once the clinical and health economic evidence was summarised, the GDG drafted the recommendations. In making recommendations, the GDG took into account the trade-off between the benefits and harms of the intervention/instrument, as well as other important factors, such as economic considerations, values of the GDG and society, the requirements to prevent discrimination and to promote equality<sup>6</sup>, and the GDG's awareness of practical issues (Eccles et al., 1998; NICE, 2012b).

Finally, to show clearly how the GDG moved from the evidence to the recommendations, each chapter has a section called 'linking evidence to recommendations'. Underpinning this section is the concept of the 'strength' of a recommendation (Schünemann et al., 2003). This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare professionals and service users would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However,

---

<sup>6</sup>See NICE's equality scheme: [www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp](http://www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp)

there is often a closer balance between benefits and harms, and some service users would not choose an intervention whereas others would. This may happen, for example, if some service users are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of service users. The strength of each recommendation is reflected in the wording of the recommendation, rather than by using ratings, labels or symbols.

Where the GDG identified areas in which there are uncertainties or where robust evidence was lacking, they developed research recommendations. Those that were identified as 'high priority' were developed further in the NICE version of the guideline, and presented in Appendix 10.

### 3.8 STAKEHOLDER CONTRIBUTIONS

Professionals, service users, and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- service user and carer stakeholders: national service user and carer organisations that represent the interests of people whose care will be covered by the guideline
- local service user and carer organisations: but only if there is no relevant national organisation
- professional stakeholders' national organisations: that represent the healthcare professionals who provide the services described in the guideline
- commercial stakeholders: companies that manufacture drugs or devices used in treatment of the condition covered by the guideline and whose interests may be significantly affected by the guideline
- providers and commissioners of health services in England and Wales
- statutory organisations: including the Department of Health, the Welsh Assembly
- Government, NHS Quality Improvement Scotland, the Care Quality Commission and the National Patient Safety Agency
- research organisations: that have carried out nationally recognised research in the area.

NICE clinical guidelines are produced for the NHS in England and Wales, so a 'national' organisation is defined as one that represents England and/or Wales, or has a commercial interest in England and/or Wales.

Stakeholders have been involved in the guideline's development at the following points:

- commenting on the initial scope of the guideline and attending a scoping workshop held by NICE
- contributing possible review questions and lists of evidence to the GDG
- commenting on the draft of the guideline.



### **3.9 VALIDATION OF THE GUIDELINE**

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. Following the consultation, all comments from stakeholders and experts (see Appendix 4B) were responded to, and the guideline updated as appropriate. NICE also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE for a quality assurance check. Any errors were corrected by the NCCMH, then the guideline was formally approved by NICE and issued as guidance to the NHS in England and Wales.

# 4 CARERS' EXPERIENCE

## 4.1 INTRODUCTION

This chapter is new for the 2014 guideline and aims to evaluate and discuss the experience of health and social care services of carers of people with severe mental illness, including psychosis and schizophrenia (see Section 4.2). The chapter also evaluates the effectiveness of interventions that aim to improve carers' experience of caring and of services (see Section 4.3). The GDG has sought to identify and evaluate factors and attributes of health and social care services that positively or negatively affect the carers' experiences of services and what can be done by health and social care services to improve the experience of services and the wellbeing of carers. For the purposes of this guideline, 'carers' are defined as family and friends who may or may not live with the service user, and who provide informal and regular care and support to someone with a severe mental illness such as psychosis and schizophrenia.

The population of interest in this chapter is carers of people with severe mental illness, including psychosis and schizophrenia. Service user experience of the treatment and management of these conditions in adult mental health services has been comprehensively reviewed in *Service User Experience in Adult Mental Health* (NICE, 2011). Therefore it is important that this chapter is taken in conjunction with that guidance because service user experience is not the focus of this review.

In the UK just over half of people with schizophrenia are in contact with a close relative of whom 65% will be female and 36% a parent (Roick et al., 2007). It is important to acknowledge that caring can be a strongly positive experience. Nevertheless, most who write about it describe the impact in terms of a 'burden' that is both subjective (perceived) and objective (for example, contributing directly to ill health and financial problems or in displacing other daily routines) (Awad & Voruganti, 2008), and varies between different cultures (Rosenfarb et al., 2006). A European study (based in Italy, England, Germany, Greece and Portugal) reported that carers for adults with schizophrenia spent an average of 6 to 9 hours per day providing care (Magliano et al., 1998). Many people are not able to work or have to take time off work to provide care, and when these costs are combined with those of replacing carers with paid workers, the annual estimate of the potential cost to the NHS is £34,000 per person with schizophrenia (Andrew et al., 2012).

Supporting carers can be very challenging and it is sometimes difficult for health and social care professionals to identify what carers find the most helpful at different stages of the care pathway. Information and support that is offered at the early stages of care can be the most effective, particularly if it provides a sound base of knowledge and skills from which carers can draw upon at different times. It is recognised that families and friends can either help or hinder the recovery of service user, but some interventions, such as family intervention, have a substantial

impact on relapse rates (see Chapter 9 which gives an account of this and shows the beneficial effects of family intervention for the families of people with psychosis and schizophrenia). However, these interventions remain difficult to access (Fadden & Heelis, 2011). At times of crisis the needs of carers are much more urgent; therefore easy access to supportive allies can be very helpful at these times.

European studies of the relatives of people with schizophrenia showed that the burden of care was lower when psychosocial interventions were provided to service users and their relatives and professional and social network support was available (Jeppesen et al., 2005; Magliano et al., 2006). Information sharing and the issue of confidentiality is a particular concern of people with psychosis and schizophrenia and their families and carers because of the sensitive nature of mental health problems, which is compounded by differences of opinion held by professionals about what information can be shared. This contrasts with clinical practice in other areas of health where increasingly the emphasis is on healthcare being seen as a partnership between professionals, service users and their families and carers, based on appropriate sharing of information. In its guidance *Carers and Confidentiality*, the Royal College of Psychiatrists has recognised the importance of training practitioners in confidentiality and information sharing to empower service users and their carers (Royal College of Psychiatrists, 2010).

### *Current practice*

There are huge variations in the provision of family intervention or other support for carers and in the extent to which professionals appreciate the important role of carers in the lives and recovery of many (but not all) service users. Moreover, professionals are often confused about issues such as confidentiality and information sharing, leaving carers often feeling isolated and alone. Many carers therefore turn to voluntary sector organisations such as 'Rethink'. As a result there is not a consistent approach to health and social care support to carers across the country. In some areas carers are well supported through mental health services, although this is probably the exception. Carers are often unsure about their role or even about their rights, such as the right to a carers' assessment. The 2002 and 2009 guidelines if not fully address these needs and evaluate more precisely the needs of carers.

This chapter attempts to redress this imbalance in two ways. First, the GDG has conducted a review of qualitative studies of carers' experiences of health and social care services. Second, the GDG decided to search for and evaluate quantitative trials of interventions specifically aimed at improving the experience of carers.

## **4.2 CARERS' EXPERIENCE (QUALITATIVE REVIEW)**

### **4.2.1 Introduction**

#### *Definition and aim of review*

The aim of this qualitative review is to evaluate the experience of care from the perspective of informal carers of people with severe mental illness. Specifically, the

review includes studies that focus on factors relating to health and social services that have a beneficial or detrimental effect on the carers' overall experience of care.

This qualitative review precedes a review of interventions that examines which modifications to health and social services improve the experience of using services for carers of adults with severe mental illness (Section 4.3).

## 4.2.2 Review protocol (carers' experience qualitative review)

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 6 (a complete list of review questions and the full review protocol can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 6: Clinical review protocol summary for the qualitative review of carers' experience**

Component	Description
<i>Review question</i>	What factors improve or diminish the experience of health and social services for carers of people with severe mental illness?
<i>Objectives</i>	To identify factors that improve or diminish carers' experiences of health and social services and carers' wellbeing.
<i>Population</i>	<p><b>Included</b></p> <p>Carers of adults (18+) and people in early intervention services (which may include people 14 years and older) with severe mental illness who use health and social services in community settings.</p> <p><i>Include papers with a service user population of at least:</i></p> <ul style="list-style-type: none"> <li>66% schizophrenia or</li> <li>66% schizophrenia and bipolar disorder or</li> <li>66% schizophrenia and 'mood disorders' or</li> <li>66% undefined severe mental illness</li> <li>66% bipolar disorder.</li> </ul> <p><b>Excluded</b></p> <p>Studies conducted in low and middle income countries were excluded as the service provision is not comparable to the UK.</p>
<i>Intervention(s)</i>	<p>Actions by health and social services that could improve or diminish carers' experience of health and social services for example:</p> <ul style="list-style-type: none"> <li>• form, frequency, and content of interactions with carers</li> <li>• organisation of services and interactions with carers</li> <li>• sharing information with carers and receiving information from carers.</li> </ul>
<i>Comparison</i>	N/A
<i>Critical outcomes</i>	Themes and specific issues that carers identify as improving or diminishing their experience of health and social care
<i>Study design</i>	<ul style="list-style-type: none"> <li>• Metasynthesis of qualitative studies including people who care for people with severe mental illness</li> <li>• Qualitative primary studies (focus group, semi-structured interviews and written responses to open-ended questions) including people who care for people with severe mental illness</li> </ul> <p>NB: Studies that examined the views of carers in addition to other stakeholders (including healthcare professionals and service users) were only included if the</p>

	views of carers were separable from non-carers.
<i>Electronic databases</i>	Core databases: CENTRAL, CDSR, DARE, HTA, Embase, MEDLINE, MEDLINE In-Process Topic specific databases: AEI, ASSIA, BEI, CINAHL, ERIC, IBSS, PsycINFO, Sociological Abstracts, SSA
<i>Date searched</i>	2002 to June 2013 The GDG decided that knowledge, understanding and experience of health and social care prior to 2002 would not be relevant to present day services.
<i>Review strategy</i>	Thematic synthesis of qualitative studies.

## 4.2.3 Method

A systematic review and a narrative thematic synthesis of qualitative studies was carried out using the methods described by Thomas and Harden (2008) (see Chapter 3 for further information). Quality checklists were completed for all included studies (see Section 4.2.5 for a summary and Appendix 15b for the full checklists).

## 4.2.4 Studies considered<sup>7</sup>

Twenty-six primary studies (N = 695) providing relevant data met the eligibility criteria for this review: ASKEY2009 (Askey et al., 2009), BARNABLE2006 (Barnable et al., 2006), BERGNER2008 (Bergner et al., 2008), CHIU2006 (Chiu et al., 2006), GOODWIN2006 (Goodwin & Happell, 2006), HUGHES2011 (Hughes et al., 2011), JANKOVIC2011 (Jankovic et al., 2011), KNUDSON2002 (Knudson & Coyle, 2002), LAIRD2010 (Laird et al., 2010), LEVINE2002 (Levine & Ligenza, 2002), LOBBAN2011 (Lobban et al., 2011), LUMSDEN2011 (Lumsden & Rajan, 2011), MCAULIFFE2009 (McAuliffe et al., 2009), MCCANN2011 (McCann et al., 2011), MCCANN2012 (McCann et al., 2012a), NICHOLLS2009 (Nicholls & Pernice, 2009), NORDBY2010 (Nordby et al., 2010), REID2005 (Reid et al., 2005), RILEY2011 (Riley et al., 2011), ROONEY2006 (Rooney et al., 2006), SAUNDERS2002 (Saunders & Byrne, 2002), SMALL2010 (Small et al., 2010), TANSKANEN2011 (Tanskanen et al., 2011), TRANVAG2008 (Tranvag & Kristoffersen, 2008), WAINWRIGHT (Wainwright et al., In press), WEIMAND2011 (Weimand et al., 2011). Of the included studies, all but one were published in peer-reviewed journals between 2002 and 2011. Further information about excluded studies can be found in Appendix 15a.

Of the 26 included studies, 10 were conducted in the UK. The remaining studies were conducted in Australia (k = 6), Norway (k = 3), the USA (k = 3), New Zealand (k = 2), Canada (k = 1) and Hong Kong and Taiwan (k = 1). Table 7 provides an overview of the included studies.

---

<sup>7</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

**Table 7: Study characteristics table for qualitative studies of carers' experience**

Study ID and year	Country	N	Relationship to service user	% living with service user	Service user diagnosis	Mean age (years)	% female	% white	Principal experience explored	Data collection	Analysis
ASKEY2009	UK	22	NR	45%	Psychosis	51	72%	59%	Needs from mental health services	Focus groups and semi-structured interviews	Thematic analysis
BARNABLE2006	Canada	6	Siblings	NR	Schizophrenia	NR	NR	NR	Life experience with service user	Semi-structured interviews	Hermeneutic phenomenology
BERGNER2008	USA	12	7 mothers 2 fathers 1 sister 1 grandmother 1 uncle	NR	Schizophrenia spectrum disorder	47.8	75%	0%	Duration of untreated psychosis before treatment in service users with first-episode psychosis	Individual semi-structured interviews	Thematic analysis
CHIU2006	Hong Kong and Taiwan	11	4 sisters 4 mothers 2 daughters 1 father	NR	Severe mental illness	NR	90%	NR	Experiences of the carer	Semi-structured interviews	Thematic analysis
GOODWIN2006	Australia	19	NR	NR	Consumers of mental health services	NR	NR	NR	Barriers to participation in healthcare	Focus groups	Content analysis
HUGHES2011	UK	10	9 parents 1 sibling	40%	Schizophrenia	57	90%	80%	Experience of assertive outreach	Semi-structured interviews	Interpretive phenomenological analysis
JANKOVIC2011	UK	31	16 parents 7 partners 4 siblings 2 children 1 grandmother 1 elderly relative	NR	8 schizophrenia 6 bipolar 7 other psychotic disorder 1 manic episode 1 borderline personality disorder 1 no mental	NR	61%	67%	Experience of involuntary psychiatric hospital admission of their relatives	Semi-structured interviews	Thematic analysis

					illness 2 unavailable						
KNUDSON2002	UK	8	6 mothers 2 fathers	62%	Schizophrenia	61	75%	NR	Experience of caring for a son or daughter with schizophrenia	Semi structured interviews	Thematic analysis
LAIRD2010	New Zealand	58	Family members	NR	70% schizophrenia, bipolar disorder, depression	NR	NR	NR	Understanding and opinions on the utility of diagnostic labels	Semi- structured interviews	Unclear
LEVINE2002	USA	55	Parents (74%), spouses, siblings and children	NR	Schizophrenia, schizoaffective disorder, mood disorder or mixture	63	NR	100%	Identify needs of carers (family members) of people with serious mental illness during a crisis	Focus groups	Unclear
LOBBAN2011	UK	23	22 parents 1 husband	NR	Psychosis, bipolar tendencies	NR	NR	74%	Views on design of an educated and coping toolkit for relative of people with psychosis	Focus groups	Thematic analysis
LUMSDEN2011	UK	20	NR	NR	NR	NR	75%	40 %	Carer satisfaction with assertive outreach	Open-ended questionnaire s self- completed or interview administered	Unclear
MCAULIFFE2009	Australia	31	16 mothers 9 fathers 3 partners 3 siblings	25%	96% schizophrenia 4.2% bipolar	NR	61%	NR	Experience and support needs of carers of people with severe mental illness	Focus groups	Thematic analysis
MCCANN2011	Australia	20	17 parents 1 partner 1 grandparent 1 aunt	90%	First episode psychosis	49	85%	NR	Experience of accessing first- episode psychosis services	Semi- structured interviews	Interpretive phenomenological analysis
MCCANN2012	Australia	20	17 parents 1 partner	90%	First episode psychosis	49	85%	NR	Satisfaction with clinicians	Semi- structured	Interpretive phenomenological

			1 grandparent 1 aunt						response to them as informal carers	interviews	analysis
NICHOLLS2009	New Zealand	7	6 parents 1 sibling	NR	5 schizophrenia 1 bipolar 1 major depression	NR	100%	NR	Perceptions of relationships with mental health professionals	Individual semi-structured interviews	Thematic analysis
NORDBY2010	Norway	18	Relatives	NR	Severe mental illness	NR	NR	NR	Factors that contribute to carers' participation in treatment and rehabilitation of family members with severe mental illness	Focus groups	Qualitative content analysis
REID2005	Australia	8	Parents	NR	Schizophrenia, bipolar disorder or schizoaffective disorder	NR	87%	NR	Educational needs of parents	Semi-structured in-depth interviews	Unclear
RILEY2011	UK	12	NR	NR	First episode psychosis	NR	NR	NR	Evaluation of an educated programme for carers	Focus groups	Thematic analysis
ROONEY2006	Australia	9	NR	NR	Bipolar disorder, schizophrenia, major depression	NR	NR	33%	Experience of carers from culturally and linguistically diverse backgrounds	Semi-structured interviews	Unclear
SAUNDERS2002	USA	26	NR	NR	Schizophrenia	59	NR	NR	Family functioning	Postal questionnaire consisting of open ended questions	Thematic analysis
SMALL2010	UK	13	NR	NR	Schizophrenia	NR	54%	NR	Carers' burden	3-month diaries combined with	Unclear



										unstructured audio- taped interviews	
TANSKANEN2011	UK	9	6 mothers 1 sisters 1 partner 1 mother in law	NR	First episode psychosis	NR	89%	77%	Experiences of seeking help for first episode psychosis	Structured interviews	Thematic analysis
TRANVAG2008	Norway	8	6 spouses 2 cohabitants	100%	Bipolar affective disorder	NR	50%	NR	Experiences of living with a partner with bipolar affective disorder over time.	Individual semi-structured interviews	Ricoeur's phenomenological hermeneutics
WAINWRIGHT	UK	23	12 mothers 10 fathers 1 husband	NR	Severe mental illness	59.5	52%	74%	Supporting a relative in early psychosis	Focus groups	Thematic analysis
WEIMAND2011	Norway	216	156 parents 18 partners 27 siblings 10 children 2 grand-parents 1 foster parent 2 in-laws	NR	NR	NR	75%	NR	Encounters with mental health services	Questionnaire (open-ended questions)	Content analysis
Note. NR = Not reported											

## 4.2.5 Quality assessment summary

Table 8 presents specific questions from the quality checklists that are relevant to the methodology of the studies. Full quality checklists can be found in Appendix 15b. The methodological quality and potential risk of bias was unclear across studies, with 12 out of 26 providing insufficient information about the methods employed. Of these, two (KNUDSON2002, SMALL2010) failed to describe the study objectives clearly. Seven (GOODWIN2006, KNUDSON2002, LAIRD2010, LUMSDEN2011, SAUNDERS2002, SMALL2010, WEIMAND2011) provided insufficient information regarding the rationale for the methodology as well as a justification for sampling and data analysis methods selected. Details regarding data collection, including a clear description of the procedure, were insufficiently described in seven studies (HUGHES2011, KNUDSON2002, LAIRD2010, LUMSDEN2011, SAUNDERS2002, SMALL2010, WEIMAND2011). Furthermore, 10 studies (ASKEY2009, GOODWIN2006, HUGHES2011, KNUDSON2002, LAIRD2010, LUMSDEN2011, SAUNDERS2002, SMALL2010, TRANVAG2008, WEIMAND2011) failed to adequately describe the reliability of the methodology and/or analysis, such as how many researchers were involved with data analysis or whether and how any differences and discrepant results were addressed. Two studies did not provide an adequate conclusion (LAIRD2010, LEVINE2002) and two (LUMSDEN2011, SMALL2010) provided only very limited definition of the implications of the study as well as an adequate consideration of the limitations.

**Table 8: Summary of quality assessment**

Study ID	Clear objectives	Defensible	Data collection	Methods reliable	Analysis reliable?	Conclusions adequate
ASKEY2009	+	+	+	+	?	+
BARNABLE2006	+	+	+	+	+	+
BERGNER2008	+	+	+	+	+	+
CHIU2006	+	+	+	+	+	+
GOODWIN2006	+	?	+	?	?	+
HUGHES2011	+	+	?	+	+	+
JANKOVIC2011	+	+	+	+	+	+
KNUDSON2002	?	?	?	?	?	+
LAIRD2010	+	?	?	?	?	-
LEVINE2002	+	+	+	+	+	-
LOBBAN2011	+	+	+	+	+	+
LUMSDEN2011	+	?	?	?	?	?
MCAULIFFE2009	+	+	+	+	+	+
MCCANN2011	+	+	+	+	+	+

MCCANN2012	+	+	+	+	+	+
NICHOLLS2009	+	+	+	+	?	+
NORDBY2010	+	+	+	+	+	+
REID2005	+	+	+	+	+	+
RILEY2011	+	+	?	+	+	+
ROONEY2006	+	+	+	+	+	+
SAUNDERS2002	+	?	?	?	+	+
SMALL2010	-	?	?	?	?	?
TANSKANEN2011	+	+	+	+	+	+
TRANVAG2008	+	+	?	?	?	+
WAINWRIGHT	+	+	+	+	+	+
WEIMAND2011	+	?	?	?	+	+
Key: Assessment of these aspects was: +: Clear/appropriate; -: Unclear/ inappropriate, ?: unsure						

#### 4.2.6 Evidence from qualitative studies of carers' experience of health and social care services

The findings from this review focus on features of mental health and social care services that carers believe either improve or diminish their experience of caring for adults with severe mental illness, including psychosis and schizophrenia. The review identified five themes: (1) relationships with healthcare providers; (2) valuing the identity and experience of the carer; (3) sharing decision making and involvement; (4) providing clear and comprehensible information; and (5) access to health services. A summary of the findings is presented below.

##### *Relationships with healthcare providers*

Carers reported that healthcare professionals who were welcoming, empathic and interested in the individual needs of carers resulted in a culture of trust, reassurance and mutual respect. This in turn enabled carers to feel connected with mental health services and develop an ongoing relationship, which was central to their experience of care. Building trust and continuous dialogue with healthcare providers was important for both ensuring and facilitating care for the service users, as well as to ensure that their own needs as carers were recognised and met. For example, a sustained connection with healthcare professionals allowed carers to feel that someone understood their difficulties, which helped to reduce feelings of isolation. Factors that further enabled this process included healthcare professionals demonstrating that they were reliable and respectful and also proactively reaching out to carers to offer support:

*Yeah cos if the professional want to contact you, you know they're going to, whereas if you have to contact them you might think oh I'm being a nuisance or whatever [group agreement] so really it needs to come from them...it does, the contact yeah.*  
(WAINWRIGHT)

Carers often stated that better relationships with healthcare professionals were built through ease of access to staff who were flexible to the individual needs of the carers and families:

*Simply being there and offering the opportunities. I know I'm 100% confident that I can pick up the phone and ring any of...[daughter's name] treating team and I have done it. I have every confidence in the world that they are there for me.*  
(MCCANN2011)

In contrast some carers experienced difficulty in accessing healthcare providers and reflected on their frustration when services failed to provide information or return telephone calls:

*It took a while because no one responded. No one was there, and I had to leave a message...I was told they would call me, and no one ever called back, or they weren't in, so that was the main thing. [They should] just call you back. Ya know, if I'm calling, ya know, telling you something is going on with my brother, just call back.*  
(BERGNER2008)

Cooperation between healthcare professionals and carers was also facilitated when staff listened to the needs and requests of carers and responded appropriately:

*I don't think there is any time that I have voiced my opinion about something that they haven't done something about. They always do something about it.*  
(HUGHES2011)

*I was pleasantly surprised by the positive conversation as well as the way we were received and listened to here.* (NORDBY2010)

Conversely carers felt angered and frustrated when healthcare professionals appeared not to listen to their views and opinions:

*Sometimes the professionals don't listen and understand what's actually happening with X. They should listen to what carers are saying more. It makes me feel frustrated.* (ASKEY2009)

Carers also described how a lack of empathy from healthcare professionals diminished their experience of services. In particular a dismissive attitude from staff made carers feel undervalued and problematic. These frustrations resulted in feelings of distrust and undermined collaborative relationships:

*I felt that I as a mother was totally ignored from the start. I had to fight and get angry to be heard. I felt, quite simply, that I was troublesome.* (NORDBY2010)

Finally, carers reflected on the difficulty in developing ongoing relationships with services when they frequently saw different members of the team. Having a single

point of contact and continuity in healthcare providers was therefore highly valued by some carers.

### *Valuing the identity and experience of the carer*

Prior to contact with services, carers described how they carried the main responsibility of care for their family member, often in isolation and without external help. Across the studies contributing to this theme, carers stated how it was important for healthcare professionals to recognise and acknowledge the roles they had played in managing the service users' symptoms and to utilise their acquired knowledge in the service users' care plans, for example:

*They [carers] suggested that as they knew their relatives well and demonstrated expertise in their care delivery they should be seen as part of the multidisciplinary team and respected by professionals. (ASKEY2009)*

However, carers described feeling disempowered and alienated when their expectations of being valued by healthcare professionals were not met. Professionals were perceived as ignoring and discounting the views of carers and ultimately appeared arrogant and overconfident:

*He [the psychiatrist] wasn't remotely interested in anything I had to say about my daughter- he made out that he knew her better than I did. (NICHOLLS2009)*

*...the shock from putting him in the hospital became so much greater when we discovered how the system worked. We came with confidence to the professionals; that they would take care of our son...and that our experiences and knowledge about him might be useful in the treatment. Instead we experienced to be harshly rejected, in an almost arrogant manner. (WEIMAND2011)*

Carers also felt undervalued and angered when healthcare providers did not recognise their expertise and apply it to the care of the service user:

*You know what is normal for this person. You know what is abnormal. You are the people who know that and what you say should be taken seriously. This should be included as part of the initial assessment. (MCAULIFFE2009)*

In contrast, carers also identified positive examples with services in which they were seen as a useful resource and invited to partake in discussions about the service user's treatment and care. In these situations, carers described having 'faith' in the system and healthcare professionals, which in turn was associated with a reduced sense of stress and burden:

*At the first time of hospitalization we felt we were excluded and they (i.e. the staff) had to use their own experiences and would not listen to ours. But this time we have been invited to tell them about our experiences of his functioning in everyday life at home. (NORDBY2010)*

For carers, the sense of being valued was not solely through having an input into the service users' care plan. Healthcare providers acknowledging the carer's important role and keeping them informed, where appropriate, also enabled carers to feel valued.

*...the best thing I think was being informed...even if they say, we can't divulge anything, it's still contact, it's still saying well you are the mum. (REID2005)*

### ***Sharing decision making and involvement***

The carers' ability and desire to be actively involved in the service users' care varied across studies. However, it was evident that when carers felt informed and understood the care plan, feelings of anxiety and stress were reduced.

Feeling excluded and increased stress were particularly evident when carers were unaware of changes to the service users' treatment plan, which often had implications for increased responsibility for carers. Lack of information and opportunities for involvement was largely influenced by the need to balance the service user's confidentiality with the carer's need to be informed. Often carers noted that members of staff would cite concerns over confidentiality as an explanation for excluding them from discussions relating to the service user's care:

*We ourselves, really, have been largely side-lined. Uh, things were said 'Well, these are now confidential matters' and, um, we still find that very difficult because, uh, how can you not be informed about somebody that you're caring for? Um you need to know certain things- Otherwise you can't care properly for that person. (KNUDSON2002)*

Poor communication and lack of involvement led carers to report feeling taken for granted and unprepared for changes in responsibility. Carers reflected how healthcare professionals sometimes assumed the carer would automatically take responsibility without consulting them, which resulted in feelings of anger and frustration:

*One carer related a story about how she was disengaged from discharge planning discussions only to find that her son was to be discharged to her at a time when she had arranged to be out of the city visiting a friend. This situation caused a great deal of trauma for all concerned, and could have been avoided had communication been more open. (MCAULIFFE2009)*

These feelings were heightened when there was disagreement between the carer and healthcare providers regarding treatment or discharge of the service user:

*...we were shattered...I didn't really want him to come home and spend the night at home already, and one day I went in and it took me completely by surprise Dr X wanted him released that day, and I think that [name of service user] had only just had his first weekend at home...he [name of service user] was being really bolshy and still very argumentative, and I said you know perhaps we could just sit quietly and*

*have some time and he was being really horrible...and I really knew I wasn't ready to have him home, but it was really obvious that the doctor wanted him to come home and thought that he was well, and he came home. (JANKOVIC2011)*

Carers also provided examples of experiences that fostered effective communication with healthcare professionals and enabled them to be involved and informed. This included situations in which carers had been routinely copied into letters and other documentation, as well as when they had been proactively contacted by staff about care planning and treatment.

Offers to remain in contact with healthcare professionals and support at follow-up were highly valued by carers and facilitated opportunities to be involved with the service user's recovery process. Carers reflected on the importance of 'shared responsibility' with healthcare services, which helped diminish feelings of isolation and burden. Feeling supported by services was associated with a perceived reduction in the carers' anxiety and burden:

*...now I don't feel so stressed out, because I know that there is so close monitoring of his progress...That's a great relief. (HUGHES2011)*

Likewise the absence of such support was associated with carers feeling overburdened by their caring responsibilities and feeling overlooked by services:

*I have almost no communication with the people treating her. I feel as if they are saying: 'You're an outsider, we're the professionals, you must just stay out of it'. Nobody tells me how we are supposed to handle this after her discharge. It's tough not knowing what I should do if she gets ill. I have a bag full of medicines I'm supposed to give her. That's the support apparatus we have. (TRANVAG2008)*

### ***Providing clear and comprehensible information***

Central to carers' experience of service were issues relating to individualised information provision. The findings highlighted the need for healthcare providers to strike a balance between providing too much information and too little.

Across studies it was also evident that there was a clear need for information provision to be improved and to be tailored to the specific needs and circumstances of carers. For example, some reflected on how the timing of the information had an impact on their understanding and retention of the information provided. Often this was because of emotional factors that interfered with processing information. This was particularly noticeable at critical stages in the care pathway, such as during admission of the service user into acute care or during first episode psychosis:

*We were almost in shock when we came here for the first time, we felt as if we were 'walking beside' ourselves and could not take it all in. (NORDBY2010)*

Providing written information to carers was met with mixed opinions. For some it allowed information to be revisited regularly and also helped maintain distance between emotions and information about the disorder:

*In a way it's easier to read about these diseases on a more general level. It does not seem so personal. I can manage to keep a distance and see it as something many people suffer from. (NORDBY2010)*

However, carers also reflected that the information they received was too complicated, overwhelming and frightening to read alone. Difficulties such as dyslexia and language barriers also highlighted the drawbacks of some written information. Carers suggested that information should be proactively offered, particularly before a crisis could develop, so that it could be more easily understood and retained.

Carers were often unaware and unprepared for the challenges that awaited them over the course of the care pathway. The need for information to be presented earlier in the process of care was therefore highlighted as crucial in terms of avoiding distress associated with a lack of information at a later date, particularly at times of crisis and discharge from acute care:

*You discover things gradually after discharge. You do not think to ask of such things before. (NORDBY2010)*

### ***Access to health services***

The final theme related to issues around access. Carers suggested that a barrier to accessing support and services was a lack of knowledge about the structure and functioning of mental health services. This was perceived to increase levels of stress and feelings of helplessness in some carers as they reported often not knowing who to contact in times of crisis. This was particularly evident during first hospital admission. Carers described needing prompt access to support but instead were directed from one service to another without clear direction:

*I mean one day he had me in tears, I had to walk out of the house and I just walked into the police station and I spoke to somebody on the desk, and they gave me a little bit of advice and they told me who to contact and stuff, and the next day I rang, I actually spoke to somebody but even that was a long process. I phoned them one day and they said they would get back to me and I said like, I need help now not like tomorrow or next week. I think they got back to me three months later, it was really hard to get any kind of help to start with. (JANKOVIC2011)*

Carer support groups were considered by some to be a valuable resource in addressing some of these difficulties as they allowed an opportunity for carers to access staff who were able to support them in understanding psychiatric services, how they operate and the sources of help available:



*I think for me it was just having a point of contact as well, which I've never had before, I didn't have any idea of anybody that I could contact or...for any advice or anything, till I came here. (RILEY2011)*

Carers also reported difficulty contacting services when needed. Frustration arose from the inflexibility of appointments, insufficient scheduling, and a lack of out-of-hours opening times and availability:

*I suppose the major difficulty is when we have crisis ...My frustration with them (Crisis Assessment Treatment team) was their inability to come out one night during an episode and then another time on a weekend. (MCCANN2011)*

In order to improve access to these services carers also highlighted the need for them to be organised flexibly in terms of timing so as to minimise disruption to caring responsibilities. The location of services and interventions was also important, for example having support groups closer to carers' homes facilitated attendance:

*Sometimes their relatives were admitted to places at a distance from their family home, which caused immense stress for both the carer and service user. (ASKEY2009)*

#### **4.2.7 Evidence from qualitative studies of carers' views and experiences of interventions for carers**

Five studies (LOBBAN2011, MCCANN2011, REID2005, RILEY2011, WAINWRIGHT) described carers' experience of interventions and their views on desirable components of a carer-focused intervention to improve the carers' experience of care or reduce their burden.

##### ***Self-management toolkit***

One study provided the views of carers of young people with first episode psychosis regarding the feasibility of a carer self-management toolkit (LOBBAN2011). Carers generally welcomed a self-management toolkit aimed at alleviating levels of distress in carers of people with psychosis. The carers described a number of perceived benefits, including improved knowledge and understanding as well as reduced distress and better coping skills. Carers stated that the toolkit should include information about psychosis, treatment options, and information about the structure and functioning of mental health services. Information about accessing help during a crisis and the legal rights of relatives particularly in relations to confidentiality were particularly important. A modular format was preferred as carers' felt this would be more manageable to digest. Carers also encouraged a personalised approach to the toolkit, which would vary according to the individual's reading ability. Practical support in navigating the content was suggested. Carers were emphatic that the toolkit should supplement and not replace other forms of face-to-face support from care coordinators and the opportunity to attend important review meetings. The most appropriate time to receive the toolkit was felt to be after the onset of the service user's symptoms but prior to receiving a diagnosis, in order to avoid delays to treatment.

### *Group psychoeducation*

Three studies examined carers' views and experiences of group psychoeducation for carers (RILEY2011, LOBBAN2011, REID2005). Participants expressed positive feelings about sharing their experiences with other carers. Psychoeducation groups were considered to provide a safe environment in which carers felt they could speak freely and be truthful about their relatives' mental health. The carers felt supported by each other and by the professionals facilitating the groups. Carers described how information about the purpose of group psychoeducation needed to be clearer to allow carers to decide whether it was appropriate for their needs.

Psychoeducation was believed to have a number of practical benefits including a providing a greater understanding of mental health issues, how to recognise early warning signs of relapse, and how psychiatric services work. Perceived emotional benefits included the ability to support other carers in similar circumstances through involvement as graduate carers, reduced guilt, and improved confidence to deal with problems resulting in better relationships with the service user. Carers considered the need for information and advice and the need to hear the stories of other relatives as particularly important. Carers reported that speaking to others who had been through similar experiences gave them new ideas about how to cope, and made them feel less isolated by being able to share and talk openly.

Carers in one study discussed the location and practicalities of delivering a psychoeducation programme. Several thought that the delivery of the programme should be delivered in a central location and at different times of the day to give carers a choice. The majority of carers in this study also stated that home-based programmes would not be well tolerated as they would disrupt other members of the family and were unfair for the person hosting the group.

### *Carer support groups*

Four studies described carers' experience of carer support groups (MCCANN2011, REID2005, RILEY2011, WAINWRIGHT). Carers reported that these groups improved their knowledge of mental illness and also helped them to develop better coping skills. These skills allowed carers to feel more in control and improved their relationship with the service user. In addition carers gained the skills and knowledge to be able to proactively access services.

Support groups were valued for addressing the feeling of isolation many carers felt. The importance of sharing experiences with others carers who were in similar situations was also preferred over discussing such issues with professionals. The timing of the group sessions was also important. Because of the positive impact on improving feelings of isolation and loneliness, carers wanted to be able to access support groups earlier. Others preferred to attend when they had overcome the shock of their relative's illness. Carers also valued the possibility of becoming graduate carers and helping others going through similar experiences.

A number of barriers to taking part in support groups were highlighted, including the timing and location of the sessions.

#### **4.2.8 Evidence summary**

The thematic synthesis identified five themes that carers of adults with severe mental illness believed would improve their experience of health and social care services and reduce carers' burden. These themes were: (1) building trusting relationships with healthcare providers; (2) valuing the identity and experience of the carer; (3) sharing decision making and involvement; (4) providing clear and comprehensible information; and (5) access to health services. The five major themes which emerged from the included studies were relevant to all points along the care pathway. However, some of the themes, for example access to health services or the provision of clear and compensable information, were also found to be of particular importance during first episode psychosis and a crisis.

Carers in the included studies also valued carer-focused interventions such as a self-management toolkit, group psychoeducation and carer support groups as useful means of receiving information. Group psychoeducation and carer support groups were also considered to be useful for sharing experiences with others.

### **4.3 INTERVENTIONS TO IMPROVE CARERS' EXPERIENCE**

#### **4.3.1 Introduction**

##### *Definition and aim of review*

This aim of this review is to evaluate interventions delivered by health and social care services to carers of people with severe mental illness, including psychosis and schizophrenia, to improve their experience of caring. Interventions included in this review were designed to facilitate the improvement of carers' experience and reduce burden. The review aims to evaluate the benefits of the interventions on carer-focused outcomes and not on the therapeutic outcomes of the service user, thus the latter were not evaluated or extracted from the papers.

A number of interventions are not included in this review. The provision of financial and practical support (for example, personal assistance or direct payments) is outside of the scope of this guideline and is therefore not covered here. Furthermore, family intervention, which may or may not include the carer or provide carer outcomes, are evaluated separately in Chapter 9. Interventions where the service user is included in the majority of sessions are also not included as they are evaluated in Chapter 9. Additionally, this review does not aim to evaluate the effectiveness of psychological and pharmacological interventions for carers' mental health problems as these are covered by existing NICE guidelines.

## *Definitions and aim of interventions*

Interventions reviewed in this chapter include, but were not limited to, the following:

### **Psychoeducation**

Psychoeducation/support and education interventions were defined as:

- any structured programme offered individually or in a group involving an interaction between an information provider and the carer, which has the primary aim of offering information about the condition, and
- the provision of support and management strategies to carers, and
- delivered to the carer without the service user being present<sup>8</sup>.

Where psychoeducation could be either:

- ‘standard’ including only basic information about the nature, prognosis, symptoms, evolution of illness and treatment of the disorder (including medication management) and delivered via videos and/information leaflets, or
- ‘enhanced’ as above but practitioner delivered and including information and support about additional issues such as how to identify and manage a crisis, available support services and resources, coping strategies, problem solving, self-care goals and communication techniques.

### **Support groups**

Support groups were defined as usually a group intervention (although this does not preclude one-to-one delivery) providing help and support from others. Support groups can be facilitated by a mental health or social care service provider or a carer employed by healthcare services (for example, carer support worker). Support provided is either:

- reciprocal and mutually beneficial for participants who have similar experiences and who need similar levels of support and (mutual support), or
- primarily in one direction with a clearly defined peer supporter and recipient of support (peer support).

### **Self-help interventions**

Self-help interventions were defined as:

- including health technologies (for example, written, audio, video and internet) designed to improve the carers’ experience of care
- including information about the condition and about mental health services and the support available for the carer
- being guided with support (initial or ongoing support) from a mentor or healthcare professional, or can be self-directed
- being delivered face-to-face, via telephone or the internet.

---

<sup>8</sup> Psychoeducation involving the service user (with or without the carer) are evaluated in Chapter 7.

### 4.3.2 Clinical review protocol (interventions to improve carers' experience)

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 9 (a complete list of review questions and the full review protocol can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 9: Clinical review protocol summary for the review of interventions to improve carers' experience**

Component	Description
<i>Review question</i>	What modification to health and social services improve the experience of using services for carers of adults with severe mental illness?
<i>Objectives</i>	To evaluate the effectiveness of interventions for improving the experience of health and social services for carers of people with severe mental illness.
<i>Population</i>	Carers of any age who care for adults (18 years of age and over) with severe mental illness who use health and social services in community settings.  <i>Include papers with a service user population of at least:</i> 66% schizophrenia or 66% schizophrenia + bipolar disorder or 66% schizophrenia + 'mood disorders' or 66% undefined severe mental illness 66% bipolar disorder.
<i>Intervention(s)</i>	<b>Included interventions</b> Only interventions delivered directly to carers of people with severe mental illness will be included. These may include, for example: <ul style="list-style-type: none"> <li>• specific interventions for carers</li> <li>• peer-led interventions for carers (for example, carer support groups)</li> <li>• changes in the delivery and organisation of services for the benefit of carers.</li> </ul>
<i>Comparison</i>	Existing services and alternative strategies
<i>Critical outcomes</i>	Carers': <ul style="list-style-type: none"> <li>• quality of life</li> <li>• mental health (anxiety or depression)</li> <li>• burden of care (including 'burnout', stress, and coping)</li> <li>• satisfaction with services (validated measures only, specific items will not be analysed).</li> </ul>
<i>Electronic databases</i>	Core databases: CENTRAL, CDSR, DARE, HTA, Embase, MEDLINE, MEDLINE In-Process Topic specific databases: AEI, ASSIA, BEI, CINAHL, ERIC, IBSS, PsycINFO, Sociological Abstracts, SSA
<i>Date searched</i>	SR: 1995 to June 2013 RCT: database inception to June 2013
<i>Study design</i>	Systematic reviews of RCTs RCT
<i>Review strategy</i>	<b>Time-points</b> <ul style="list-style-type: none"> <li>• End of intervention</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• Greater than 6 months' follow-up (long term)</li> </ul>

	<p>Where more than one follow-up point within the same period was available, the latest one was reported.</p> <p><b>Analysis</b></p> <p>Data were analysed and presented by:</p> <ul style="list-style-type: none"> <li>• carer interventions versus any control</li> <li>• head-to head comparison of carer interventions.</li> </ul> <p>Within these comparisons, subgroups were based on service user diagnosis.</p> <p>Where data was available, sub-analyses was conducted for UK/Europe studies.</p>
--	--

### 4.3.3 Studies considered<sup>9</sup>

Twenty four RCTs (N = 1758) met the eligibility criteria for this review: CARRA2007 (Carrà et al., 2007), CHENG2005 (Cheng & Chan, 2005), CHIEN2004A (Chien, 2004a), CHIEN2004B (Chien & Chan, 2004b), CHIEN2007 (Chien & Wong, 2007), CHIEN2008 (Chien et al., 2008), CHOU2002 (Chou et al., 2002), COZOLINO1988 (Cozolino et al., 1988), GUTIERREZ-MALDONADO2007 (Gutierrez-Maldonado & Caqueo-Urizar, 2007), KOOLAE2009 (Koolae & Etemadi, 2009), LEAVEY2004 (Leavey et al., 2004), LOBBAN2013 (Lobban et al., 2013), MADIGAN2012 (Madigan et al., 2012), MCCANN2012 (McCann et al., 2012b), PERLICK2010 (Perlick et al., 2010), POSNOR1992 (Posner et al., 1992), REINARES2004 (Reinares et al., 2004), SHARIF2012 (Sharif et al., 2012), SMITH1987 (Smith & Birchwood, 1987), SO2006 (So et al., 2006), SOLOMON1996 (Solomon et al., 1996), SZMUKLER1996 (Szmukler et al., 1996), SZMUKLER2003 (Szmukler et al., 2003) and VANGENT1991 (Van Gent & Zwart, 1991). All included studies were published in peer-reviewed journals between 1987 and 2013. Further information about both included and excluded studies can be found in Appendix 15a.

Of the 24 eligible trials, 20 (N = 1364) included sufficient data to be included in the statistical analysis. Three trials did not include any relevant outcomes (CARRA2007, COZOLINO1988, VANGENT1991) and one trial (N = 225) included critical outcomes that could not be included in the meta-analyses because of the way the data had been reported (SOLOMON1996), therefore a brief narrative synthesis is given to assess whether the findings support or refute the meta-analyses.

The majority of the included trials involved a control arm of treatment as usual comparing it with psychoeducation (k = 11), a support group (k = 3), a combined psychoeducation and support group intervention (k = 1), problem-solving bibliotherapy (k = 1) and self-management (k = 1). Four of the included trials were three-arm trials comparing two active interventions with treatment as usual. One trial compared postal psychoeducation with practitioner-delivered standard psychoeducation, and one trial evaluated group versus individual psychoeducation.

---

<sup>9</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

Table 10, Table 11 and Table 12 provide an overview of the trials included in each category. One study (MADIGAN2012) included an arm evaluating an intervention termed 'psychotherapy'. However, this arm was not included because the content of the intervention was poorly described and the suggestion that the intervention was therapeutic and therefore beyond the scope of this review. Of the eligible trials, 14 included a large proportion (greater than 75%) of service users with a primary diagnosis of psychosis or schizophrenia and thus the results of sub-analysis are reported. Only six were based in the UK/Europe and not all trials were included in the same analysis, thus sub-analysis for UK/Europe based studies was not conducted.

**Table 10: Study information table for trials included in the meta-analysis of carer interventions versus any control**

	<b>Psychoeducation versus any control</b>	<b>Support group versus any control</b>
<i>Total no. of trials (k); participants (N)</i>	k = 11; N = 737	k = 3; N = 208
<i>Study ID(s)</i>	CHENG2005 CHIEN2004B CHIEN2007 GUTIERREZ-MALDONADO2007 KOOLAE2009 <sup>1</sup> LEAVEY2004 MADIGAN2012 POSNOR1992 REINARES2004 SHARIF2012 SO2006 SZMUKLER1996	CHOU2002 CHIEN2004A CHIEN2004B <sup>7</sup> CHIEN2008
<i>Country</i>	Australia (k = 1) Canada (k = 1) Chile (k = 1) China (k = 4) Iran (k = 2) Ireland (k = 1) Spain (k = 1) UK (k = 1)	China (k = 4)
<i>Year of publication</i>	1992 to 2012	2002 to 2008
<i>Mean age of carers (range)</i>	48.77 years (40.6 to 55.4 years) <sup>2</sup>	40.66 years (35.9 to 44.15 years) <sup>8</sup>
<i>Mean percentage of women carers (range)</i>	66.38% (31.01 to 100%) <sup>3</sup>	52.06% (31.01 to 66%)
<i>Mean percentage relationship of carer to service user</i>	Parent = 56.29% Spouse = 19.05% Sibling = 6.53% (Adult) Child = 6.99% Other = 11.14%	Parent = 38.18% Spouse = 31.56% Sibling = 2.85% (Adult) Child = 16.51% Other = 10.91%
<i>Mean age of service users (range)</i>	32.88 years (29.1 to 42 years) <sup>4</sup>	28.52 years (25.35 to 31.68 years) <sup>9</sup>
<i>Mean percentage of women service users (range)</i>	41.77% (27 to 65%) <sup>5</sup>	46.67% (35.44 to 57.89%) <sup>8</sup>
<i>Mean percentage of service users with primary diagnosis of</i>	81.82% (0 to 100%) <sup>6</sup>	100% (100 to 100%)

<i>psychosis/schizophrenia (range)</i>		
<i>Length of treatment (range)</i>	5 to 36 weeks	8 to 24 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> CHENG2005 CHIEN2007 GUTIERREZ-MALDONADO2007 REINARES2004 SO2006  <i>Up to 6 months</i> CHIEN2004B KOOLAE2009 LEAVEY2004 POSNOR1992 SHARIF2012 SZMUKLER1996  <i>&gt;6 months</i> CHIEN2004B CHIEN2007 MADIGAN2012	<i>Up to 6 months</i> CHOU2002 CHIEN2004A CHIEN2004B  <i>&gt;6 months</i> CHIEN2004B CHIEN2008
<i>Intervention type</i>	Psychoeducation (k = 11) Counselling (psychoeducation + coping strategies) (k = 1)	Mutual support (k = 3) Support group (k = 1)
<i>Comparisons</i>	TAU (k = 8) Waitlist control (k = 1) No treatment (k = 2) Information only (k = 1)	TAU (k = 3) Waitlist control (k = 1)
<p>Note. TAU = treatment as usual.</p> <p><sup>1</sup>Two active arms combined.</p> <p><sup>2</sup>POSNOR1992, LEAVEY2004 and CHENG2005 did not report data.</p> <p><sup>3</sup>POSNOR1992, SZMUKLER1996, LEAVEY2004 and SHARIF2012 did not report data.</p> <p><sup>4</sup>LEAVEY2004 and CHENG2005 did not report data.</p> <p><sup>5</sup>SZMUKLER1996 and CHENG2005 did not report data.</p> <p><sup>6</sup>100% of service users in REINARES2004 and MADIGAN2012 had a diagnosis of bipolar disorder.</p> <p><sup>7</sup>CHIEN2004B is a three-arm trial.</p> <p><sup>8</sup>CHOU2002 did not report data.</p> <p><sup>9</sup>CHOU2002 and CHIEN2004A did not report data.</p>		

**Table 11: Study information table for trials included in the meta-analysis of carer interventions versus any alternative management strategy**

	<b>Psychoeducation + support group versus TAU</b>	<b>Problem-solving bibliotherapy versus TAU</b>	<b>Self-management versus TAU</b>
<i>Total no. of trials (k); participants (N)</i>	k = 1; N = 61	k = 1; N = 124	k = 1; N = 103
<i>Study ID(s)</i>	SZMUKLER2003	MCCANN2012	LOBBAN2013
<i>Country</i>	UK (k = 1)	Australia (k = 1)	UK (k = 1)
<i>Year of publication</i>	2003	2012	2013
<i>Mean age of carers</i>	54 years	47.2 years	Not reported
<i>Mean percentage of women carers</i>	82%	82.3%	82.5%
<i>Mean percentage of relationship of carer to service user</i>	Parent = 62% Spouse = 10% Sibling = 13%	Parent = 91.1% Other = 8.9%	Parent = 74% Other = 26%



	(Adult) Child = 5% Other = 10%		
Mean age of service users (range)	Not reported	Not reported	Not reported
Mean percentage of women service users	Not reported	Not reported	Not reported
Mean percentage of service users with primary diagnosis of psychosis/ schizophrenia (range)	73%	100%	57%
Length of treatment	39 weeks	5 weeks	26 weeks
Length of follow-up	7- 12 months SZMUKLER2003	Up to 6 months MCCANN2012	End of treatment only LOBBAN2013
Intervention type	Psychoeducation + support group (k = 1)	Problem-solving bibliotherapy intervention (k = 1)	Self-management (k = 1)
Comparisons	No treatment (k = 1)	TAU (k = 1)	TAU (k = 1)
Note. TAU = treatment as usual.			

**Table 12: Study information table for head-to-head trials comparing different formats of carer interventions**

	<b>Enhanced psychoeducation versus standard psychoeducation</b>	<b>Practitioner-delivered psychoeducation versus postal psychoeducation</b>	<b>Group psychoeducation versus individual psychoeducation</b>
Total no. of trials (k); participants (N)	k = 1; N = 46	k = 1; N = 40	k = 1; N = 225
Study ID(s)	PERLICK2010	SMITH1987	SOLOMON1996
Country	USA (k = 1)	UK (k = 1)	USA (k = 1)
Year of publication	2010	1987	1996
Mean age of carers	52.77 years	Not reported	55.7 years
Mean percentage of women carers	84%	Not reported	88%
Mean percentage of relationship of carer to service user	Parent = 70% Spouse = 14% (Adult) child = 14% Other = 2%	Parent = 70% Spouse = 17.5% Other = 12.5%	Parent = 76.4% Spouse = 4.4% Sibling = 11.1% (Adult) child = 5.8% Other = 2.2%
Mean age of service users	34.72 years	36.4 years	35.8 years
Mean percentage of women service users	63%	22%	Not reported
Mean percentage of service users with primary diagnosis of psychosis/ schizophrenia	0% <sup>1</sup>	100%	63.5%
Length of treatment	12 to 15 weeks	4 weeks	10 weeks
Length of follow-up	End of treatment only PERLICK2010	Up to 6 months SMITH1987	7- 12 months SOLOMON1996
Intervention type	Enhanced psycho-education (k = 1)	Practitioner delivered psychoeducation (k = 1)	Group psycho-education (k = 1)
Comparisons	Standard psycho-education (k = 1)	Postal psychoeducation (k = 1)	Individual psycho-education (k = 1)
Note. <sup>1</sup> 100% of service users had a diagnosis of bipolar disorder.			

#### **4.3.4 Clinical evidence for any intervention versus any control**

In the included trials, the interventions were compared with a variety of control groups that were categorised as any control (treatment as usual, attention control, waitlist control and no treatment). Further information about the control group used in each trial can be found in Table 10, Table 11 and Table 12.

##### ***Psychoeducation versus control***

Evidence from each important outcome and overall quality of evidence are presented in

. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Low to very low quality evidence from up to seven studies (N = 399), showed that psychoeducation was more effective than control in improving carers' experience of care and these effects are maintained at long-term follow-up. No difference was observed between groups in quality of life or satisfaction with services. Although no difference was observed between groups in psychological effect at the end of the intervention and at short-term follow-up, one study (N = 18) provided high quality evidence that psychoeducation is more effective than control at long-term follow-up.

##### ***Support group versus control***

Evidence from each important outcome and overall quality of evidence are presented in Table 14. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Low to very low quality evidence from up to three studies (N = 194) showed that support groups improved the experience of caring at the end of the intervention and at short-term follow-up but no benefit was observed at long-term follow-up. One study with 70 participants presented low quality evidence that support groups were more effective than control for reducing psychological distress at the end of the intervention and at short-term follow-up.

##### ***Psychoeducation plus support group versus control***

Evidence from each important outcome and overall quality of evidence are presented in Table 15. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

One study with 49 participants found no difference between psychoeducation plus support group and control in terms of the experience of caring and psychological distress. No other follow-up data or other critical outcome data were available.

**Table 13: Summary of findings table for psychoeducation compared with any control**

Patient or population: Carers of adults with severe mental illness Intervention: Psychoeducation Comparison: Any control			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Psychoeducation		
Experience of caring - end of intervention	Mean experience of caring (end of intervention) in the intervention groups was 1.03 standard deviations higher (0.36 to 1.69 higher)	399 (7 studies)	⊕⊕⊕⊕ very low <sup>1,2</sup>
Experience of caring - up to 6 months' follow-up	Mean experience of caring (up to 6 months' follow-up) in the intervention groups was 0.92 standard deviations higher (0.32 to 1.51 higher)	215 (4 studies)	⊕⊕⊕⊕ very low <sup>1,2</sup>
Experience of caring - >6 months' follow-up	Mean experience of caring (>6 months' follow-up) in the intervention groups was 1.29 standard deviations higher (0.18 to 2.4 higher)	151 (3 studies)	⊕⊕⊕⊕ very low <sup>1,2</sup>
Quality of life - end of intervention	Mean quality of life (end of intervention) in the intervention groups was 0.31 standard deviations higher (0.31 lower to 0.93 higher)	41 (1 study)	⊕⊕⊕⊕ low <sup>1,3</sup>
Satisfaction with services - end of intervention	Mean satisfaction with services (end of intervention) in the intervention groups was 0.42 standard deviations higher (0.22 lower to 1.06 higher)	39 (1 study)	⊕⊕⊕⊕ low <sup>1,3</sup>
Satisfaction with services - up to 6 months' follow-up	Mean satisfaction with services (up to 6 months' follow-up) in the intervention groups was 0.41 standard deviations higher (0.23 lower to 1.04 higher)	39 (1 study)	⊕⊕⊕⊕ low <sup>1,3</sup>
Psychological distress - end of intervention	Mean psychological distress (end of intervention) in the intervention groups was 0.3 standard deviations lower (0.84 lower to 0.24 higher)	86 (2 studies)	⊕⊕⊕⊕ very low <sup>1,2,3</sup>
Psychological distress- up to 6 months' follow-up	Mean psychological distress (up to 6 months' follow-up) in the intervention groups was 0.34 standard deviations lower (0.76 lower to 0.08 higher)	86 (2 studies)	⊕⊕⊕⊕ low <sup>1,3</sup>
Psychological distress - >6 months' follow-up	Mean psychological distress (> 6 months' follow-up) in the intervention groups was 1.79 standard deviations lower (3.01 to 0.56 lower)	18 (1 study)	⊕⊕⊕⊕ high
<p>Note. CI = confidence interval.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Concerns regarding risk of bias.</p> <p><sup>2</sup> Concerns regarding heterogeneity.</p> <p><sup>3</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>			

**Table 14: Summary of findings table for support group compared with any control**

Patient or population: Carers of adults with severe mental illness Intervention: Support groups Comparison: Any control			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Support groups		
<i>Experience of caring - end of intervention</i>	Mean experience of caring (end of intervention) in the intervention groups was 1.16 standard deviations higher (0.36 to 1.96 higher)	194 (3 studies)	⊕⊕⊕⊕ very low <sup>1,2,3</sup>
<i>Experience of caring - up to 6 months' follow-up</i>	Mean experience of caring (up to 6 months' follow-up) in the intervention groups was 0.67 standard deviations higher (0.35 to 0.99 higher)	166 (3 studies)	⊕⊕⊕⊕ low <sup>1,3</sup>
<i>Experience of caring - &gt;6 months' follow-up</i>	Mean experience of caring (>6 months' follow-up) in the intervention groups was 1.95 standard deviations lower (4.22 lower to 0.31 higher)	123 (2 studies)	⊕⊕⊕⊕ very low <sup>1,2,3,4</sup>
<i>Psychological distress - end of intervention</i>	Mean psychological distress (end of intervention) in the intervention groups was 0.99 standard deviations lower (1.48 to 0.49 lower)	70 (1 study)	⊕⊕⊕⊕ low <sup>1,3</sup>
<i>Psychological distress - up to 6 months' follow-up</i>	Mean psychological distress (up to 6 months' follow-up) in the intervention groups was 0.99 standard deviations lower (1.48 to 0.49 lower)	70 (1 study)	⊕⊕⊕⊕ low <sup>1,3</sup>
<p>Note. CI = confidence interval</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Concerns regarding risk of bias.</p> <p><sup>2</sup> Concerns regarding heterogeneity.</p> <p><sup>3</sup> Studies all based in East Asia - may not be applicable to UK setting.</p> <p><sup>4</sup> Confidence interval crosses clinical decision threshold.</p>			

**Table 15: Summary of findings table for psychoeducation plus support group compared with any control**

Patient or population: Carers of adults with severe mental illness Intervention: Psychoeducation + support group Comparison: Any control			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Psychoeducation + support group		
<i>Experience of caring - &gt;6 months' follow-up</i>	Mean experience of caring (>6 months' follow-up) in the intervention groups was 0.05 standard deviations higher (0.51 lower to 0.61 higher)	49 (1 study)	⊕⊕⊕⊕ low <sup>1,2</sup>
<p>Note. CI = confidence interval</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Concerns regarding risk of bias.</p> <p><sup>2</sup> Confidence interval crosses decision making threshold.</p>			

### *Self-management versus control*

Evidence from each important outcome and overall quality of evidence are presented in Table 16. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

One study with 86 participants found no difference between groups in terms of experience of caring and psychological distress at the end of the intervention.

**Table 16: Summary of findings table for self-management compared with any control**

Patient or population: Carers of adults with severe mental illness Intervention: Self-management Comparison: Any control			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Self-management		
<i>Experience of caring - end of intervention</i>	Mean experience of caring (end of intervention) in the intervention groups was 0.19 standard deviations lower (0.58 lower to 0.2 higher)	86 (1 study)	⊕⊕⊕⊖ moderate <sup>1</sup>
<i>Psychological distress - end of intervention</i>	Mean psychological distress (end of intervention) in the intervention groups was 0.32 standard deviations lower (0.73 lower to 0.09 higher)	86 (1 study)	⊕⊕⊕⊖ moderate <sup>1</sup>
Note. CI = confidence interval *The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnote below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). <sup>1</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).			

### *Problem-solving bibliotherapy versus control*

Evidence from each important outcome and overall quality of evidence are presented in Table 17. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

One study with 114 participants found no difference between groups in terms of the experience of caring. The same study provided low quality evidence that problem-solving bibliotherapy was effective at improving quality of life at short-term follow-up (although no difference was observed at the end of the intervention).

**Table 17: Summary of findings table for problem-solving bibliotherapy compared with any control**

Patient or population: Carers of adults with severe mental illness Intervention: Problem-solving bibliotherapy Comparison: Any control			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Problem-solving bibliotherapy		
Experience of caring – end of intervention	Mean experience of caring (end of intervention) in the intervention groups was 0.17 standard deviations higher (2.11 lower to 2.45 higher)	114 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
Experience of caring – up to 6 months' follow-up	Mean experience of caring (up to 6 months' follow-up) in the intervention groups was 1.09 standard deviations higher (0.34 lower to 2.52 higher)	114 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
Quality of life – end of intervention	Mean quality of life (end of intervention) in the intervention groups was 0.14 standard deviations higher (0.23 lower to 0.5 higher)	114 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
Quality of life – up to 6 months' follow-up	Mean quality of life (up to 6 months' follow-up) in the intervention groups was 0.5 standard deviations higher 0.12 to 0.87 higher)	114 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
Psychological distress – end of intervention	Mean psychological distress (end of intervention) in the intervention groups was 1.57 standard deviations lower (1.79 to 1.35 lower)	114 (1 study)	⊕⊕⊕⊕ moderate <sup>1</sup>
Psychological distress – up to 6 months' follow-up	Mean psychological distress (up to 6 months' follow-up) in the intervention groups was 1.54 standard deviations lower (1.95 to 1.13 lower)	111 (1 study)	⊕⊕⊕⊕ moderate <sup>1</sup>
Note. CI = confidence interval. *The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). <sup>1</sup> Concerns regarding risk of bias. <sup>2</sup> CI crosses clinical decision making threshold			

### *Enhanced psychoeducation versus standard psychoeducation*

Evidence from each important outcome and overall quality of evidence are presented in Table 18. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

One trial with 43 participants provided moderate quality evidence that enhanced psychoeducation was more effective than standard psychoeducation in improving experience of caring and self-care behaviour when measured at the end of the intervention. No difference was observed between groups in carer mental health. No follow-up data were available.

***Practitioner-delivered versus postal-delivered standard psychoeducation***

Evidence from each important outcome and overall quality of evidence are presented in Table 19. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

One study with 40 participants provided data for this comparison. There was no evidence of a difference between groups in family burden and psychological distress at the end of the intervention and up to 6 months' follow-up. No other follow-up data or other critical outcome data were available.

**Table 18: Summary of findings table for enhanced psychoeducation compared with standard psychoeducation**

Patient or population: Carers of adults with severe mental illness Intervention: Enhanced psychoeducation Comparison: Standard psychoeducation			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Enhanced psychoeducation		
<i>Experience of caring - end of intervention</i>	Mean experience of caring (end of intervention) in the intervention groups was 0.64 standard deviations higher (0.3to 1.25 higher)	43 (1 study)	⊕⊕⊕⊖ moderate <sup>1</sup>
<i>Carer mental health - end of intervention</i>	Mean carer mental health (end of intervention) in the intervention groups was 0.32 standard deviations higher (0.29 lower to 0.92 higher)	43 (1 study)	⊕⊕⊕⊖ moderate <sup>1</sup>
<i>Self-care - end of intervention</i>	Mean self-care (end of intervention) in the intervention groups was 0.68 standard deviations lower (1.31 to 0.06 lower)	43 (1 study)	⊕⊕⊕⊖ moderate <sup>1</sup>
<p>Note. CI = confidence interval</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnote below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>			

**Table 19: Summary of findings table for practitioner-delivered compared with postal-delivered standard psychoeducation**

Patient or population: Carers of adults with severe mental illness Intervention: Psychoeducation-practitioner delivered Comparison: Psychoeducation-postal delivered			
Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Standard psychoeducation (practitioner-delivered)		
<i>Family burden - end of intervention</i>	Mean family burden (end of intervention) in the intervention groups was 0.41 standard deviations lower (1.04 lower to 0.21 higher)	40 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
<i>Family burden - up to 6 months' follow-up</i>	Mean family burden (- up to 6 months' follow-up) in the intervention groups was 0.41 standard deviations lower (1.03 lower to 0.22 higher)	40 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
<i>Psychological distress - end of intervention</i>	Mean psychological distress (end of intervention) in the intervention groups was 0.38 standard deviations lower (1 lower to 0.25 higher)	40 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
<i>Psychological distress - up to 6 months' follow-up</i>	Mean psychological distress (up to 6 months' follow-up) in the intervention groups was 0 standard deviations higher (0.62 lower to 0.61 higher)	40 (1 study)	⊕⊕⊕⊖ low <sup>1,2</sup>
<p>Note. CI = confidence interval.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of</p>			



the intervention (and its 95% CI).

<sup>1</sup> Concerns regarding risk of bias.

<sup>2</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

### *Individual versus group enhanced psychoeducation versus treatment as usual*

The trial eligible for this review (SOLOMON1996) could not be included in meta-analysis. The study reported no significant difference between groups in terms of carers' burden or satisfaction with services.

### **4.3.5 Clinical evidence summary**

The limited evidence suggests that psychoeducation is effective in reducing carers' burden and these effects are maintained at long-term follow-up. Furthermore, evidence suggests that although no immediate benefit can be found at the end of the intervention, psychoeducation can reduce psychological distress in the long term. Support groups were also found to be effective in improving carers' experience of caring and reducing psychological distress. However, these findings should be viewed with caution as the studies included in this review are based in East Asia and the services provided there are not directly comparable to the UK. In addition, there was limited evidence that enhanced psychoeducation (providing information, as well as focusing on self-carer skills, coping skills and problem-solving) was more effective than standard psychoeducation (information only) in improving the experience of caring and self-care behaviour at the end of the intervention. However, longer-term effects are not known. Self-management was not found to be beneficial over control on any critical outcomes. However, this was based on a single high quality study and a trend favouring self-management was observed. Problem-solving bibliotherapy was not found to be effective at improving any critical outcomes at the end of the intervention, however, it was found to improve quality of life at short-term follow-up. Finally, there was no detectable difference in effectiveness between psychoeducation delivered by post or delivered by a practitioner, or between group and individual psychoeducation.

## **4.4 HEALTH ECONOMICS EVIDENCE**

No studies assessing the cost effectiveness of interventions aiming to improve carers' experience of caring and of health and social care services were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

The clinical studies on interventions, mainly psychoeducation, aiming to improve carers' experience of caring and of health and social care services included in the guideline systematic literature review (GUTIERREZ-MALDONADO2007, SHARIF2012, CHENG2005, SZMUKLER1996) described interventions consisting of 13 sessions on average (range 6 to 26). These programmes are usually delivered by either a psychologist or psychiatric nurse/psychiatrist to an average group of seven people (range 1 to 9) and have an average duration of 1.5 hours (range 1 to 2). The

unit cost of a clinical psychologist is £136 per hour of client contact in 2011/12 prices (Curtis, 2012). This estimate has been based on the median full-time equivalent basic salary for Agenda for Change salaries band 8a of the April 2012 NHS Staff Earnings Estimates (Health and Social Care Information Centre, 2012). It includes basic salary, salary oncosts, travel, overheads and capital overheads, but does not take into account qualification costs because the latter are not available for clinical psychologists. The unit cost of a mental health nurse is £76 per hour of client contact in 2011/12 prices (Curtis, 2012). This estimate has been based on the median full-time equivalent basic salary for Agenda for Change salaries band 5 of the April-June 2012 NHS Staff Earnings Estimates for Qualified Nurses (Health and Social Care Information Centre, 2012). It includes basic salary, salary oncosts, qualifications, overheads and capital overheads, and travel. The unit cost of a psychiatric consultant is £289 per hour of client contact in 2011/12 prices (Curtis, 2012). This estimate has been based on the Electronic Staff Records system that shows the mean full-time equivalent total earnings for a psychiatric consultant in April to June 2012 (Health and Social Care Information Centre, 2012). It includes basic salary, salary oncosts, qualifications, ongoing training, overheads and capital overheads. Based on the estimated resource utilisation associated with interventions aiming to improve carers' experience of caring and of services (as described above) and the unit cost of a clinical psychologist, a mental health nurse and a psychiatric consultant the average cost per person participating in such a programme would range between £190 and £1,095 (mean of £582) in 2011/12 prices.

## 4.5 LINKING EVIDENCE TO RECOMMENDATIONS

### *Relative value placed on the outcomes considered:*

The main aim of the qualitative review was to evaluate carers' experience of health and social care services. The outcomes of interest were any themes and specific issues that carers identified as improving or diminishing their experience of health and social care. Furthermore, the GDG aimed to evaluate the effectiveness of interventions designed to improve the carers' experience of caring. The outcomes the GDG considered to be critical for carers were their:

- quality of life
- mental health (anxiety or depression)
- burden of care (including 'burnout', stress and coping)
- satisfaction with services

### *Trade-off between clinical benefits and harms*

The factors identified by the qualitative review revealed a broad range of issues that resonated with the experience of the carers, service users and healthcare professional members of the GDG.

The qualitative analysis revealed that carers thought a key determinant of their experience of services and experience of caring was building trusting relationships with healthcare professionals. An empathic and understanding healthcare

professional allows the carer to build confidence in their role as a carer and reduces feelings of stress and burden.

Two linked themes were identified in the qualitative literature. Carers felt that services should identify and value their experience and involve them in decision making. This theme also included issues about confidentiality – carers felt that confidentiality was often used as a reason to exclude them from receiving important information about the service user's care and treatment, resulting in a stressful, burdensome and isolated experience for them. This theme was prevalent throughout the care pathway and specifically during first episode psychosis, crises and subsequent exacerbations, as well as during the planning of discharge from a hospital. The GDG used these findings to make recommendations about the involvement of carers and the negotiation of information sharing among the service user, the carer and the healthcare professionals. Furthermore, in taking a broad overview of all the themes identified, combined with the collective experience of the whole GDG, the GDG came to the view that the guideline should explicitly support collaboration among the carer, service user and healthcare professional through all phases of care, where this is possible, while respecting the independence of the service user.

Importantly, a theme affecting both carers and service users is access to services. Carers expressed a need to have easy access to services, interventions and support for the service user, which thus reduces the carer's own burden and stress. Carers discussed the importance of swift access to reliable services at all points in the care pathway but particularly during a crisis and during first episode psychosis. Carers stated that other practical concerns such as flexible services in terms of times and dates, and appropriate location of services also reduced carers' burden and stress. Furthermore, carers also stressed the need for access to support for themselves. Carer support groups were said to be of great value as an informal way of receiving regular support from others who have had similar experiences.

Carers valued the provision of clear and comprehensible information. However what was also evident from the literature was that carers valued the information more at certain points in the care pathway. For example, carers stated they needed more information during the early stages of assessment and first episode psychosis, but the information should not be too copious (and thus overwhelming) or too brief (and therefore of little use). Furthermore, carers stressed that an individualised approach to providing information should be used and that the information given to them should be in a format and delivered at times tailored to the specific needs of the carer and the service user.

A key point present across identified themes was that carers, like service users, would like an atmosphere of optimism and hope when in contact with services and healthcare professionals. The GDG considered this important and decided to reflect this in the recommendations.

Carers were generally positive about, and suggested components for, a self-management toolkit. They were concerned, however, that healthcare professionals might see the toolkit as a reason to disengage with them. Carers' experience of group psychoeducation was positive overall, but carers stated that the aim of the group should be very clear in order to avoid disappointment if the group did not meet individual needs. Carer support groups were found to be very useful and valued by carers.

The literature evaluating the effectiveness of the carer-focused interventions was limited but promising. Psychoeducation and support groups both provided evidence of benefits on carers' experience of care, quality of life and satisfaction. A self-management toolkit and bibliotherapy intervention did not statistically show any benefit over control, although a trend favouring the interventions was observed. The review of carer-focused interventions included trials of people with psychosis, schizophrenia or bipolar disorder as well as mixed diagnosis populations. Although the majority of the available evidence was with a psychosis and schizophrenia population, the GDG believed that the issues faced by carers of adults with psychosis and schizophrenia would be applicable to carers of adults with bipolar disorder or other severe mental illnesses. The analyses were highly underpowered and the GDG considered that the further trials would increase the power of the analysis and could show a benefit over control.

On the basis of the quantitative review of interventions for carers, the GDG decided that interventions specifically aimed to help carers should be provided. The evidence did not permit a recommendation of a particular type of intervention. However, it was evident, from both the qualitative and quantitative literature, that carers require support, education and information and therefore the GDG made a recommendation that states the components of an intervention that should be provided for the carer.

### *Trade-off between net health benefits and resource use*

No economic studies assessing the cost effectiveness of interventions aimed at improving carers' experience were identified. The cost of providing such interventions was estimated at roughly between £190 and £1,095 (mean of £582) in 2011/12 prices. The GDG judged this cost to be small taking into account the effects of the intervention, leading to a reduction in carers' burden, potential depression and other health vulnerabilities which may be costly to other parts of the NHS, especially considering that the burden of care can last for many years and increase carer morbidity and stress. In addition, increased knowledge and improved confidence helps carers to contribute to care more effectively. Despite the small, emerging evidence base, interventions that aim to improve carers' experience of caring and of services were judged by the GDG to represent good value for money and be worth the investment.

### *Quality of the evidence*

The evidence ranged from very low to moderate quality across critical outcomes. Reasons for downgrading included: risk of bias in the included studies and high

heterogeneity or lack of precision in confidence intervals. Wide confidence intervals were also a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most and the small number of participants in the included trials could have contributed to the lack of precision. Furthermore, some of the included studies for support groups were based in settings that may not be appropriate to the UK healthcare setting (for example, East Asia). In these instances, the evidence was downgraded for indirectness. The evidence showed a benefit of support groups for the carer, but the GDG was cautious about making a recommendation specifically for support groups for this reason. However, the GDG believed that there was also qualitative evidence of great benefits of support groups and therefore could still be considered when drafting recommendations.

### *Other considerations*

At the time of drafting the 2014 guideline, the *Service User Experience in Adult Mental Health* guidance was in the public domain. The GDG judged that it was of prime importance that a cross-reference to this guidance was made because the 2014 guideline has not re-reviewed any of the qualitative evidence for service user experience.

The GDG considered all identified themes to be important and as a basis for recommendations. However, they also discussed that the recommendations should not be biased towards the carer over the service user's needs, but should be complementary. This is likely to benefit both the carer and the service user because a carer who is well informed and supported is more likely to provide better support and care for the service user. This is also important because carers are an integral part of family intervention. The GDG considered that although this chapter does not explicitly review family intervention (the evidence for it was reviewed for the 2009 guideline [see Chapter 9] ), it remains essential that the offer of any carer-focused intervention is a part of family intervention. Consideration should be given to the most appropriate timing for psychoeducation offered on an individual basis.

The GDG discussed the term 'psychoeducation' used to describe some of the interventions reviewed. The GDG felt that the term was outdated and that it does not reflect the nature of current interventions, which do not aim to 'teach' things. Interventions that showed some benefit for the carer usually included aspects that also provided emotional support for the carer. The GDG decided to use the term 'education and support', which they judged to be appropriate in underlining the dyadic relationship between the healthcare professional or worker providing the education and support and the carer to emphasise the fact that the intervention is usually more than the provision of written information. The GDG also decided that the recommendation should contain guidance about what education and support programmes should entail.

## **4.6 RECOMMENDATIONS**

### **4.6.1 Clinical practice recommendations**

**4.6.1.1** Offer carers of people with psychosis or schizophrenia an assessment (provided by mental health services) of their own needs and discuss with them their strengths and views. Develop a care plan to address any identified needs, give a copy to the carer and their GP and ensure it is reviewed annually. [new 2014]

**4.6.1.2** Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this. [new 2014]

**4.6.1.3** Give carers written and verbal information in an accessible format about:

- diagnosis and management of psychosis and schizophrenia
- positive outcomes and recovery
- types of support for carers
- role of teams and services
- getting help in a crisis.

When providing information, offer the carer support if necessary. [new 2014]

**4.6.1.4** As early as possible negotiate with service users and carers about how information about the service user will be shared. When discussing rights to confidentiality, emphasise the importance of sharing information about risks and the need for carers to understand the service user's perspective. Foster a collaborative approach that supports both service users and carers, and respects their individual needs and interdependence. [new 2014]

**4.6.1.5** Review regularly how information is shared, especially if there are communication and collaboration difficulties between the service user and carer. [new 2014]

**4.6.1.6** Include carers in decision-making if the service user agrees. [new 2014]

**4.6.1.7** Offer a carer-focused education and support programme, which may be part of a family intervention for psychosis and schizophrenia, as early as possible to all carers. The intervention should:

- be available as needed
- have a positive message about recovery. [new 2014]

### **4.6.2 Research recommendation**

**4.6.2.1** What are the benefits for service users and carers for family intervention combined with a carer-focused intervention compared with family intervention alone? [new 2014]

# 5 PREVENTING PSYCHOSIS AND SCHIZOPHRENIA: TREATMENT OF AT RISK MENTAL STATES

This chapter is new for the 2014 guideline. It is taken from a review undertaken for *Psychosis and Schizophrenia in Children and Young People* (NCCMH, 2013 [full guideline]) of recognition of at risk mental states and of pharmacological, psychosocial and dietary interventions for people at risk of developing psychosis and schizophrenia. The review of the interventions was updated by a subsequent systematic review by Stafford and colleagues (2013). The populations in the studies in the review included people over the age of 18 years and were, therefore, deemed relevant by the GDG for the 2014 guideline.

## 5.1 INTRODUCTION

Over the past 2 decades there has been a wealth of research examining the possibility of early recognition of psychosis, with an emphasis on reducing duration of untreated psychosis (DUP), which has been shown to be associated with poor outcomes. More recently, there has also been increased interest in the identification of people who are at high risk of developing a first psychotic episode with the hope that intervention could prevent or delay the development of a psychosis. Many people who go on to develop a psychosis experience a variety of psychological, behavioural and perceptual disturbances prior to the psychosis, sometimes for several months. Previously described as a prodromal period, most studies have adopted other terms including at risk, or ultra-high risk, states.

### 5.1.1 Recognition, identification and treatment strategies for at risk mental states

Recent studies have examined the feasibility of detecting and treating people in the 'at risk' stage, prior to the development of psychosis. This approach rests on three assumptions: (1) it is possible to detect such people; (2) these people will be at markedly increased risk of later psychosis; and (3) an effective intervention will reduce this risk. There is evidence to support (1) and (2) in people with a strong family history of psychosis who are therefore at high genetic risk (Miller et al., 2001) and in those reporting particular perceptual abnormalities (Klosterkotter et al., 2001). When those at risk have been identified, there is the question of what can effectively be done to prevent, delay or ameliorate psychosis. To date, there have been nine RCTs, each using similar operational definitions of 'at risk', which have reported findings regarding antipsychotic medication, omega-3 polyunsaturated fatty acids and/or psychological interventions including CBT. These studies have been conducted in Australia (McGorry et al., 2002; Phillips et al., 2009), North America (Addington et al., 2011; McGlashan et al., 2006) and Europe (Amminger et al., 2010; Bechdolf et al., 2012; Morrison et al., 2007; Morrison et al., 2004) and have aimed to

achieve one or more of the following outcomes: to prevent, delay or ameliorate rates of transition to psychosis; to reduce severity of psychotic symptoms; to reduce distress and emotional dysfunction; and to improve quality of life.

The following therapeutic approaches have been identified:

- pharmacological interventions:
  - olanzapine
  - risperidone
- dietary interventions:
  - omega-3 fatty acids
- psychological interventions:
  - cognitive behavioural therapy (CBT)
  - integrated psychological therapy
  - supportive counselling.

Some researchers have combined more than one intervention in order to improve the likelihood of achieving the intended outcomes. For example, an antipsychotic medication can be combined with a psychological therapy such as cognitive therapy, or several psychosocial interventions may be combined (such as cognitive therapy, CRT and family intervention). These combinations do not form a homogenous group and therefore cannot be analysed together in a meta-analysis.

## 5.2 CLINICAL REVIEW PROTOCOL FOR AT RISK MENTAL STATES FOR PSYCHOSIS AND SCHIZOPHRENIA

A summary of the review protocol, including the review questions, information about the databases searched and the eligibility criteria used for this section of the guideline can be found in Table 20. (A full review protocol can be found in Appendix 6 and further information about the search strategy can be found in Appendix 13).

**Table 20: Clinical review protocol for the review of at risk mental states for psychosis and schizophrenia**

Component	Description
<i>Review questions</i>	For people who are at risk of developing psychosis <sup>1</sup> and schizophrenia (at risk mental state), does the provision of pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes? <sup>2</sup>
<i>Objectives</i>	To evaluate if pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes for people who are at risk of developing psychosis and schizophrenia.
<i>Population</i>	<p><b>Inclusion:</b> People considered to be at high risk of developing a first episode psychosis.</p> <p><b>Exclusion:</b> Study samples consisting of individuals with a formal diagnosis of psychosis, schizophrenia or bipolar disorder.</p>
<i>Interventions</i>	Licensed antipsychotics drugs. <sup>2</sup>



	<p>Psychological interventions, including:</p> <ul style="list-style-type: none"> <li>• CBT</li> <li>• CRT</li> <li>• Counselling and supportive psychotherapy</li> <li>• Family intervention (including family therapy)</li> <li>• Psychodynamic psychotherapy and psychoanalysis</li> <li>• Psychoeducation</li> <li>• Social skills training</li> <li>• Arts therapies</li> </ul> <p>Dietary interventions, including:</p> <ul style="list-style-type: none"> <li>• Any dietary/nutritional supplements</li> </ul>
<i>Comparison</i>	<p>Alternative management strategies:</p> <ul style="list-style-type: none"> <li>• Placebo</li> <li>• Treatment as usual</li> <li>• Waitlist</li> </ul> <p>Any of the above interventions offered as an alternative management strategy.</p>
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Transition to psychosis.</li> <li>• Time to transition to psychosis.</li> </ul>
<i>Important but not critical outcomes</i>	<ul style="list-style-type: none"> <li>• Mental state (symptoms, depression, anxiety, mania)</li> <li>• Mortality (including suicide)</li> <li>• Global state</li> <li>• Psychosocial functioning</li> <li>• Social functioning</li> <li>• Leaving the study early for any reason</li> <li>• Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity)</li> </ul>
<i>Electronic databases</i>	<p>Core databases: Embase, MEDLINE, MEDLINE In-Process.</p> <p>Topic-specific databases: PsycINFO.</p>
<i>Date searched</i>	2011 to October 2013
<i>Study design</i>	Systematic reviews
<i>Review strategy</i>	<ul style="list-style-type: none"> <li>• This updates an existing review (Stafford et al., 2013) in which searches for systematic reviews and RCTs were conducted to November 2011. RCT evidence was identified from the Stafford review (2013), and from searches conducted for Chapter 5 of CG155, generated to May 2012.</li> <li>• Two independent reviewers reviewed the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol.</li> <li>• The initial approach was to conduct a meta-analysis evaluating the benefits and harms of pharmacological, psychological, dietary and combination treatment. However, in the absence of adequate data, the literature was presented via a narrative synthesis of the available evidence.</li> <li>• Unpublished data was included when the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence had to be submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline. Unpublished data was not included where the evidence submitted was commercial and in confidence.</li> </ul>
<p><i>Note.</i> <sup>1</sup> People who are at risk of developing psychosis and those who have early psychosis but do not have a formal diagnosis of either schizophrenia or bipolar disorder.</p>	

### 5.2.1 Ethical considerations

There has been considerable debate within the scientific and clinical communities regarding the desirability of ‘labelling’ people as being at high risk of developing psychosis and schizophrenia. This is partly because the rates of transition suggest that the majority of such samples (between 80 and 90%) do not convert to first episode psychosis within a 12-month period (that is, there are many ‘false positives’), and there is some evidence that these rates are declining (Yung et al., 2007). This may mean exposing people to risks associated with the label, such as unnecessary stigma (Bentall & Morrison, 2002; Yang et al., 2010), restrictions that people may impose upon themselves (such as avoidance of stress) (Warner, 2001) and unwanted consequences for employment or obtaining insurance, for example (Corcoran et al., 2010). There are also concerns about the risks of exposure to unnecessary treatments with potential adverse effects within this population, and hence the risks and benefits of any intervention must be balanced carefully (Bentall & Morrison, 2002; Warner, 2001). The proposal to include a psychosis risk syndrome, so-called ‘attenuated psychotic disorder’ in DSM-5, has led to many concerns for such reasons (Carpenter, 2009; Corcoran et al., 2010; Morrison et al., 2010). Nevertheless, the GDG considered that the benefits for individuals, families and the wider society that could result from preventing the development of psychosis is so substantial, given the often devastating effects that many people experience as a result of psychosis, that a full review of strategies to prevent psychosis in at risk states outweighed these important ethical considerations.

## 5.3 PHARMACOLOGICAL INTERVENTIONS

### 5.3.1 Studies considered

The GDG selected an existing review (Stafford et al., 2013) as the basis for this section of the guideline. The existing Stafford review (2013) included four RCTs (N = 358 ) providing relevant clinical evidence and meeting the eligibility criteria for the review: MCGLASHAN2003 (McGlashan et al., 2003), MCGORRY2002 (McGorry et al., 2002), PHILLIPS2009 (Phillips et al., 2009), RUHRMANN2007 (Ruhrmann et al., 2007). Three studies were published in peer reviewed journals between 2002 and 2007 and one study contained unpublished data (PHILLIPS2009). All studies contained participants who were judged to be at risk of developing psychosis on the basis of a clinical assessment identifying prodromal features. Further information about both included and excluded studies can be found in (Stafford et al., 2013).

Of the four included trials, there was one comparing olanzapine with placebo, two comparing risperidone plus CBT with supportive counselling, one comparing risperidone plus CBT with placebo plus CBT, and one comparing amisulpride and a needs based intervention with the needs based intervention alone. PHILLIPS2009 had three treatment groups and was included in two of the pair wise comparisons (see Table 21 for a summary of the study characteristics).

**Table 21: Study information table for trials of antipsychotic medication**

	<b>Olanzapine versus placebo</b>	<b>Risperidone + CBT versus supportive counselling</b>	<b>Risperidone + CBT versus placebo + CBT</b>	<b>Amisulpride + NBI versus NBI</b>
<i>Total no. of studies (N)</i>	1 (N = 60)	2 (N = 130)	1 (N = 87)	1 (N = 124)
<i>Study ID</i>	MCGLASHA N2003	(1) MCGORRY2002 (2) PHILLIPS2009	PHILLIPS2009	RUHRMANN2007
<i>Screening tool</i>	SIPS <sup>1</sup>	(1) Not reported (2) CAARMS <sup>2</sup>	CAARMS2	ERiraos <sup>4</sup>
<i>Diagnosis</i>	At-risk mental state	Ultra-high risk mental state	Ultra-high risk mental state	
<i>Mean age (range)</i>	17.8 (range 12 to 36)	(1) 20 (range 14 to 28) (2) 17.9 (not reported) <sup>3</sup>	17.9 (not reported) <sup>3</sup>	25.6 (not reported)
<i>Sex (% male)</i>	65	(1) 58 (2) 39 <sup>3</sup>	39 <sup>3</sup>	56
<i>Ethnicity (% white)</i>	67	(1)–(2) Not reported	Not reported	Not reported
<i>Mean (range) medication dose (mg/day)</i>	8 (range 5 to 15)	(1) 1.3 (range 1 to 2) (2) 2 (not reported)	2 (not reported)	118.7 (range 50 to 800)
<i>Sessions of therapy</i>	N/A	(1) Mean (SD) sessions attended: CBT: 11.3 (8.4); Supportive counselling: 5.9 (4.3). (2) Up to of 35 hours of CBT or supporting counselling	Up to 35 hours	Not reported
<i>Treatment length (weeks)</i>	52	(1) 26 (2) 52	52	12
<i>Treatment follow-up (weeks)</i>	104	(1) 156 to 208 (2) 104	104	N/A
<i>Setting</i>	Specialist clinic/ward	(1)–(2) Specialist clinic/ward	Specialist clinic/ward	Specialist clinic/ward
<i>Country</i>	US	(1)–(2) Australia	Australia	Germany

*Note.* N = Total number of participants. CBT= Cognitive behavioural therapy; NBI=Needs based intervention  
<sup>1</sup>Structured Interview for Prodromal Symptoms.  
<sup>2</sup>Comprehensive assessment of at-risk mental states.  
<sup>3</sup>In whole study (N = 115; PHILLIPS2009 is a three way comparison evaluating risperidone, CBT and SC).  
<sup>4</sup>Early Recognition Inventory

### **5.3.2 Clinical evidence for olanzapine versus placebo**

#### *Efficacy*

One study (N = 60) compared olanzapine with placebo. At 1 year post-treatment 16 participants had transitioned to psychosis and there was no statistically significant difference between groups. Effects on symptoms of psychosis, depression, and mania were also not significant. Evidence from each reported outcome and overall quality of evidence are presented in Table 22 and Table 23.

#### *Side effects*

There were more olanzapine dropouts at 1 year, but the difference was not statistically significant. Participants taking olanzapine gained significantly more weight at 1-year post-treatment. Furthermore, compared with the placebo group the sitting pulse of participants in the olanzapine group increased significantly more from baseline to post-treatment (very low quality evidence). Effects on standing pulse were not significant. At 104 weeks' follow-up transition to psychosis and side effects were measured, however, the data were considered unusable because there were fewer than 10 people remaining in each group. Evidence from each reported outcome and overall quality of evidence are presented in Table 22 and Table 23.

### **5.3.3 Clinical evidence for risperidone plus CBT versus supportive counselling**

#### *Efficacy*

Two studies (N = 130) compared risperidone plus CBT with supportive counselling. Within the first 26 weeks of treatment, fewer people receiving risperidone plus CBT transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder), but these trials included 17 events (very low quality evidence). By 52 weeks' follow-up the effect was no longer significant and this remained non-significant at 156 to 208 weeks' follow-up. At follow-up, only data for completers were reported and therefore a sensitivity analysis for transition to psychosis was conducted, assuming dropouts had made transition. In sensitivity analysis the effect remained non-significant. Both studies reported mean endpoint scores for symptoms of psychosis, quality of life, depression, anxiety, mania and psychosocial functioning. No significant differences between treatment groups were found on these outcomes at post-treatment or follow-up. At post-treatment, there was no dropout in one study (MCGORRY2002) and dropout in the other (PHILLIPS2009) was similar between groups. Evidence from each reported outcome and overall quality of evidence are presented in Table 24, Table 25, and Table 26.

#### *Side effects*

For the participants for whom side effect data were reported, there was no significant difference between groups at post-treatment (see Table 24).

**Table 22: Summary of findings table for outcomes reported for olanzapine versus placebo at 52 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	-0.12 [-0.63, 0.39]	N/A	Very low <sup>1,2,3</sup>
<i>Positive symptoms (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	-0.40 [-0.91, 0.12]	N/A	Very low <sup>1,2,3</sup>
<i>Negative symptoms (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	0.05 [-0.46, 0.56]	N/A	Very low <sup>1,2,3</sup>
<i>Global state (severity) (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	-0.17 [-0.68, 0.34]	N/A	Very low <sup>1,2,3</sup>
<i>Depression (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	0.32 [-0.19, 0.83]	N/A	Very low <sup>1,2,3</sup>
<i>Mania (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	-0.15 [-0.66, 0.36]	N/A	Very low <sup>1,2,3</sup>
<i>Psychosocial functioning (SMD)</i>	MCGLASHAN2003	K = 1, N = 59	-0.16 [-0.67, 0.35]	N/A	Very low <sup>1,2,3</sup>
<i>Transition to psychosis (RR)</i>	MCGLASHAN2003	K = 1, N = 60	0.43 [0.17, 1.08]	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	MCGLASHAN2003	K = 1, N = 60	1.59 [ 0.88, 2.88]	N/A	Very low <sup>1,2,3</sup>
<i>Weight gain (kg; SMD)</i>	MCGLASHAN2003	K = 1, N = 59	1.18 [0.62, 1.73]*	N/A	Very low <sup>1,2,3</sup>
<i>Sitting pulse (beats per minute [BPM]; SMD)</i>	MCGLASHAN2003	K = 1, N = 60	0.61 [0.08, 1.13]*	N/A	Very low <sup>1,2,3</sup>
<i>Standing pulse (BPM; SMD)</i>	MCGLASHAN2003	K = 1, N = 59	0.37 [-0.15, 0.88]	N/A	Very low <sup>1,2,3</sup>
<p>Note. <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p>*Favours placebo</p> <p><sup>1</sup> Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup> Serious risk of reporting bias</p>					

**Table 23: Summary of findings table for outcomes reported for olanzapine versus placebo at 104 weeks' follow-up (change scores from post-treatment until follow-up when no treatment was received)**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Leaving the study early for any reason (RR)</i>	MCGLASHAN2003	K = 1, N = 60	0.98 [0.71, 1.35]	N/A	Very low <sup>1,2,3</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.<sup>1</sup>Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

**Table 24: Summary of findings table for outcomes reported for risperidone plus CBT versus supportive counselling at post-treatment**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 102	0.15 [-0.39, 0.70]	(P = 0.12); I <sup>2</sup> = 59%	Very low <sup>1,2,3</sup>
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.02 (-0.33, 0.37)	(P = 0.39); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.13 (-0.68, 0.94)	(P = 0.02); I <sup>2</sup> = 81%	Very low <sup>1,2,3</sup>
Depression (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.24 (-0.12, 0.59)	(P=0.003) I <sup>2</sup> = 88%	Very low <sup>1,2,3</sup>
Mania (SMD)	MCGORRY2002	K = 1, N = 59	-0.20 [-0.71, 0.32]	N/A	Very low <sup>1,2,3</sup>
Anxiety (SMD)	MCGORRY2002	K = 1, N = 59	-0.15 [-0.66, 0.36]	N/A	Very low <sup>1,2,3</sup>
Psychosocial functioning (SMD)	PHILLIPS2009	K = 1, N = 43	-0.12 [-0.73, 0.49]	N/A	Very low <sup>1,2,3</sup>
Quality of life (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	-0.13 [-0.49, 0.22]	(P = 0.31); I <sup>2</sup> = 2%	Very low <sup>1,2,3</sup>
Transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.35 [0.13, 0.95]	(P = 0.44); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.76 [0.28, 2.03]	N/A [no events observed by MCGORRY2002]	Very low <sup>1,2,3</sup>
EPS (RR)	PHILLIPS2009	K = 1, N = 21	0.55 [0.13, 2.38]	N/A	Very low <sup>1,2,3</sup>
<p>Note.</p> <p><sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data)</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

**Table 25: Summary of findings table for outcomes reported for risperidone plus CBT versus supportive counselling at 52 weeks' follow-up**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K=2, N = 101	0.07 [-0.32, 0.46]	(P = 0.39); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K=2, N = 101	0.05 [-0.35, 0.44]	(P = 0.90); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K=2, N = 101	0.08 [-0.31, 0.47]	(P = 0.41); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Depression (SMD)	MCGORRY2002 PHILLIPS2009	K=2, N = 68	0.15 [-0.33, 0.62]	(P = 0.93); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Mania (SMD)	MCGORRY2002	K=1, N = 59	0.00 [-0.51, 0.51]	N/A	Very low <sup>1,2,3</sup>
Anxiety (SMD)	MCGORRY2002	K = 1, N = 59	0.06 [-0.45, 0.57]	N/A	Very low <sup>1,2,3</sup>
Psychosocial functioning (SMD)	MCGORRY2002	K = 1, N = 59	0.00 [-0.51, 0.51]	N/A	Very low <sup>1,2,3</sup>
Quality of life (SMD)	MCGORRY2002 PHILLIPS2009	K=2, N = 102	-0.07 [-0.46, 0.32]	(P = 0.84); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.63 [0.33, 1.21]	(P = 0.61); I <sup>2</sup> = 0%	Very low <sup>1,2,3</sup>
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	K=2, N = 130	0.85 [0.43, 1.67]	(P = 0.19); I <sup>2</sup> = 43%	Very low <sup>1,2,3</sup>
<p>Note. <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).</p> <p><sup>2</sup>Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.</p> <p><sup>3</sup>Serious risk of reporting bias.</p>					



**Table 26: Summary of findings table for outcomes reported for risperidone plus CBT versus supportive at 156 to 208 weeks' follow-up**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	MCGORRY2002	K = 1, N = 41	-0.33 [-0.96, 0.29]	N/A	Very low <sup>1,2,3</sup>
<i>Positive symptoms (SMD)</i>	MCGORRY2002	K = 1, N = 41	-0.04 [-0.66, 0.58]	N/A	Very low <sup>1,2,3</sup>
<i>Negative symptoms (SMD)</i>	MCGORRY2002	K = 1, N = 41	-0.24 [-0.87, 0.38]	N/A	Very low <sup>1,2,3</sup>
<i>Depression (SMD)</i>	MCGORRY2002	K = 1, N = 41	0.23 [-0.39, 0.86]	N/A	Very low <sup>1,2,3</sup>
<i>Mania (SMD)</i>	MCGORRY2002	K = 1, N = 41	-0.36 [-0.98, 0.27]	N/A	Very low <sup>1,2,3</sup>
<i>Anxiety (SMD)</i>	MCGORRY2002	K = 1, N = 41	0.14 [-0.49, 0.76]	N/A	Very low <sup>1,2,3</sup>
<i>Psychosocial functioning (SMD)</i>	MCGORRY2002	K = 1, N = 41	-0.15 [-0.77, 0.47]	N/A	Very low <sup>1,2,3</sup>
<i>Quality of life (SMD)</i>	MCGORRY2002	K = 1, N = 41	0.08 [-0.54, 0.71]	N/A	Very low <sup>1,2,3</sup>
<i>Completer analysis: transition to psychosis (RR)</i>	MCGORRY2002	K = 1, N = 41	0.59 [0.34, 1.04]	N/A	Very low <sup>1,2,3</sup>
<i>Number of participants requiring hospitalisation (RR)</i>	MCGORRY2002	K = 1, N = 41	0.51 [0.19, 1.33]	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	MCGORRY2002	K = 1, N = 59	0.57 [0.26, 1.28]	N/A	Very low <sup>1,2,3</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data)</p> <p><sup>2</sup>Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

### **5.3.4 Clinical evidence for risperidone plus CBT versus placebo plus CBT**

#### *Efficacy*

One study (N = 87) compared risperidone plus CBT with placebo plus CBT. By 52 weeks post-treatment, seven participants in each group had transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder) and there was no significant difference between groups. Differences in symptoms of psychosis, depression, psychosocial functioning and quality of life were not significant, and dropout was similar between groups. Evidence from each reported outcome and overall quality of evidence are presented in Table 27.

#### *Side effects*

For participants whom side effect data were reported experienced EPS (as measured by the UKU Neurologic Subscale). However, there was no significant difference between groups. Evidence from each reported outcome and overall quality of evidence are presented in Table 27.

### **5.3.5 Clinical evidence for amisulpride plus a 'needs based intervention' versus a 'needs based intervention'**

#### *Efficacy*

One study (N = 102) compared amisulpride and a needs based intervention with the needs based intervention alone. Transition to psychosis was not reported. Within six months, effects on total and negative symptoms of psychosis were not significant, but amisulpride was associated with a moderate reduction in positive symptoms, and depression. Evidence from each reported outcome and overall quality of evidence are presented in Table 28.

#### *Side effects*

The addition of amisulpride was associated with a moderate reduction in dropout. Of the 19 participants who dropped out of the amisulpride group, three were a result of adverse events provoked by prolactin-associated symptoms, that is, galactorrhoea in two participants and sexual dysfunction in another. There was however no significant difference between groups at post treatment. Evidence from each reported outcome and overall quality of evidence are presented in Table 28.

**Table 27: Summary evidence profile for outcomes reported for risperidone plus CBT versus placebo plus CBT at 52 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	PHILLIPS2009	K = 1, N = 51	-0.24 [-0.79, 0.31]	N/A	Very low <sup>1,2,3</sup>
<i>Positive symptoms (SMD)</i>	PHILLIPS2009	K = 1, N = 51	-0.07 [-0.62, 0.48]	N/A	Very low <sup>1,2,3</sup>
<i>Negative symptoms (SMD)</i>	PHILLIPS2009	K = 1, N = 51	0.12 [-0.43, 0.67]	N/A	Very low <sup>1,2,3</sup>
<i>Psychosocial functioning (SMD)</i>	PHILLIPS2009	K = 1, N = 9	0.24 [-0.31, 0.78]	N/A	Very low <sup>1,2,3</sup>
<i>Quality of life (SMD)</i>	PHILLIPS2009	K = 1, N = 52	-0.23 [-0.78, 0.33]	N/A	Very low <sup>1,2,3</sup>
<i>Transition to psychosis (RR)</i>	PHILLIPS2009	K = 1, N = 51	1.02 [0.39, 2.67]	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	PHILLIPS2009	K = 1, N = 56	1.09 [0.62, 1.92]	N/A	Very low <sup>1,2,3</sup>
<i>EPS (RR)</i>	PHILLIPS2009	K = 1, N = 87	0.87 [0.18, 4.24]	N/A	Very low <sup>1,2,3</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, allocation concealment, trial registration not found, uneven sample sizes).</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

**Table 28: Summary evidence profile for outcomes reported for amisulpride plus a ‘needs-based intervention’ versus a ‘needs-based intervention’ at up to 6 months’ follow-up**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)[95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	RUHRMANN2007	K = 1, N = 102	-0.36 [-0.75, 0.04]	N/A	Very low <sup>1,2,3</sup>
<i>Positive symptoms (SMD)</i>	RUHRMANN2007	K = 1, N = 102	-0.53 [-0.93, -0.13]	N/A	Very low <sup>1,2,3</sup>
<i>Negative symptoms (SMD)</i>	RUHRMANN2007	K = 1, N = 102	-0.26 [-0.65, 0.14]	N/A	Very low <sup>1,2,3</sup>
<i>Depression (SMD)</i>	RUHRMANN2007	K = 1, N = 102	-0.51 [-0.91, -0.11]	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	RUHRMANN2007	K = 1, N = 124	0.59 [0.38, 0.94]	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early due to side effects (RR)</i>	RUHRMANN2007	K = 1, N = 124	6.36 [0.34, 120.67]	N/A	Very low <sup>1,2,3</sup>
<p><i>Note.</i> <sup>a</sup> The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data)</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

### 5.3.6 Clinical evidence summary for pharmacological interventions

Four RCTs (N = 358) conducted in people with an at-risk mental state for psychosis or schizophrenia were reviewed. One study investigated the effect of an antipsychotic medication alone against placebo (two studies investigated the effect of an antipsychotic medication in combination with CBT against a psychological therapy and one study investigated the effect of antipsychotic medication in combination with a needs based intervention against a needs based intervention alone. The findings suggest that antipsychotic medication is no more effective than a psychological intervention or placebo in preventing transition to psychosis and has little or no effect in reducing psychotic symptoms. What is more, olanzapine treatment can result in significant weight gain.

## 5.4 DIETARY INTERVENTIONS

### 5.4.1 Studies considered

The GDG selected an existing review (Stafford et al., 2013) as the basis for this section of the guideline. The existing Stafford review (2013) included one RCT (N = 81) providing relevant clinical evidence that met the eligibility criteria for this review: AMMINGER2010 (Amminger et al., 2010) (see Table 29 for a summary of the study characteristics).

**Table 29: Study information table for trials of dietary interventions**

<b>Omega-3 fatty acids versus placebo</b>	
<i>Total no. of studies (N)</i>	1 (N = 81)
<i>Study ID</i>	AMMINGER2010
<i>Screening tool</i>	Positive and Negative Syndrome Scale (PANSS)
<i>Diagnosis</i>	Ultra-high risk mental state
<i>Mean age (range)</i>	16.4 (not reported)
<i>Sex (% male)</i>	33
<i>Ethnicity (% white)</i>	Not reported
<i>Mean (range) medication dose (mg/day)</i>	1200
<i>Treatment length (weeks)</i>	12
<i>Treatment follow-up (weeks)</i>	52
<i>Setting</i>	Specialist clinic/ ward
<i>Country</i>	Austria
<i>Funding</i>	Stanley Medical Research Institute

### 5.4.2 Clinical evidence for omega-3 fatty acids versus placebo

One study compared omega-3 polyunsaturated fatty acids ( $\omega$ -3 PUFAs) with placebo. At 12 weeks post-treatment significantly more participants in the placebo group had transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder). However, there were only nine events in total. As only data for completers were reported a sensitivity analysis for transition to psychosis was

conducted, assuming dropouts had made transition, and the effect became non-significant. No other outcomes were reported at this time point. At 52 weeks' follow-up including all participants randomised the effect was significant. Large effects on total symptoms of psychosis, positive and negative symptoms of psychosis, depression and psychosocial functioning also favoured omega-3 fatty acids at 52 weeks' follow-up. Dropout after 52 weeks was low and similar between groups. Evidence from each reported outcome and overall quality of evidence are presented in Table 30 and Table 31.

### **5.4.3 Clinical evidence summary for dietary interventions**

One RCT (N = 81) comparing omega-3 fatty acids with placebo was reviewed. Although the study was well conducted, sample sizes were small. The findings suggest that omega-3 fatty acids may be effective at preventing transition to psychosis and improving symptoms of psychosis, depression and psychosocial functioning in young people (low quality evidence). However, owing to the paucity of evidence (lack of independent replication) no robust conclusions can be made.

**Table 30: Summary of findings table for outcomes reported for omega-3 fatty acids versus placebo at 12 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Completer analysis: transition to psychosis (RR)</i>	AMMINGER2010	K = 1, N = 76	0.13 [0.02, 0.95]*	N/A	Low <sup>2, 3</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p>*Favours omega-3 fatty acids</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of reporting bias</p>					

**Table 31: Summary of findings table for outcomes reported for omega-3 fatty acids versus placebo at 52 weeks' follow-up**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	AMMINGER2010	K = 1, N = 81	-1.26 [-1.74, -0.78]*	N/A	Low <sup>1, 2</sup>
<i>Positive symptoms (SMD)</i>	AMMINGER2010	K = 1, N = 81	-2.08 [-2.63, -1.54]*	N/A	Low <sup>1, 2</sup>
<i>Negative symptoms (SMD)</i>	AMMINGER2010	K = 1, N = 81	-2.22 [-2.77, -1.66]*	N/A	Low <sup>1, 2, 3</sup>
<i>Depression (SMD)</i>	AMMINGER2010	K = 1, N = 81	-0.56 [-1.01, -0.12]*	N/A	Low <sup>2, 1, 2</sup>
<i>Psychosocial functioning (SMD)</i>	AMMINGER2010	K = 1, N = 81	-1.28 [-1.76, -0.80]*	N/A	Low <sup>1, 2</sup>
<i>Transition to psychosis (RR)</i>	AMMINGER2010	K = 1, N = 81	0.18 [0.04, 0.75]*	N/A	Low <sup>1, 2</sup>
<i>Leaving the study early for any reason (RR)</i>	AMMINGER2010	K = 1, N = 81	1.46 (0.26 to 8.30)	N/A	Low <sup>1, 2</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p>*Favours omega-3 fatty acids</p> <p><sup>1</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>2</sup>Serious risk of reporting bias</p>					

## 5.5 PSYCHOSOCIAL INTERVENTIONS

### 5.5.1 Studies considered

The GDG selected an existing review (Stafford et al., 2013) as the basis for this section of the guideline. The existing Stafford review (2013) included seven RCTs (N = 879 ) providing relevant clinical evidence met the eligibility criteria for this review: ADDINGTON2011 (Addington et al., 2011), MORRISON2004 (Morrison et al., 2004), MORRISON2011 (Brown et al., 2011), PHILLIPS2009 (Phillips et al., 2009), VANDERGAAG2012 (Attux et al., 2013). Of these, two contained some unpublished data (MORRISON2004 and PHILLIPS2009) and the remaining trials were published between 2004 and 2012. Further information about the included and excluded studies can be found in Stafford et al. (2013).

Of the seven included trials, five studies compared individual CBT with supportive counselling, one study compared a multimodal intervention (integrated psychological therapy) with supportive counselling, and one study compared a similar multimodal intervention with standard care (see Table 32 for a summary of the study characteristics).

### 5.5.2 Clinical evidence for CBT versus supportive counselling

Five RCTs (N = 672) compared CBT with supportive counselling. Within the first 26 weeks of treatment CBT did not significantly reduce transition to psychosis (defined as the development of a DSM-IV psychotic disorder) compared with supportive counselling, observing 40 events in total (N = 591). However, at 52 weeks' follow-up, moderate quality evidence found a medium effect of CBT on transition to psychosis. As one study in the meta-analysis only reported data for completers a sensitivity analysis for transition to psychosis (assuming dropouts had made transition) was conducted. In sensitivity analysis this effect remained significant. Furthermore, at 78 weeks' (or more) follow-up CBT was significantly associated with fewer transitions to psychosis; however, this did not remain significant in sensitivity analysis.

Combined effects for total symptoms of psychosis, positive and negative symptoms of psychosis, depression, anxiety, psychosocial functioning and quality of life were not significant at any time point. However, one study (VANDERGAAG2012) reported secondary outcomes only for participants who had not transitioned; participants with the most severe symptoms were omitted from these analyses. In sensitivity analyses excluding this study, there was a significant effect for positive symptoms at 52 weeks' follow-up, but effects for other outcomes remained non-significant. Dropout was similar between groups within the first 6 months. Evidence from each reported outcome and overall quality of evidence are presented in Table 33, Table 34, and Table 35.



**Table 32: Study information table for trials of psychosocial interventions**

	<b>CBT versus supportive counselling</b>	<b>Integrated psychological therapy versus supportive counselling</b>	<b>Integrated psychological therapy versus standard care</b>
<i>Total no. of studies (N)</i>	5 (N = 672)	1 (N = 128)	1 (N = 79)
<i>Study ID</i>	(1) ADDINGTON2011 (2) MORRISON2004 (3) MORRISON2011 (4) PHILLIPS2009 (5) VANDERGAAG2012	BECHDOLF2012	NORDONTOFT2006
<i>Screening tool</i>	(1) SIPS (2) PANSS (3)-(5) CAARMS	Early Recognition Inventory and Interview for the Retrospective Assessment of the Onset of Schizophrenia	ICD-10
<i>Diagnosis</i>	'At risk/ ultra-high risk mental state'	Early initial prodromal state	Schizotypal disorder
<i>Mean age (range)</i>	(1) 20.9 (not reported) (2) 22 (range 16 to 36) (3) 20.7 (range 14 to 34) (4) 17.9 (not reported) <sup>1</sup> (5) 22.7	25.8 (not reported)	(2) 24.9 (not reported)
<i>Sex (% male)</i>	(1) 71 (2) 67 (3) 63 (4) 39 <sup>1</sup> (5) 49	66	67
<i>Ethnicity (% white)</i>	(1) 57 (2) Not reported (3) 88 (4)-(5) Not reported	Not reported	Not reported
<i>Sessions of therapy</i>	(1) CBT and supportive counselling: up to 20 (2) CBT: 26; supportive	25 individual therapy sessions; 15 group sessions; 12 CRT sessions; three information and counselling of relatives	Needs based

	counselling: 13 (3) CBT: 26; supportive counselling: not reported (4) Up to of 35 hours (5) CBT: up to 26; supportive counselling: not reported	sessions	
<i>Treatment length (weeks)</i>	(1) 26 (2) 52 (3) 26 (4) 52 (5) 26	52	104
<i>Treatment follow-up (weeks)</i>	(1) 78 (2) 156 (3) 104 (4) 52 (5) 78	104	N/ A
<i>Setting</i>	(1) Specialist clinic/ ward (2)-(3) Not reported (4) Specialist clinic/ ward (5) Mental health centres (multisite)	Specialist clinic/ ward	Specialist clinic/ ward
<i>Country</i>	(1) Canada (2)-(3) UK (4) Australia (5) Netherlands	Germany	Denmark
Note. <sup>1</sup> In the whole study (a three-way comparison evaluating risperidone, CBT and supportive counselling, N = 115).			

**Table 33: Summary of findings table for outcomes reported for CBT versus supportive counselling at post-treatment (within 26 weeks)**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
Total symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	K = 2, N = 123	0.004[-0.32, 0.40]	(P = 0.77); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
Completer analysis: positive symptoms (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 489	-0.12 [-0.30, 0.06]	(P = 0.90); I <sup>2</sup> = 0%	Moderate <sup>1</sup>
Negative symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	K = 2, N = 123	0.17 [-0.19, 0.53]	(P = 0.54); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
Depression (completer analysis) (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 478	0.12 [-0.20, 0.47]	(P = 0.03); I <sup>2</sup> = 67%	Low <sup>1,2</sup>
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 172	0.01 [-0.28, 0.31]	N/A	Low <sup>1,2</sup>
Psychosocial functioning (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 291	0.02 [-0.22, 0.26]	(P = 0.96); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
Quality of life (completer analysis) (SMD)	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 3, N = 383	0.01 [-0.19, 0.21]	(P = 0.78); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
Transition to psychosis (completer analysis) (RR)	ADDINGTON2011* MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 591	0.62 [0.29, 1.31]	(P = 0.31); I <sup>2</sup> = 17%	Low <sup>1,2</sup>
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 411	1.01 [0.75, 1.36]	(P = 0.93); I <sup>2</sup> = 0%	Low <sup>1,3</sup>
<p>Note. <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome. <sup>b</sup>The sensitivity analysis excluded VANDERGAAG2012* 15 weeks during treatment <sup>1</sup>Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data). <sup>2</sup>Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. <sup>3</sup> I<sup>2</sup> ≥ 50%, p&lt;.05</p>					

**Table 34: Summary of findings table for outcomes reported for CBT versus supportive counselling at 52 weeks' follow-up**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	0.05 [-0.27, -0.37]	(P = 0.08); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Positive symptoms (completer analysis) (SMD)</i>	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 493	-0.17 [-0.35, 0.01]	(P = 0.47); I <sup>2</sup> = 0%	Moderate <sup>1</sup>
<i>Negative symptoms (SMD)</i>	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	0.11 [-0.21, 0.43]	(P = 0.95); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Completer analysis: depression (SMD)</i>	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 385	-0.05 [-0.25, 0.15]	(P = 0.63); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Anxiety (social; SMD)</i>	MORRISON2011	K = 1, N = 188	0.15 [-0.15, 0.44]	N/A	Low <sup>1,2</sup>
<i>Psychosocial functioning (SMD)</i>	ADDINGTON2011 MORRISON2011	K = 2, N = 240	-0.10 [-0.36, 0.15]	(P = 0.70); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Completer analysis: quality of life (SMD)</i>	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 3, N = 329	-0.01[-0.23, 0.21]	(P = 0.75); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Completer analysis: transition to psychosis (RR)</i>	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 645	0.54 [ 0.34, 0.86]	(P = 0.64); I <sup>2</sup> = 0%	Moderate <sup>2</sup>

<i>Leaving the study early for any reason (RR)</i>	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 665	1.03 [0.82, 1.30]	(P = 0.83); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<p>Note. <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>b</sup>The sensitivity analysis excluded VANDERGAAG2012</p> <p>*Favours CBT</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, , trial registration could not be found, missing data).</p> <p><sup>2</sup>Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p>					

**Table 35: Summary of findings table for outcomes reported for CBT versus supportive counselling ≥78 weeks' follow-up**

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Total symptoms (SMD)</i>	ADDINGTON2011	K = 1, N = 51	-0.04 [-0.59, 0.51]	N/A	Low <sup>1,2</sup>
<i>Completer analysis: positive symptoms (SMD)</i>	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 256	-0.17 [-0.42, 0.07]	(P = 0.72); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Sensitivity analysis: positive symptoms (SMD)<sup>b</sup></i>	ADDINGTON2011 MORRISON2011	K = 2, N = 116	-0.14 [-0.50, 0.23]	(P = 0.45); I <sup>2</sup> = 0%	-
<i>Negative symptoms (SMD)</i>	ADDINGTON2011	K = 1, N = 51	-0.10 [-0.65, 0.45]	N/A	Low <sup>1,2</sup>
<i>Completer analysis: depression (SMD)</i>	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 352	-0.11[-0.36, 0.13]	(P = 0.49); I <sup>2</sup> = %	Low <sup>1,2</sup>
<i>Sensitivity analysis: depression (SMD)<sup>b</sup></i>	ADDINGTON2011 MORRISON2011	K = 2, N = 112	-0.05[-0.46, 0.37]	(P = 0.27); I <sup>2</sup> = 19%	-
<i>Anxiety (social; SMD)</i>	MORRISON2011	K = 1, N = 58	-0.46 [-0.99, 0.06]	N/A	Low <sup>1,2</sup>
<i>Psychosocial functioning (SMD)</i>	ADDINGTON2011	K = 2, N = 116	-0.03 [-0.45, 0.40]	(P = 0.25); I <sup>2</sup> = 25%	Low <sup>1,2</sup>

	MORRISON2011				
<i>Completer analysis: quality of life (SMD)</i>	MORRISON2011 VANDERGAAG2012	K = 2, N = 188	0.18 [-0.10, 0.47]	(P = 0.39); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Sensitivity analysis: quality of life (SMD)<sup>b</sup></i>	MORRISON2011	K = 1, N = 48	0.40[-0.17, 0.98]	N/A	-
<i>Completer analysis: transition to psychosis (RR)</i>	ADDINGTON2011 MORRISON2011 MORRISON2004 VANDERGAAG2012	K = 4, N = 570	0.63 [0.40, 0.99]	(P = 0.48); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<i>Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)</i>	ADDINGTON2011 MORRISON2011 MORRISON2004 VANDERGAAG2012	K = 4, N = 595	0.55 [0.25, 1.19]	(P = 0.002); I <sup>2</sup> = 79%	Low <sup>1,2</sup>
<i>Leaving the study early for any reason (RR)</i>	ADDINGTON2011 MORRISON2004 MORRISON2011 VANDERGAAG2012	K = 4, N = 593	1.09 [0.88, 1.35]	(P = 0.58); I <sup>2</sup> = 0%	Low <sup>1,2</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>b</sup>The sensitivity analysis excluded VANDERGAAG2012</p> <p><sup>1</sup>Serious risk of bias (including unclear sequence generation, , trial registration could not be found, missing data).</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p>					

### **5.5.3 Clinical evidence for integrated psychological therapy versus supportive counselling**

One study (N = 128) compared integrated psychological therapy with supportive counselling in participants in the early initial prodromal state. Integrated psychological therapy included individual CBT, group skills training, CRT and family treatments, in the absence of antipsychotic medication. Transition to psychosis was defined as either the development of attenuated (subclinical) or transient symptoms (subthreshold psychosis) or a DSM-IV psychotic disorder. At 1-year post-treatment fewer people receiving integrated psychological therapy transitioned. The effect was maintained at 2 years' follow-up. Dropout was similar between groups at 1 year and 2 years post-treatment. Other symptoms were not reported as outcomes, although the PANSS and Global Assessment of Functioning (GAF) were recorded at baseline. Evidence from each reported outcome and overall quality of evidence are presented in Table 36 and Table 37.

### **5.5.4 Clinical evidence for integrated psychological therapy versus standard care**

One study (N = 79) compared integrated psychological therapy with standard care in first contact patients diagnosed with schizotypal disorder. Within 12 months, fewer people receiving integrated psychotherapy transitioned to psychosis, but the effect was not quite significant after 24 months. There was no effect for positive or negative symptoms of psychosis at either time point. Dropout was similar between groups at 12 months and 24 months. Evidence from each reported outcome and overall quality of evidence are presented in Table 38 and Table 39.

**Table 36: Summary of findings table for outcomes reported for integrated psychological therapy versus supportive counselling at 52 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Transition to psychosis (RR)</i>	BECHDOLF2012	K = 1, N = 125	0.19 [0.04, 0.81]*	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	BECHDOLF2012	K = 1, N = 128	1.55 [0.68, 3.53]	N/A	Very low <sup>1,2,4</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p>*Favours integrated psychological therapy</p> <p><sup>1</sup> Serious risk of bias (missing data).</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met</p> <p><sup>3</sup>Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder)</p> <p><sup>4</sup> Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state)</p>					

**Table 37: Summary of findings table for outcomes reported for integrated psychological therapy versus supportive counselling at 104 weeks follow-up**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Transition to psychosis (RR)</i>	BECHDOLF2012	K = 1, N = 125	0.32 [0.11, 0.92]*	N/A	Very low <sup>1,2,3</sup>
<i>Leaving the study early for any reason (RR)</i>	BECHDOLF2012	K = 1, N = 128	0.95 [0.61, 1.49]	N/A	Very low <sup>1,2,3</sup>
<p><i>Note.</i> ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference. *Favours integrated psychological therapy</p> <p><sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup> Serious risk of bias (missing data).</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.</p> <p><sup>3</sup>Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder).</p>					



**Table 38: Summary of findings table for outcomes reported for integrated psychological therapy versus standard care at 52 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Completer analysis: transition to psychosis (RR)</i>	NORDONTOFT2006	K = 1, N = 67	0.24 [0.07, 0.81]*	N/A	Low <sup>1,2</sup>
<i>Positive symptoms (SMD)</i>	NORDONTOFT2006	K = 1, N = 62	-0.30 [-0.76, 0.16]	N/A	Low <sup>1,2</sup>
<i>Leaving the study early for any reason (RR)</i>	NORDONTOFT2006	K = 1, N = 79	0.63 [0.22, 1.81]	N/A	Low <sup>1,2</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p>*Favours integrated psychological therapy.</p> <p><sup>1</sup> Serious risk of bias.</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.</p>					

**Table 39: Summary of findings table outcomes reported for integrated psychological therapy versus standard care at 104 weeks post-treatment**

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR) [95% CI]	Heterogeneity	Quality of evidence (GRADE) <sup>a</sup>
<i>Completer analysis: transition to psychosis (RR)</i>	NORDONTOFT2006	K = 1, N = 65	0.52 [0.26, 1.02]	N/A	Low <sup>1,2</sup>
<i>Positive symptoms (SMD)</i>	NORDONTOFT2006	K = 1, N = 57	-0.36 [-0.89, 0.16]	N/A	Low <sup>1,2</sup>
<i>Negative symptoms (SMD)</i>	NORDONTOFT2006	K = 1, N = 57	-0.42 [-1.09, 0.25]	N/A	Low <sup>1,2</sup>
<i>Leaving the study early for any reason (RR)</i>	NORDONTOFT2006	K = 1, N = 79	0.66 [0.25, 1.73]	N/A	Low <sup>1,2</sup>
<p><i>Note.</i> <sup>a</sup>The GRADE approach was used to grade the quality of evidence for each outcome.</p> <p><sup>1</sup> Serious risk of bias.</p> <p><sup>2</sup> Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.</p>					

### 5.5.5 Clinical evidence summary for psychosocial interventions

Seven RCTs investigated the efficacy of psychological interventions in young people at risk of developing psychosis or schizophrenia. Five trials compared CBT with supportive counselling and the findings suggest that CBT may have a beneficial effect on rate of transition to psychosis. However, CBT was found to be no more effective on than supportive counselling on psychotic symptoms, depression, psychosocial functioning and quality at life. One RCT compared integrated psychological therapy with supportive counselling and found small effects that integrated psychological therapy decreases transition to psychosis. Another RCT found a similar beneficial effect of integrated psychological therapy, when compared with standard care, on the rate of transition to psychosis at 12 months, but this significant effect was not found at 24 months. Moreover, when dropouts in both groups were assumed to have transitioned the significant beneficial effect of integrated psychological therapy on transition to a DSM-IV psychotic disorder, as opposed to an ultra-high/high risk mental state (attenuated/transient symptoms), was lost. Integrated psychological therapy appeared no more effective than standard treatment on positive or negative symptoms of psychosis, or dropout. Overall, heterogeneity between samples in terms of their degree of risk for developing psychosis, alongside the paucity and low quality of evidence, means that no robust conclusions can be drawn.

## 5.6 HEALTH ECONOMIC EVIDENCE

### *Systematic literature review*

This section adapted systematic literature review of existing economic evidence on interventions in people at risk of psychosis from *Psychosis and Schizophrenia in Children and Young People* (NCCMH, 2013 [full guideline]). The populations and interventions in adapted literature review were deemed to be relevant by the GDG for this guideline. Also, an update search was generated from the date of the last search (2012 to October 2013) to identify any new existing economic evidence. The systematic search of the economic literature undertaken for *Psychosis and Schizophrenia in Children and Young People* (NCCMH, 2013 [full guideline]) identified two eligible studies on people at risk of psychosis (Phillips et al., 2009; Valmaggia et al., 2009). An update search for this guideline identified one more eligible study (McCrone et al., 2013). Two studies were conducted in the UK (McCrone et al., 2013; Valmaggia et al., 2009) and one in Australia (Phillips et al., 2009). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

In the UK McCrone and colleagues (2013) developed a decision model to assess the cost of EIS compared with standard care (SC) in young people who either have psychotic illness, are in an 'at risk' mental health state or have another mental health problem. SC was defined as care by child and adolescent mental health services (CAMHS). In the model young people with signs of psychosis are initially referred to CAMHS. Following referral, a decision is made to refer on to a specialist EIS team or to continue to provide SC. If psychosis has developed, then the treatment options were either to admit the service user to inpatient care or to provide community-based support. If the service user was in an 'at risk' state, then either psychosocial intervention, medical intervention, a combination of these or no treatment was provided. The time horizon of the analysis was 6 months and the perspective of a mental health services was adopted, with impacts on other health services and social care not included. In the analysis the transition probabilities were based on various published sources and where necessary were supplemented with authors' assumptions. The study included medication costs, psychiatrist and psychologist contacts, nurse/care coordinator contacts, and inpatient care. The resource use estimates were based on various published sources; data provided by mental health trust (that is, service monitoring records and clinical reporting system), and authors' assumptions. The unit costs were obtained from national sources. The mean cost per person over 6 months was £13,186 for EIS and £18,000 for SC group in 2009/10 prices. This represents a cost savings of £4,814 associated with the intervention. The costs savings were mainly due to the reduced length of stay for those with psychosis who were admitted. The model was robust to changes in most parameters and only changing the probability of admission and increasing the length of stay for EIS service users had an impact on the results; however changes in these parameters would need to be relatively high. The analysis was judged by the GDG to be partially applicable to this guideline review and the NICE reference case. Even though the study was conducted in the UK, the authors have measured costs only from the mental health service perspective, and haven't looked at health effects. The estimates of transition probabilities were obtained from various published sources and where necessary were supplemented with authors' assumptions; some of the resources use estimates were derived from one mental health trust; and therefore there may be issues of generalisability. Time horizon of the analysis was only 6 months which may not be sufficiently long to reflect all important differences in costs. The authors have conducted extensive deterministic sensitivity analysis, however due to the lack of data probabilistic sensitivity analysis was not undertaken. Overall, this study was judged by the GDG to have potentially serious methodological limitations.

Valmaggia and colleagues (2009) conducted a cost-effectiveness analysis of an EIS service for people at high risk of psychosis. The study assessed Outreach and Support in South London (OASIS), a service for people with an at risk mental state for psychosis and schizophrenia. The service comprised information about symptoms, practical and social support, and the offer of CBT and medication. The early intervention was compared with care as usual, which did not include any provision of specialised mental health interventions. The data on care as usual was

obtained from the same geographical area of south London. The decision analytic model was developed for a period of 1 and 2 years from two perspectives (the health sector and society).

The decision analytic model took into account the cost of the intervention and usual care, initial GP visit, outpatient care (including contact with the community mental health team), informal inpatient stay and formal inpatient stay. The societal perspective also included lost productivity costs incurred during DUP. The resource use and cost data are acquired from national published sources and the studies reviewed.

The clinical evidence showed that EIS for people at high risk of psychosis reduced the risk of developing psychosis, and it also reduced the DUP. These outcomes were used as key parameters in the economic analysis. The long and short DUP were defined as more than or less than 8 weeks of untreated psychosis.

Valmaggia and colleagues (2009) showed that probability of transition to psychosis with an EIS is 0.20 compared with 0.35 in the case of usual care. Data from OASIS indicate that transition takes place on average 12 months after contact with GP or OASIS. The probability of long DUP in the intervention group (OASIS) is 0.05. This is lower than the usual care probability of 0.80, which consequently leads to a higher proportion of formal and informal inpatients in the usual care group.

According to the cost results, at 1 year the expected total service cost per person was £2,596 for EIS and £724 for usual care in 2004 prices. The 1-year duration did not capture the transition to psychosis because it was assumed to occur at 12 months after referral. The model estimated the expected cost of intervention at £4,313 per person and £3,285 for usual care. Including cost of lost productivity, the 2-year model showed cost savings with expected intervention costs of £4,396 per person and usual care of £5,357. Therefore, the perspective taken in the analysis, health sector or societal, is important as it changes the findings of the model. Using the reported data, the estimated incremental cost-effectiveness ratio (ICER) is £6,853 per person of avoiding risk of psychosis in 2004 prices.

The one-way sensitivity analysis showed that the 2-year model from a societal perspective is robust to changes in parameter values. There was no sensitivity analysis conducted using the NHS perspective. The economic model only covered the 2 years' duration of the study, however psychotic disorders can be life-long. A longer study is required to analyse whether a lower rate of transition to psychosis in the intervention group is temporary or permanent. The lower rate of transition to psychosis and long DUP in the intervention group could also have substantial economic benefits accruing beyond 2 years. Another limitation of the model is that it used data from observational studies and not from RCTs, which could affect the robustness of the results. The settings of the service and the local cost estimates might not be applicable to other areas. However, sensitivity analysis mitigates this limitation and the tree model structure can be tailored to other settings and estimates

of costs and transition probabilities. The model only took into account indirect cost of lost employment. The cost to parents and carers for unpaid care, to social care, and to the criminal justice system might also contribute to indirect costs that are not accounted for. Based on the above considerations the analysis was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case; and it was also judged by the GDG to have potentially serious methodological limitations.

Phillips and colleagues (Phillips et al., 2009) conducted a cost-minimisation study of specific and non-specific treatment for young people at ultra-high risk of developing first episode of psychosis in Australia. The analysis compared the costs of a specific preventive intervention with a needs-based intervention. The specific preventive intervention comprised a combination of risperidone and cognitively-oriented psychotherapy in addition to 'needs-based treatment' (supportive counselling, regular case management and medication) for 6 months.

The mean age of participants in both groups was 20 years. The analysis took the perspective of the Australian healthcare sector. The costs of inpatient and outpatient services and pharmacological interventions were calculated at the end of treatment (at 6 months) and at 12 and 36 months' follow-up for young people attending the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia. The costs were measured in Australian dollars in 1997 prices and the 36 months' follow-up costs were discounted at 3%.

As the cost analysis was conducted after the completion of the trial, several assumptions were made regarding resource use during the treatment. Resource use was calculated via a patient questionnaire during follow-up, which could have introduced errors. The unit costs were acquired from the budget and financial information of the service and national published sources on mental health costs in Australia.

The results were presented as mean costs for both groups for inpatient and outpatient services and pharmacological interventions and total costs of the treatment phase (6 months) and 12 and 36 months' follow-up. The specific preventive intervention had significantly higher cost for outpatient services of AU\$2,585 during the treatment phase compared with the needs-based intervention of AU\$1,084. However, the outpatient cost of specific preventive intervention at 36 months is AU\$4,102, which is significantly lower than the needs-based intervention cost of AU\$10,423. The differences between total costs and other components of the two intervention groups during the treatment phase and 12 and 36 months' follow-up were not statistically significant.

The findings of the study were not definitive; however, the analysis indicated substantial cost savings associated with the specific preventive intervention in the longer term. Most importantly, the study highlights that despite high outpatient costs of the specific preventive intervention during the treatment phase and at

12 months' follow-up, it incurred significantly lower outpatient costs than the needs-based intervention at 36 months' follow-up. The lower cost of the specific preventive intervention at 36 months was not associated with the treatment outcome as there were no differences in functioning or quality of life. The side effects of the intervention captured in the clinical trial are not accounted for in the health economic analysis, which could alter the findings substantially. The analysis is valuable because it used patient-level data and compared two services of different levels of intensity. However, the sample size of the study is small and not representative beyond the ultra-high risk subgroup, which is a limitation. In addition, the resource-use data were based on assumptions because the cost analysis was conducted after the completion of the trial and the patient questionnaire at follow-up could have led to patients erroneously recalling resource use. Based on the above considerations the analysis was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case; and it was also judged by the GDG to have potentially serious methodological limitations. On reflection, the GDG concluded that the health economic analysis was unsupportable within the context of this guideline.

## 5.7 LINKING EVIDENCE TO RECOMMENDATIONS

### *Relative value placed on the outcomes considered*

The GDG considered the critical outcomes to be:

- Transition to psychosis
- Time to transition to psychosis.

However, this is often a highly comorbid, help-seeking group that requires support and treatment. Therefore, the GDG also thought it pertinent to consider:

- Mental state (symptoms, depression, anxiety, mania)
- Mortality (including suicide)
- Global state
- Psychosocial functioning
- Social functioning
- Leaving the study early for any reason
- Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity).

### *Trade-off between clinical benefits and harms*

We found no evidence to support the early promise of some antipsychotic drugs in delaying or preventing transition to psychosis. In addition, antipsychotic drugs are associated with clinically significant side effects. Although this is best described as an absence of evidence rather than evidence of absence, this review identifies no reason to pursue this line of enquiry. Many people at ultra-high risk will not progress to psychosis, and we expect that any evidence indicating that the benefits outweigh the harms in this population would have been published. Psychological

treatment might be associated with an increase in stigma and other consequences for participants who would not develop psychosis without treatment.

When meta-analysed, there was no clear evidence to suggest that antipsychotic medication can prevent transition. Moreover, adverse effects, specifically weight gain, were clearly evident and indicate that the harms associated with antipsychotic medication significantly outweigh the benefits.

Overall, the results for psychosocial interventions suggest that transition to psychosis from a high-risk mental state may be preventable. These findings also provide a baseline for developing future research strategies, and they highlight treatments that have the most potential for reducing transition to psychosis. An important additional consideration is that there is good evidence from data in adults that family intervention is effective in reducing relapse rates in both first episode psychosis and in established schizophrenia, providing strong empirical evidence that the treatment strategies used here are effective in reducing the likelihood of (subsequent) psychosis. Importantly, family intervention was a key component of integrated psychological therapy.

Finally, one small RCT indicated that omega-3 fatty acids may also be effective in preventing transition from at risk mental states to the development of psychosis (even when sensitivity analysis is applied and dropouts are assumed to have transitioned) and improving symptoms of psychosis, depression and psychosocial functioning. Given the very small sample from which these results were obtained, there is insufficient evidence with which to recommend the use of omega-3 fatty acids.

Ultimately, the majority of individuals in these at risk samples do not convert to psychosis and as a result there are serious concerns regarding the risk of exposure to unnecessary interventions. The harms associated with intervening include stigma and the fear of becoming psychotic (the reason why they have been included in the trial or offered the treatment). However, the GDG considered that these risks were acceptable if the treatments offered added no further important potential harms. The GDG felt that, on balance, psychological treatments and the use of omega-3 fatty acids were unlikely to be associated with other important potential harms. However, the side effects of antipsychotic medication include weight gain, the potential for type 2 diabetes, long-term cardiovascular disease and the risk of irreversible brain changes resulting in effectively untreatable and permanent movement disorders when antipsychotic drugs are used at higher dose in the long term. Given the seriousness of these effects, that only a small proportion of individuals will go on to develop psychosis and that the evidence suggested that antipsychotics were unlikely to produce any benefit, antipsychotic treatment will result in unacceptable harm. Consequently, there is a strong basis for not prescribing antipsychotic medication or researching its use further in this population.

On the other hand, the GDG noted that because these people are treatment seeking, often distressed and have comorbidities, they should have access to help for their

distress (CBT) and treatments recommended in NICE guidance for any comorbid conditions such as anxiety, depression, emerging personality disorder or substance misuse, or whatever other problem presents. Although the numbers of episodes of psychosis prevented affect a small percentage of people at high risk of psychosis, many others in these trials are likely to benefit from CBT for the treatment of these other, non-psychotic psychological problems.

### *Trade-off between net health benefits and resource use*

There were two UK-based economic studies that assessed the economic impact of EIS for people at high risk or with signs of psychosis; however the GDG judged both studies to have potentially serious methodological limitations. The time frame of the analyses was very limited, however psychotic disorders can be lifelong. Also, both studies used data from either observational studies, other published sources and authors' assumptions and not from RCTs. The findings of the Australian study were not definite either. Even though it indicated potential cost savings the sample size of the study was small and not representative beyond the ultra high-risk subgroup. Moreover, some of resource use estimates were based on assumptions and patient questionnaire at follow-up. As a result, the analysis was judged by the GDG to have potentially serious methodological limitations and on reflection the GDG concluded that the analysis was unsupportable within the context of this guideline. Consequently, based on existing economic evidence the GDG could not draw definite conclusions pertaining to the cost effectiveness of EIS for people at high risk of psychosis.

### *Quality of the evidence*

For all interventions, the quality of the evidence ranged from very low to moderate. The evidence for pharmacological interventions was of particular poor quality and was rated as very low across all critical outcomes. A primary reason for downgrading the quality of the evidence was risk of bias across the trials. Almost all of the trials included in the review were rated as high risk of bias due to various limitations within them making them difficult to interpret. Such limitations included small sample sizes, lack of outcome assessor blinding and likely publication bias; the latter being especially likely for antipsychotics. Furthermore, there is some suggestion that among this high risk group, the number of transitions increases over 3 years and then settles. Therefore, trials require longer periods of follow-up. Other reasons for downgrading the quality of evidence across interventions concerned limited information size, indirectness or risk of reporting bias. There were also some concerns in the definition of 'transition to psychosis' which varied across included studies.

### *Other considerations*

Recent studies have examined the feasibility of detecting and treating individuals with at risk mental states, prior to the development of psychosis and schizophrenia. Criteria are now available to identify and recognise help-seeking individuals who



are at high risk of imminently developing schizophrenia and related psychoses, using standardised semi-structured interviews. These criteria require further refinement in order to better predict the course of these 'at risk' behaviours and symptoms, as well as recognition of those who will and those who will not go on to develop psychosis. In addition, in order to obtain precise estimates of rates of transition to psychosis in this population, further work is needed that looks at the influence of sampling strategies in this population.

The GDG considered it important that people experiencing transient psychotic symptoms or other experiences suggestive of possible psychosis were referred urgently to a specialist mental health service where a multidisciplinary assessment should be carried out (see recommendations 5.8.1.1 and 5.8.2.1). In addition, the GDG decided to recommend individual CBT with or without family intervention for people at risk of developing psychosis delivered with the aim of lowering the risk of transition to psychosis and reducing current distress (see recommendation 5.8.4.1). It was also deemed important to monitor individuals for up to 3 years (see recommendation 5.8.4.1), offering follow-up appointments to those who requested discharge from the service (see recommendation 5.8.4.2). Further studies to examine the use of family intervention to prevent a first occurrence of psychosis in those at high risk were considered an important direction for further research.

As no evidence was found to support the early promise that some antipsychotics may delay or prevent transition, and because antipsychotics are associated with significant side effects, the GDG decided there was no reason to pursue this line of enquiry, particularly since many people at ultra-high risk will not progress to psychosis and schizophrenia (see recommendation 5.8.3.2).

## **5.8 RECOMMENDATIONS**

### **5.8.1 Referral from primary care**

**5.8.1.1** If a person is distressed, has a decline in social functioning and has:

- transient or attenuated psychotic symptoms **or**
- other experiences suggestive of possible psychosis **or**
- a first-degree relative with psychosis or schizophrenia

refer them for assessment without delay to a specialist mental health service or an early intervention in psychosis service because they may be at increased risk of developing psychosis. [new 2014]

### **5.8.2 Specialist assessment**

**5.8.2.1** A consultant psychiatrist or a trained specialist with experience in at-risk mental states should carry out the assessment. [new 2014]

### 5.8.3 Treatment options to prevent psychosis

**5.8.3.1** If a person is considered to be at increased risk of developing psychosis (as described in recommendation 5.8.1.1):

- offer individual cognitive behavioural therapy (CBT) with or without family intervention (delivered as described in recommendations 9.4.10.3 and 9.7.10.3) **and**
- offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. [new 2014]

**5.8.3.2** Do not offer antipsychotic medication:

- for people considered to be at increased risk of developing psychosis (as described in recommendation 5.8.1.1) **or**
- with the aim of decreasing the risk of or preventing psychosis [new 2014]

### 5.8.4 Monitor and follow-up

**5.8.4.1** If, after treatment (as described in recommendation 5.8.3.1), the person continues to have symptoms, impaired functioning or is distressed, but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using a structured and validated assessment tool. Determine the frequency and duration of monitoring by the:

- severity and frequency of symptoms
- level of impairment and/or distress **and**
- degree of family disruption or concern. [new 2014]

**5.8.4.2** If a person requests discharge from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's GP to continue monitoring changes in their mental state. [new 2014]

# 6 ACCESS AND ENGAGEMENT

This chapter has been updated for the 2014 guideline. The review of early intervention has been updated and is now included in Chapter 12, Teams and service-level interventions. Sections of the guideline where the evidence has not be updated since 2009 are marked by asterisks (\*\*2009\*\*\_\*\*2009\*\*).

## 6.1 INTRODUCTION

**\*\*2009\*\*** Although there is great emphasis on clinical practice and service organisation to deliver effective clinical interventions, it is well known that there are significant social and ethnic inequalities regarding access to and benefit from such effective clinical interventions. Schizophrenia is likely to impact negatively on finances, employment and relationships, especially if the illness begins when the person is very young, which is a vulnerable time and when the adverse social impact of an illness can be most devastating. More attention is now rightly focused on ensuring early access to effective interventions for psychosis, to reduce periods of untreated psychosis, and also to ensure prompt and precise diagnosis, and quicker recovery to minimise social deficits, following the onset of illness.

There is substantial evidence that patterns of inequality regarding access to and benefit from treatment show some ethnic groups are disadvantaged and might benefit from prompt and precise diagnosis and intervention. Furthermore, some people from specific ethnic groups may fear services, or respond to stigma, or find that services do not understand their personal, religious, spiritual, social and cultural needs or their cultural identity. These needs are important for them to sustain and maintain a healthy identity.

## 6.2 ACCESS AND ENGAGEMENT TO SERVICE-LEVEL INTERVENTIONS

### 6.2.1 Introduction

#### *Background and approach*

Schizophrenia is known to be a devastating illness with significant social and psychological deficits, and it is crucial that service users receive treatments and services that are collectively sanctioned as appropriate approaches in the context of dominant ethical, clinical and legal frameworks of practice and service organisation. These frame- works and standards of care are informed by the evolving evidence base and expert opinion. African-Caribbean people in the UK have been shown to have a higher incidence of schizophrenia, while the treatment practices and service organisation for recovery have not been especially tailored to meet their needs (Kirkbride et al., 2006). South Asian people may also have a higher incidence of schizophrenia, but there is less compelling evidence (Kirkbride et al., 2006). Migrants, people living in cities, and those at the poorer and less advantaged end of society are also at risk (Cantor-Graae & Selten, 2005). Asylum seekers and refugees

may face additional risks of poor mental health, but their experience, to date, has not been directly linked to a higher incidence of schizophrenia, although it is related to complex social and health needs among those developing schizophrenia (Royal College of Psychiatrists, 2007). More generally, culture is known to influence the content and, some would argue, the form and intensity of presentation of symptoms; it also determines what is considered to be an illness and who people seek out for remedy. Cultural practices and customs may well create contexts in which distress is generated; for example, where conformity to gender, age, and cultural roles is challenged.

### *Paradigms for quality improvement*

The dominant paradigms for improved standards of care (including service organisation, effective interventions, and integrated care pathways and patterns of treatment received by ethnic groups and migrants) are the cultural psychiatry and equalities paradigms.

The cultural psychiatry paradigm tries to understand the cultural origins of symptoms, as well as: (a) how these symptoms are coloured when expressed across cultural boundaries; (b) which treatments are sanctioned; and (c) whether treatments themselves, ostensibly evidence-based, are really culturally constructed solutions that work best for people sharing the same cultural norms and expectations of what constitutes illness and treatment. This endeavour is largely clinically motivated and responds to frontline evidence of a lack of appropriate knowledge and skills to benefit all people equally using existing guidelines and treatment approaches. It also draws upon sociology and anthropology as key disciplines.

The equalities paradigm is heavily underpinned by two national policies: Inside Outside (National Institute for Mental Health in England, 2003) and Delivering Race Equality (Bhui et al., 2004; Department of Health, 2003; Department of Health, 2005). These policies promote race equality through institutional and national programmes of actions with leadership from health authorities, mental health trusts and locally organised groups of stakeholders. These actions have not been specific to schizophrenia, but have certainly been motivated by the perceived crisis in the care and treatment of African-Caribbean people with schizophrenia, to which providers have not previously responded in a consistent and visibly effective manner. To date, results from the Care Quality Commission's patient census ('Count Me In') indicate that policies and programmes in this area have not yet had the desired effects (Healthcare Commission, 2008). Perceived, individual and institutional prejudice and racism are also tackled within a broader equalities framework that addresses multiple forms of social exclusion and stigma (McKenzie & Bhui, 2007).

### *Cultural competence*

Encompassed in the above two paradigms is the notion of cultural competence. A recent systematic review (Bhui et al., 2007) suggested that staff cultural competence training may produce benefits in terms of cultural sensitivity, staff knowledge and staff satisfaction. However, despite these promising findings, clinicians should be

aware of the problems and controversies surrounding the definition or current understandings of cultural competence. Kleinman and Benson (2006) propose that a cultural formulation, based upon a small scale ethnographic study of the individual or on the DSM-IV cultural formulation, should be written for each patient. This cultural formulation can then be used to help determine and inform appropriate clinical interventions at the individual patient level. On the other hand, others, such as Papadopoulos and colleagues (2004), have suggested a more model-based approach, in which cultural competence is seen as part of a four stage conceptual map, wherein competence is informed by and informs three other processes, namely cultural sensitivity, cultural knowledge and cultural awareness. Whichever approach is taken, it is clear from the literature that cultural competence is now recognised as a core requirement for mental health professionals. Yet despite this increased awareness of its importance, little evaluative work has been done to assess the effects of cultural competence (at both an individual and organisational level) on a range of service user, carer and healthcare professional outcomes.

### ***The 2009 guideline: how did the Guideline Development Group take account of race, ethnicity and culture?***

For the 2009 guideline, the GDG did not attempt to examine all evidence relevant to race, culture and ethnicity, but instead focused on three main approaches. First, the two topic groups examining psychological/psychosocial interventions and pharmacological interventions reviewed evidence of benefits for ethnic groups. Second, where there was little evidence for specific effects for ethnic groups, included studies (for the recommended interventions) were reviewed to assess the ethnic diversity of the samples. This was done to establish whether the findings may be of relevance to ethnic groups as well as the majority population. Third, a specific topic group examining clinical questions related to access and engagement was formed with input from special advisers. In particular, the group requested that the literature search should cover specialist ethnic mental health services, that studies of service-level interventions should be examined to assess the ethnic diversity of the samples and that preliminary subgroup analyses of existing datasets should be conducted to inform research recommendations (see Section 6.2.11).

### ***Limitations***

The focus on race, culture and ethnicity in this 2009 guideline is welcomed and ground-breaking, but there is a limitation in the sense that all mental healthcare should be similarly reviewed, with a broader focus. Regarding this 2009 guideline, the methodologies developed have necessarily been targeted on some key issues and are not comprehensive in their actions. The 2009 guideline has also not been able to look at broader issues of pathways to care and effectiveness of psychological and pharmacological interventions on the basis of new and different levels of evidence. In part, this is because there is limited evidence. Furthermore, the 2009 guideline has not looked at issues that were not reviewed in the 2002 guideline. Therefore the following might be usefully accommodated in further reviews: matching the racial identity of the professional with the service user, ethnic matching (which is broader than matching racial identity and also encompasses cultural similarities), the impact

of social exclusion and racism across generations, and the impact on young people of parents who have been socially excluded, subjected to prejudice and have a mental illness. All of these might seem imperative to service users from black and minority ethnic groups, but were not within the scope of the 2009 guideline. It is vital that future guideline updates attend to these broader issues, perhaps additionally with a guideline for these issues across disease areas.

### *On evidence and ethnicity*

There are general concerns that current evidence relating to ethnicity has not come from adequate samples of ethnic groups (or any socially excluded group). There are also concerns regarding the hierarchy of evidence. First, in the absence of high-quality evidence, expert opinion and the dominant paradigms of treatment are given preference over other forms of evidence (for example, qualitative evidence); second, clinical trials are given preference over other study designs. Thus, existing institutionalised practices are sustained. Research studies propose that there are pharmacokinetic and pharmacodynamic differences in drug handling across migrant, national and ethnic groups, but our scientific understanding of these at an ethnic-group level does not permit generalised statements to be made about a group that can then be applied to the individual from that group. Psychological therapies may privilege psychologised forms of mental distress, perhaps excluding those experiencing social manifestations of distress that is not so easily recognised as having a mental component. However, this 2009 guideline could not fully address these issues.

Assuming that service users from black and minority ethnic groups can benefit from the same interventions delivered in the same way, the next question is whether black and minority ethnic groups have equal access to these effective interventions and whether they remain in contact with services. The access and engagement topic group focused on this broad question of engagement and retained contact with existing innovative services that aim to be flexible and should be culturally appropriate, namely assertive community treatment (assertive outreach teams), crisis resolution and home treatment teams, and case management. For this work, existing reviews of these services were reanalysed for data on ethnic groups with loss to follow-up and contact with services as the primary outcome. The next part reviews the literature for evidence that ethnic-specific or culturally-adapted services were effective or more effective at preventing loss to follow-up, dropout and sustained contact over time. The interventions reviewed are defined below.

### *Definitions*

#### **Assertive community treatment (assertive outreach teams)**

The bipolar disorder guideline (NCCMH, 2006 [full guideline]) review of assertive community treatment (ACT) updated the review undertaken for the 2002 schizophrenia guideline, which was based on the review by Marshall and Lockwood (2002). This latter review identified the key elements of ACT as:

- a multidisciplinary team-based approach to care (usually involving a psychiatrist with dedicated sessions)
- care is exclusively provided for a defined group of people (those with serious mental illness)
- team members share responsibility for clients so that several members may work with the same client and members do not have individual caseloads (unlike case management)
- ACT teams attempt to provide all the psychiatric and social care for each client rather than referring on to other agencies
- care is provided at home or in the work place, as far as this is possible
- treatment and care is offered assertively to uncooperative or reluctant service users ('assertive outreach')
- medication concordance is emphasised by ACT teams.

The bipolar disorder guideline (NCCMH, 2006 [full guideline]) adopted the definition of ACT used by Marshall and Lockwood (2002) which followed a pragmatic approach based upon the description given in the trial report. For a study to be accepted as ACT, Marshall and Lockwood (2002) required that the trial report had to describe the experimental intervention as 'Assertive Community Treatment, Assertive Case Management or PACT; or as being based on the Madison, Treatment in Community Living, Assertive Community Treatment or Stein and Test models.'

ACT and similar models of care are forms of long-term interventions for those with severe and enduring mental illnesses. Thus, the review did not consider the use of ACT as an alternative to acute hospital admission. The review also excluded studies of 'home-based care', as these were regarded as forms of crisis intervention, and are reviewed with crisis resolution and home treatment teams.

### **Crisis resolution and home treatment teams**

The GDG for the bipolar disorder guideline (NCCMH, 2006 [full guideline]) adopted the inclusion criteria developed by the Cochrane Review (Joy et al., 2002) for studies of crisis resolution and home treatment teams (CRHTTs) in the management of people with schizophrenia. Crisis intervention for people with serious mental health problems was selected by the bipolar disorder GDG for review and further analysis.

Crisis intervention and the comparator treatment were defined as follows:

- Crisis resolution: any type of crisis-orientated treatment of an acute psychiatric episode by staff with a specific remit to deal with such situations, in and beyond 'office hours'.
- Standard care: the normal care given to those experiencing acute psychiatric episodes in the area concerned. This involved hospital-based treatment for all studies included.

The focus of the review was to examine the effects of CRHTT models for anyone with serious mental illness experiencing an acute episode when compared with the 'standard care' they would normally receive.

## Case management

Given the variation in models of case management evaluated in the literature, the bipolar disorder GDG adopted the definition used in a Cochrane review (Marshall et al., 2000) where an intervention was considered to be 'case management' if it was described as such in the trial report. In the original review no distinction, for eligibility purposes, was made between 'brokerage', 'intensive', 'clinical' or 'strengths' models. For the purposes of the bipolar disorder guideline (NCCMH, 2006 [full guideline]) review, intensive case management (ICM) was defined as a caseload of less than or equal to 15. The UK terms 'care management' and 'care programme approach' were also treated as synonyms for case management. However, the review excluded studies of two types of intervention often loosely classed as 'case management', including ACT and 'home-based care'.

### Specialist ethnic mental health services (culturally specific or culturally skilled)

Specialist ethnic mental health services aim, by definition, to offer a culturally appropriate service and effective interventions to either a specific racial, ethnic, cultural or religious group or to deliver an effective service to diverse ethnic groups (Bhui et al., 2000; Bhui & Sashidharan, 2003). Models of specialist services have not been mapped recently but include cultural consultation service styles, and others outlined by Bhui and colleagues (2000).

## 6.2.2 Clinical review protocol

The review protocol, including the primary clinical question, information about the databases searched and the eligibility criteria can be found in Table 40. For the 2009 guideline, all studies were examined for information about ethnicity of the sample and numbers losing contact with services by ethnic group. The access and engagement topic group and special advisers developing the guideline proposed that a sample of which at least 20% of subjects were from black and minority ethnic groups could be considered 'ethnically diverse'. It was assumed that a decrease in the number of participants leaving the study early for any reason indicated that the service was more engaging.

**Table 40: Clinical review protocol for the review of services**

<i>Primary clinical questions</i>	For all people from black and minority ethnic groups (particularly, African-Caribbean people) with psychosis, do services, such as ACT, CRHTTs and case management improve the number of people remaining in contact with services?  For all people from black and minority ethnic groups with psychosis, do specialist ethnic mental health services (culturally specific or culturally skilled) improve the number of people remaining in contact with services?
<i>Electronic databases</i>	MEDLINE, EMBASE, PsycINFO, CINAHL
<i>Date searched</i>	Database inception to 6 April 2008



<i>Other resources searched</i>	Bipolar disorder guideline (NCCMH, 2006) and reference lists of included studies
<i>Study design</i>	Any
<i>Patient population</i>	People with psychosis from a black and minority ethnic group in the UK
<i>Interventions</i>	1. ACT, CRHTTs and case management 2. Specialist ethnic mental health services (culturally specific or culturally skilled)
<i>Outcomes</i>	Number of people remaining in contact with services (measured by the number of people lost to follow-up or loss of engagement with services)

However, the GDG acknowledges that people may leave a study early for reasons other than a lack of engagement with the service.

### 6.2.3 Studies considered for review

#### *Assertive community treatment (assertive outreach teams)*

The bipolar disorder guideline (NCCMH, 2006 [full guideline]) included 23 RCTs of ACT: 13 versus standard care (N = 2,244), four versus hospital-based rehabilitation (N = 286) and six versus case management (N = 890). Studies included had to conform to the definition of ACT given above, and the inclusion criteria used by Marshall and Lockwood (2002) were widened to include populations with serious mental illness.

Of the 23 trials included in the bipolar disorder guideline (NCCMH, 2006 [full guideline]), nine included adequate information about ethnicity of the sample, although none reported outcome data by ethnic group. Therefore, the GDG conducted a sensitivity analysis of seven studies that had an ethnically diverse sample (see Table 41 for further information).

#### *Crisis resolution and home treatment teams*

The bipolar disorder guideline (NCCMH, 2006 [full guideline]) included seven RCTs of a CRHTT versus inpatient care (N = 1,207). Of these, three included an ethnically diverse sample, and one (MUIJEN1992) reported the number of people leaving the study early for any reason by ethnicity (see Table 42 for further information).

#### *Case management*

The bipolar disorder guideline (NCCMH, 2006 [full guideline]) review updated the review undertaken for the 2002 schizophrenia guideline and included 17 RCTs of case management: 13 versus standard care (intensive and standard case management [SCM]), two intensive versus standard case management, one enhanced case management versus standard case management and one case management versus brokerage case management. One trial (BRUCE2004) was excluded from the present review as 100% of participants had a diagnosis of depression. Of the 16 remaining RCTs, six included an ethnically diverse sample, and three of these studies (FRANKLIN1987; MUIJEN1994; BURNS1999) reported the

number of people leaving the study early for any reason by ethnicity (see Table 42 for further information).

### *Specialist ethnic mental health services*

For the 2009 guideline, papers were included in the review if they reported comparisons of UK-based specialist mental-health service interventions and/or initiatives. An inclusive definition of 'specialist ethnic service' was used to include those services that were either culturally adapted or tailored to the needs of individual patients, including any religious or ethnic needs. To measure improved access and engagement, the numbers of people from different black and minority ethnic groups remaining in contact with services (as measured by loss to follow-up and loss of engagement) was the primary outcome. All study designs were considered and papers were included even if a formal evaluation of the service had not been intended.

Papers were excluded from the review if: (a) they only reported descriptions of current service use by different black and minority ethnic groups, (b) did not report any comparison between services, and (c) were non-UK based or did not report loss to follow-up/ loss of engagement within different black and minority ethnic groups. The reference lists of included papers and any relevant reviews were further checked for additional papers. The review was restricted to English language papers only. The search identified 2,284 titles and abstracts, of which 19 were collected for further consideration. All 19 papers were excluded because of lack of comparator, failure to report loss to follow-up and/or loss of engagement by ethnicity or were non- UK interventions.

## 6.2.4 Assertive community treatment or crisis resolution and home treatment teams versus control

**Table 41: Study information and evidence summary table for trials of ACT or CRHTTs**

	ACT versus standard care	ACT versus hospital-based rehabilitation	ACT versus case management	CRHTTs versus standard care
k (total N)	5 RCTs (N = 684)	1 RCT (N = 59)	1 RCT (N =	3 RCTs (N = 492)
Study ID	AUDINI1994 BOND1998 BOND1990 LEHMAN1997 MORSE1992	CHANDLER1997	BUSH1990	FENTON1998 MUIJEN1992 PASAMANICK 1964
Diagnosis	30–61% schizophrenia	61% schizophrenia	86% schizophrenia	49–100% schizophrenia
Ethnicity	AUDINI1994: 26% African-Caribbean BOND1998: 34% black, 2% Latino BOND1990: 30% black LEHMAN1997: 61% African-American (ACT), 84% African-American (control) MORSE1992: 52.5% non-white (mostly African-American)	40% African-American (ACT), 55.2% African-American (control)	50% black	FENTON1998: 14% black (CRHTTs), 28% black (control) MUIJEN1992: 25% African-Caribbean (CRHTTs), 21% African-Caribbean (control) PASAMANICK 1964: 32.9% non-white
<b>Outcomes</b>				
Leaving the study early for any reason	RR 0.63 (0.48, 0.82), k = 5, N = 684, I <sup>2</sup> = 0%  Excluding studies targeting homeless people: RR 0.62 (0.44, 0.89), k = 3, N = 416, I <sup>2</sup> = 0%	RR 1.55 (0.28, 8.62), k = 1, N = 59	RR not estimable (nobody left the study early)	RR 0.73 (0.43, 1.25), k = 3, N = 492, I <sup>2</sup> = 57%  Excluding PASAMANICK 1964: RR 0.66 (0.50, 0.88), k = 2, N = 374, I <sup>2</sup> = 0%

Leaving the study early for any reason by black and minority group				African-Caribbean: RR 1.12 (0.51, 2.45), k = 1, N = 43 Other non-white: RR 0.70 (0.21, 2.34), k = 1, N = 26
--	--	--	--	--

## 6.2.5 Case management versus control

**Table 42: Study information and evidence summary table for trials of case management**

	Standard case management (SCM) versus	Intensive case management (ICM) versus standard	ICM versus SCM
Total number of studies (number of participants)	1 RCT (N = 413)	4 RCTs (N = 362)	1 RCT (N = 708)
Study ID	FRANKLIN1987	FORD1995 HOLLOWAY1998 MUIJEN1994 SOLOMON1994	BURNS1999(UK700) <sup>10</sup>
Diagnosis	56% schizophrenia	66–83% schizophrenia	87% schizophrenia or schizoaffective disorder

<sup>10</sup>Subgroup by ethnicity data obtained from authors.

Ethnicity	25% black, 2% Hispanic (SCM), 24% black, 6% Hispanic (control)	FORD1995: 23% black and minority ethnic groups (ICM), 37% black and minority ethnic groups (control) HOLLOWAY1998: 51% non-white (ICM), 57% non-white (control) MUIJEN1994: 29% African-Caribbean, 2% Asian (ICM), 17% African-Caribbean, 5% Asian (control) SOLOMON1994: 83% black, 3% Hispanic	29% African-Caribbean, 20% other black and minority ethnic groups (ICM) 26% African- Caribbean, 20% other black and minority ethnic groups (SCM)
<b>Outcomes</b>			
Leaving the study early for any reason	RR 0.95 (0.74, 1.23), k = 1, N = 413,	RR 0.76 (0.53, 1.09), k = 4, N = 362, I <sup>2</sup> = 3.9%	RR 0.56 (0.38, 0.82), k = 1, N = 708
Leaving the study early for any reason by black and minority ethnic group	-	Black: RR 0.74 (0.48, 1.23), k = 2, N = 121	White: RR 0.73 (0.38, 1.40), k = 1, N = 267 African-Caribbean: RR 1.00 (0.53, 1.87), k = 1, N = 270
Lost contact with case manager	-	-	RR 1.71 (1.09, 2.69), k = 1, N = 708
Refused contact with case manager	-	-	RR 1.44 (0.55, 3.73), k = 1, N = 708

## 6.2.6 Secondary subgroup analyses

Given the paucity of evidence available to answer questions about the use of, and engagement with, services by people from black and minority ethnic groups, the GDG examined data from two service-level intervention studies conducted in the UK (Johnson et al., 2005; Killaspy et al., 2006). Patient-level data were made available to the GDG during the development of the guideline for the purposes of conducting secondary post hoc analyses to examine loss of contact and engagement with the service by ethnicity of the participants. These analyses were exploratory in nature and were intended to be purely hypothesis generating as opposed to generating evidence to underpin recommendations. Both studies were non-blind RCTs (see Table 43 for further details).

In both trials, participants categorised as black African, black Caribbean or black other were included in the black and minority ethnic subgroup. Additionally, in the North Islington Crisis study (Johnson et al., 2005) participants categorised as 'mixed race' were included in the subgroup analysis. As far as possible, the same procedures used in the primary papers were applied to the secondary analysis conducted for this 2009 guideline. For example, where a primary paper excluded missing data, the same procedure was subsequently applied to the present analysis. In addition to looking at engagement with services as measured by numbers losing contact, other measures of access and engagement (including contact with forensic services and engagement rating scales) were included in the present analysis. For continuous measures, because of the high potential for skewed data, Mann Whitney-U tests were applied to test for differences in the median values. For dichotomous outcomes, Chi-squared tests were applied where appropriate to test for differences with relative risks calculated for variables such as relapse and rehospitalisation. Although the main findings are summarised below, more detailed evidence tables for each subgroup comparison can be found in Appendix 23b.

### ***REACT (Killaspy et al., 2006)***

The findings can be summarised as follows:

- In the whole sample, there was no difference in the proportion consenting to treatment in the group of participants allocated to ACT versus standard care. This finding was replicated in the subgroup of black and minority ethnic participants.
- In the whole sample, ACT was associated with reduced loss to follow-up at both
- 9 and 18 months. These findings were not demonstrated in the subgroup of black and minority ethnic participants.
- In the whole sample, ACT improved service user engagement, but this finding did not hold for black and minority ethnic subgroup.
- In both the whole sample and the black and minority ethnic subgroup, ACT
- increased the number of contacts with mental health professionals at both 9 and
- 18 months.
- ACT had no effect on any measure of detention or hospitalisation (including involuntary admissions) in both the whole sample and the black and minority ethnic subgroup.

**Table 43: Details of studies included in the secondary subgroup analyses**

Study	Objective	Design/ Setting	Participants	Groups	Main outcome measures
REACT (Killaspy et al., 2006)	To compare outcomes of care from ACT with care by CMHTs for people with serious mental illnesses	Non-blind RCT/two inner London boroughs	251 men and women under the care of adult secondary mental health services with recent high use of inpatient care and difficulties engaging with community services	Intervention = treatment from ACT team (127 participants)  Comparator = continuation of care from CMHT (124 participants)	Primary outcome was inpatient bed use 18 months after randomisation. Secondary outcomes included symptoms, social function, client satisfaction, and engagement with services.
North Islington Crisis RCT  (Johnson et al., 2005)	To evaluate the effectiveness of a crisis resolution team	Non-blind RCT/ London borough of Islington	260 residents of the inner London borough of Islington who were experiencing crises severe enough for hospital admission to be considered	Intervention = acute care including a 24- hour crisis resolution team (experimental group)  Comparator = standard care from inpatient services and CMHTs (control group)	Primary outcome was hospital admission and number of inpatient bed use. Secondary outcomes included symptoms and client satisfaction.
<i>Note.</i> ACT = assertive community treatment; CMHT = community mental health team					

### *North Islington Crisis team RCT (Johnson et al., 2005)*

The findings can be summarised as follows:

- The crisis team intervention significantly reduced hospitalisation rates and number of inpatient bed days for both the whole sample and the black and minority ethnic subgroup.
- The crisis team intervention had no impact on treatment compliance or numbers lost to follow-up, for both the whole sample and the black and minority ethnic subgroup.
- The number of professional contacts, including contacts with GPs increased at 8 weeks and 6 months, and although the effect was not significant in the black and minority ethnic subgroup, the point estimate suggests this is because of a small sample size and resulting lack of statistical power, rather than the absence of an effect.
- For both the sample as a whole and the black and minority ethnic subgroup, the crisis team intervention did not impact upon any measure of involuntary detention or status under the Mental Health Act.

### **6.2.7 Other sources of evidence**

The review of ethnically-specific or adapted services yielded no UK-based studies that investigated loss to follow-up. However, some of the studies, although falling outside the guideline's inclusion criteria, offer important lessons for clinical practice and research. Bhugra and colleagues (2004) demonstrated that black people in contact with mental health services via contact with either primary care or non-primary care services were equally as dissatisfied as a white group gaining access to services from outside primary care. The most satisfied group were identified as white people accessing mental health service following contact and referral from primary care. Mohan and colleagues (2006) showed, in a non-randomised study, that subsequent to the introduction of intensive case management, black patients were more likely to have greater contact with psychiatrists and nurses, while white patients more often had greater social care contact. Black patients were less likely to require hospital admission. Khan and colleagues (2003) showed in a small qualitative study that South Asian people receiving care from a home treatment team valued the intervention because of the cultural appropriateness in terms of language, religious needs, dietary needs and stigma, while hospitals were preferred for investigations (for example, blood tests).

A systematic review of interventions that improve pathways into care for people from black and minority ethnic groups was recently completed (Moffat et al., 2009; Sass et al., 2009). This was commissioned by the Department of Health through the Delivering Race Equality programme (established in 2005). The systematic grey literature search yielded 1,309 documents, of which eight fully met inclusion criteria. The main findings of the review indicated that:



‘The key components of effective pathway interventions include specialist services for ethnic minority groups, collaboration between sectors, facilitating referral routes between services, outreach and facilitating access into care, and supporting access to rehabilitation and moving out of care. Services that support collaboration, referral between services, and improve access seem effective, but warrant further evaluation. Innovative services must ensure that their evaluation frameworks meet minimum quality standards if the knowledge gained from the service is to be generalised, and if it is to inform policy’ (Moffat et al., 2009).

The review of mainstream published literature identified 2,216 titles and abstracts with six studies meeting the review’s inclusion criteria. In only one study was the initiative UK based, and included patients with depression as opposed to psychosis. The main findings of the review indicated that

‘There was evidence that interventions led to three types of pathways change; accelerated transit through care pathways, removal of adverse pathways, and the addition of a beneficial pathway. Ethnic matching promoted desired pathways in many groups but not African Americans, managed care improved equity, a pre- treatment service improved access to detoxification and an education leaflet increased recovery’ (Sass et al., 2009).

In addition to these findings, the review concluded that further research is needed to facilitate evidence-based guidance for the development of services.

### **6.2.8 Clinical evidence summary**

Although there were no RCTs assessing the effectiveness of ACT for specific ethnic groups, five RCTs including an ethnically diverse sample indicated that when compared with standard care ACT interventions were effective in reducing loss to follow-up. When compared with standard care alone, CRHTTs were also effective at reducing loss to follow-up. Only one RCT (MUIJEN1992) included in the review permitted stratification of these effects by ethnic group. The positive findings from this RCT regarding reduced loss to follow-up held most strongly for Irish people, but was not convincing for African-Caribbean subgroups. However, it must be noted that because of the limited sample size no firm conclusions can be drawn from this one RCT alone. The review of case management included more RCTs permitting stratification of outcomes by ethnicity. Despite this, there was no consistent evidence for the effectiveness of either intensive or standard case management when compared with standard care and other service configurations.

Although the search of specialist ethnic mental health services undertaken for the 2009 guideline did not yield any eligible studies, recent reviews (Moffat et al., 2009; Sass et al., 2009) both grey and mainstream literature provided some interesting examples of how cultural adaptations can lead to improved outcomes. However it must be noted that even within these reviews, there was paucity of information, with the majority of included studies being non-UK based, thus limiting the

generalisability to specific black and minority ethnic populations within the UK. **\*\*2009\*\***

## **6.2.9 Linking evidence to recommendations**

The systematic review for the 2009 guideline did not provide any robust evidence to warrant changing the service recommendations in the 2002 guideline for people with schizophrenia from black and minority ethnic groups. However, the GDG for the 2009 guideline and the special advisers recognised that there were a number of problems specifically faced by people from different black and minority ethnic groups, including:

- **\*\*2009\*\***People from black and minority ethnic groups with schizophrenia are more likely than other groups to be disadvantaged or have impaired access to and/or engagement with mental health services.
- People from black and minority ethnic groups may not benefit as much as they could from existing services and interventions, with the aforementioned problems in access and engagement further undermining any potential benefits.
- For all people with a first episode of psychosis or severe mental distress (including those from black and minority ethnic groups), fears about the safety of the intervention may not be appropriately addressed by the clinician.
- Conflict may arise when divergent explanatory models of illness and treatment expectations are apparent.
- Clinicians delivering psychological and pharmacological interventions may lack an understanding of the patient's cultural background.
- The lack of supportive and positive relationships may impact on the future engagement with services.
- Comprehensive written information may not be available in the appropriate language.
- Participants from black and minority ethnic groups may face additional language barriers with a lack of adequate interpretation services being available. Where such services are available, clinicians may lack the training to work proficiently with such services.
- Lack of knowledge about the quality of access for specific black and minority ethnic groups and inflexible approaches to service delivery may hamper continued engagement with treatment.
- There is often a lack of collaborative work between mental health service providers and local voluntary and charitable sectors that may have expertise in the provision of the best cultural or specific services.
- Race, culture, ethnicity or religious background may challenge the clarity with which assessments and decisions regarding the Mental Health Act are undertaken, especially where clinicians do not seek appropriate advice and/or consultation. **\*\*2009\*\***

Therefore, based on informal consensus, the GDG for the 2009 guideline made recommendations that address, in at least an initial way, the problems raised above.

Additionally, where possible, specific problems faced by black and minority ethnic groups have been addressed in other parts of the guideline (for example, see Section 9.7.6).

The recommendations from the 2009 guideline remain but because of the change in population addressed by the 2014 guideline the recommendations have been changed to reflect this to say 'people with psychosis or schizophrenia'

It was further acknowledged by the GDG for the 2009 guideline that all of the recommendations in this section should be viewed as a foundation step in a longer process including the provision of good quality research and development. In particular, the GDG highlighted that the following points specifically need addressing through this process of research:

- **\*\*2009\*\***RCTs of psychological and pharmacological interventions and service organisation have not been adequately powered to investigate effects in specific ethnic groups including African-Caribbean people with schizophrenia.
- There are no well-designed studies of specialist mental health services providing care to diverse communities or to specific communities.
- The effect of the cultural competence of mental health professionals on service user experience and recovery has not been adequately investigated in UK mental health settings.
- English language teaching may be an alternative to providing interpreters to reduce costs and to encourage integration. This has not been tested for feasibility or outcomes.
- The early diagnosis and assessment of psychosis and comorbid disorders across ethnic, racial and cultural groups needs to be systematically assessed, with research projects including adequate samples from different cultural and ethnic backgrounds. **\*\*2009\*\***

Following publication of *Service User Experience in Adult Mental Health* (NICE, 2011), one recommendation about communication and provision of information, which was covered by that guideline, was removed.

## **6.2.10 Recommendations**

**6.2.10.1** Healthcare professionals inexperienced in working with people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds should seek advice and supervision from healthcare professionals who are experienced in working transculturally. [2009]

**6.2.10.2** Healthcare professionals working with people with psychosis or schizophrenia should ensure they are competent in:

- assessment skills for people from diverse ethnic and cultural backgrounds
- using explanatory models of illness for people from diverse ethnic and cultural backgrounds
- explaining the causes of psychosis or schizophrenia and treatment options
- addressing cultural and ethnic differences in treatment expectations and adherence
- addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the causes of abnormal mental states
- negotiating skills for working with families of people with psychosis or schizophrenia
- conflict management and conflict resolution. [2009]

**6.2.10.3** Mental health services should work with local voluntary black, Asian and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to people from diverse ethnic and cultural backgrounds. [2009]

## **6.2.11 Research recommendations**

**6.2.11.1** For people with schizophrenia, RCTs of psychological and psychosocial interventions should be adequately powered to assess clinical and cost effectiveness in specific ethnic groups (or alternatively in ethnically diverse samples). [2009]

**6.2.11.2** An adequately powered RCT should be conducted to investigate the clinical and cost effectiveness of CBT that has been culturally adapted for African-Caribbean people with schizophrenia where they are refusing or intolerant of medication.[2009]

**6.2.11.3** Studies of ethnically specific and specialist services and new service designs should be appropriately powered to assess effectiveness. Studies should include sufficient numbers of specific ethnic groups and be evaluated using an agreed high quality evaluation framework (Moffat et al., 2009).[2009]

- 6.2.11.4** For people with schizophrenia from black and minority ethnic groups living in the UK, does staff training in cultural competence at an individual level and at an organisational level (delivered as a learning and training process embedded in routine clinical care and service provision) improve the service user's experience of care and chance of recovery, and reduce staff burnout? [2009]
- 6.2.11.5** An adequately powered proof of principle study should be conducted to investigate the feasibility of comparing language skills development for those with English as a second language against using interpreters. [2009]
- 6.2.11.6** A study should be conducted to investigate engagement and loss to follow-up, prospective outcomes and care pathways, and the factors that hinder engagement. For example, ethnic, religious, language or racial identity matching may be important. This is not the same as ethnic matching, but matching on ability to work with diverse identities.[2009]
- 6.2.11.7** A study should be conducted to investigate the use of pre-identification services, including assessment, diagnosis and early engagement, across racial and ethnic groups.[2009]

# 7 INTERVENTIONS TO PROMOTE PHYSICAL HEALTH IN ADULTS

## 7.1 INTRODUCTION

This chapter is new for the 2014 guideline and aims to review the evidence for interventions that promote physical health in adults with psychosis and schizophrenia. For the purpose of this guideline, this chapter is divided into two sections. The first (Section 7.2) is concerned with behavioural interventions to promote physical activity and healthy eating, while the second (Section 7.3) assesses the efficacy of interventions for reducing and stopping smoking.

## 7.2 BEHAVIOURAL INTERVENTIONS TO PROMOTE PHYSICAL ACTIVITY AND HEALTHY EATING

### 7.2.1 Introduction

For people with psychosis and schizophrenia, a combination of poor diet and nutrition, weight gain and lack of physical activity are important contributors to high rates of physical comorbidities such as type 2 diabetes and reduced life expectancy particularly from cardiovascular disease. Moreover weight gain and obesity further contribute to stigma and discrimination and may explain unplanned discontinuation of antipsychotic medication leading to relapse.

Since the 2009 guideline (NICE, 2009d) a greater emphasis on prevention is indicated by increasing evidence that adverse effects associated with an increased risk of long-term health problems are prevalent with the use of antipsychotics (Newcomer et al., 2013). Additionally, cardiometabolic risks appear within weeks of commencing antipsychotics, particularly weight gain and hypertriglyceridaemia and later glucose dysregulation and hypercholesterolemia (Foley & Morley, 2011). The importance of prevention is further emphasised by evidence that over a third of people with established schizophrenia taking antipsychotics can be identified biochemically to be at high risk of diabetes (Manu et al., 2012). Indeed this group was specifically highlighted by NICE in its guidance on preventing type 2 diabetes, in which lifestyle interventions are recommended followed by metformin if lifestyle approaches are not successful (NICE, 2012c).

Developing recommendations about lifestyle interventions is hampered by a paucity of evidence, particularly large or longer-term studies or in people with first episode psychosis. The limited research has mainly been directed towards weight reduction rather than physical activity programmes, although in practice these approaches may overlap. A recent systematic review evaluated non-pharmacological interventions to reduce weight for people using antipsychotic medication (Caemmerer et al., 2012). The review observed a mean weight reduction of 3.12 kg

over a period of 8 to 24 weeks. Clinically significant reductions in waist circumference and improvements in cardiovascular risk factors were also shown. The benefits were seen irrespective of the duration of treatment, whether the intervention was delivered to an individual or in a group setting, and whether the intervention was based on CBT or a nutritional intervention. In addition, outpatient programmes appeared to be more effective than inpatient programmes. Weight reduction should not be the only concern since poor nutrition may directly contribute to physical ill health for this population. Again, however, there is a paucity of evidence about interventions to address these issues.

## 7.2.2 Clinical review protocol (behavioural interventions to promote physical activity and healthy eating)

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 44 (a complete list of review questions and the full review protocols can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 44: Clinical review protocol summary for the review of behavioural interventions to promote physical activity and healthy eating**

Component	Description
<i>Review question(s)</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote physical activity (all forms, with or without healthy eating)?  For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of behavioural interventions to promote healthy eating?
<i>Objectives</i>	To evaluate the clinical effectiveness of interventions to improve the health of people with psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	<ul style="list-style-type: none"> <li>Behavioural interventions to promote physical activity (with or without healthy eating)</li> <li>Behavioural interventions to promote healthy eating</li> </ul>
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>Physical health</li> <li>BMI/ weight</li> <li>Levels of physical activity</li> <li>Service use</li> <li>Primary care engagement (for example, GP visits)</li> <li>Quality of life</li> <li>User satisfaction (validated measures only)</li> </ul>
<i>Electronic database</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-process Topic specific: CINAHL, PsycINFO

<i>Date searched</i>	RCT: database inception to June 2013 SR: 1995 to June 2013
<i>Study design</i>	RCT
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short term)</li> <li>• 7-12 months' follow-up (medium term)</li> <li>• 12 months' follow-up (long term)</li> </ul> <p>Where more than one follow-up point within the same period was available, the latest one was reported.</p> <p><b>Sub-analysis</b></p> <p>Where data were available, sub-analyses were conducted of studies with ≥75% of the sample described as having a primary diagnosis of schizophrenia/schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>

### 7.2.3 Studies considered<sup>11</sup>

Twenty four RCTs (N = 1972) met the eligibility criteria for this review (see the sub-sections below). All studies were published in peer-reviewed journals between 1978 and 2013. Further information about both included and excluded studies can be found in Appendix 15a.

The trials identified evaluated the effectiveness of behavioural interventions to promote physical activity in combination with healthy eating and interventions to promote physical activity alone. No studies with the singular aim of promoting healthy eating were identified. Table 45 provides an overview of the trials included in each category.

#### *Behavioural interventions to promote physical activity and healthy eating*

Of the eligible trials, 15 RCTS (N = 1,337) evaluated a combined behavioural physical activity and healthy eating intervention compared with an alternative management strategy: ALVAREZ2006 (Alvarez-Jiménez et al., 2006), ATTUX2013 (Attux et al., 2013), BRAR2005 (Brar et al., 2005), BROWN2011 (Brown et al., 2011), DAUMIT2013 (Daumit et al., 2013), EVANS2005 (Evans et al., 2005), KWON2006 (Kwon et al., 2006), LITTRELL2003 (Littrell et al., 2003), MAURI2008 (Mauri et al., 2008), MCKIBBIN2006 (McKibbin et al., 2006), SCOCCO2006 (Scocco et al., 2006), SKRINAR2005 (Skrinar et al., 2005), WU2007 (Wu et al., 2007), WU2008 (Wu et al., 2008) and USHER2012 (Usher et al., 2013).

---

<sup>11</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).



All 15 trials followed a psychoeducation/information-based approach and provided information and support for how to increase levels of physical activity and healthy eating. Four of the included trials (DAUMIT2013, SKRINAR2005, WU2007, WU2008) additionally included prescribed physical activity as a part of the intervention. Participants in the intervention arm of one trial (WU2008) were prescribed metformin (N=64)<sup>12</sup>. Of the 15 trials, 13 included a large proportion ( $\geq 75\%$ ) of participants with a primary diagnosis of psychosis or schizophrenia. None of the included trials were based in the UK. Table 45 provides an overview of the included trials.

### *Behavioural interventions to promote physical activity*

Of the eight eligible trials (N = 635), seven (N = 455) evaluated a behavioural physical activity intervention compared with an alternative management strategy: ACIL2008 (Acil et al., 2008), BEEBE2010 (Beebe, 2010), CHAO2010 (Chao, 2010), COLE1997 (Cole, 1997), PAJONK2010 (Pajonk et al., 2010), SCHEEWE2013 (Scheewe et al., 2013) and VARAMBALLY2012 (Varambally et al., 2012); two trials (N = 180) evaluated one type of physical activity intervention with another programme: DURAIWAMY2007 (Duraiswamy et al., 2007) and VARAMBALLY2012. VARAMBALLY2012 was used in both comparisons.

Five of the seven eligible trials (ACIL2008, COLE1997, PAJONK2010, SCHEEWE2013, VARAMBALLY2012) included prescribed physical activity as an integral part of the intervention. A single trial (BEEBE2010) provided participants with information about physical activity and another (CHAO2010) provided participants with a pedometer that was used and monitored in daily life for the prescribed period. Two trials (DURAIWAMY2007, VARAMBALLY2012) evaluated a yoga intervention versus an aerobic training programme.

Of the eligible trials, six included a large proportion ( $\geq 75\%$ ) of participants with a primary diagnosis of psychosis or schizophrenia. None of the included trials was based in the UK. Table 45 provides an overview of the included trials.

---

<sup>12</sup>An oral diabetes medication that is used to control blood sugar levels.

**Table 45: Study information table for trials included in the meta-analysis of behavioural interventions to promote physical activity and healthy eating versus any alternative management strategy**

	Physical activity and healthy eating interventions versus any alternative management strategy	Physical activity interventions versus any alternative management strategy	Physical activity (yoga) versus physical activity (aerobic)
<i>Total no. of trials (k); participants (N)</i>	k = 15 ; N = 1337	k = 7; N = 455	k = 2; N = 180
<i>Study ID(s)</i>	ALVAREZ2006 ATTUX2013 BRAR2005 BROWN2011 DAUMIT2013 EVANS2005 KWON2006 LITTRELL2003 MAURI2008 MCKIBBIN2006 SCOCCO2006 SKRINAR2005 USHER2012 WU2007 WU2008	ACIL2008 BEEBE2010 CHAO2010 COLE1997 PAJONK2010 SCHEEWE2013 VARAMBALLY2012	DURAIWAMY2007 VARAMBALLY2012 <sup>3</sup>
<i>Country</i>	Australia (k =2) Brazil (k = 1) China (k =2) Italy (k =2) South Korea (k =1) Spain (k =1) USA (k =6)	Germany (k = 1) India (k = 1) Netherlands (k = 1) Turkey (k = 1) USA (k =3)	India (k = 2)
<i>Year of publication</i>	1996 to 2013	1997 to 2012	2007 to 2012
<i>Mean age of participants (range)</i>	38.35 years (26.3 to 54 years) <sup>1</sup>	36.41 years (29.7 to 46.9 years)	31.9 years (32.6 to 32.3 years)
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	87.46% (10.2 to 100%) <sup>2</sup>	83.19% (21.7 to 100%)	100% (100 to 100%)
<i>Mean gender % women (range)</i>	50.56% (24.6 to 68.8%)	39.84% (0% to 74.6%)	31.1% (30.3 to 30.7%)
<i>Length of treatment</i>	8 to 26 weeks	2 to 26 weeks	3 to 4 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> ATTUX2013 BRAR2005 BROWN2011 KWON2006 MAURI2008 MCKIBBIN2006 SCOCCO2006 SKRINAR2005 USHER2012 WU2007	<i>End of treatment only</i> ACIL2008 CHAO2010 COLE1997 PAJONK2010 SCHEEWE2013  <i>Up to 6 months</i> BEEBE2010 VARAMBALLY2012	<i>Up to 6 months</i> DURAIWAMY2007 VARAMBALLY2012

	<p>WU2008</p> <p><i>Up to 6 months</i>  ALVAREZ2006  DAUMIT2013  EVANS2005  LITTRELL2003  MCKIBBIN2006</p> <p><i>Up to 12 months</i>  ALVAREZ2006  DAUMIT2013</p>		
<i>Intervention type</i>	<p>Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE) (k = 1)</p> <p>Behavioural weight-loss treatment (k = 1)</p> <p>Diabetes Awareness and Rehabilitation Training (DART) (k = 1)</p> <p>Early behavioural intervention (k = 1)</p> <p>Healthy lifestyle intervention (k = 3)</p> <p>Lifestyle Wellness Program (k = 1)</p> <p>Nutrition education sessions (k = 1)</p> <p>Passport 4 Life programme (k = 1)</p> <p>Psychoeducation class - Solutions of Wellness modules (k = 1)</p> <p>Psychoeducational intervention and referral to a nutritionist (k = 1)</p> <p>Psychoeducational Program (PEP) for weight control (k = 1)</p> <p>Recovering Energy Through Nutrition and Exercise for Weight Loss (RENEW) (k = 1)</p> <p>Weight management programme (k = 1)</p>	<p>Aerobic exercise training (k = 2)</p> <p>Exercise therapy (k = 1)</p> <p>Pedometer with and without self-monitoring (k = 1)</p> <p>Physical activity programme (k = 1)</p> <p>Physical exercise: adopted from the National Fitness Corps' <i>Handbook for Middle High and Higher Secondary Schools</i> (k = 1)</p> <p>WALCS group education sessions (k = 1)</p> <p>Yoga - Swami Vivekananda Yoga Anusandhana Samsthana (k = 1)</p>	<p>Yoga- Swami Vivekananda Yoga Anusandhana Samsthana (k = 2)</p>
<i>Comparisons</i>	<p>Information booklet (k = 1)</p> <p>No treatment - waitlist (k = 1)</p> <p>Olanzapine treatment as usual (k = 3)</p> <p>Passive nutritional education from the booklet 'Food for the Mind' (k = 1)</p> <p>Standard care (k = 8)</p> <p>Usual care plus</p>	<p>No pedometer control (k = 1)</p> <p>Occupational therapy (k = 1)</p> <p>Table top football (k = 1)</p> <p>Time-and-attention control (k = 1)</p> <p>Treatment as usual (k = 3)</p>	<p>Physical exercise: adopted from the National Fitness Corps' <i>Handbook for Middle High and Higher Secondary Schools</i> (k = 2)</p>

	information (k = 1)		
<p><i>Note.</i> WALCs = Walk, Address Sensations, Learn About Exercise, Cue Exercise for schizophrenia spectrum disorders.</p> <p><sup>1</sup> One study (USHER2012) failed to report mean age.</p> <p><sup>2</sup> One study (SKRINAR2005) failed to report % diagnosis.</p> <p><sup>3</sup> VARAMBALLY2012 was composed of three arms and was used in both 'physical activity interventions versus any alternative management strategy' and 'physical activity (yoga) versus physical activity (aerobic)' comparisons.</p>			

## 7.2.4 Clinical evidence for behavioural interventions to promote physical activity and healthy eating

Evidence from each important outcome and overall quality of evidence are presented in Table 46, Table 47 and Table 48. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

### *Behavioural interventions to promote physical activity and healthy eating*

Low quality evidence from up to 14 trials (N = 1,111) showed that a behavioural physical activity and healthy eating intervention had a significant effect on reducing body weight at the end of treatment and at short-term follow-up. There was no difference between the intervention and control groups at short-term follow-up for weight reduction. There was inconsistent evidence for changes in activity level.

Moderate to low quality evidence from up to six trials with 353 participants showed that behavioural interventions to promote physical activity and healthy eating had a small but significant positive effect on quality of life and participant satisfaction at the end of treatment. No data evaluating this at follow-up were identified.

None of the trials evaluated provided data for the crucial outcome of primary care engagement.

### *Sub-analysis (psychosis and schizophrenia only)*

For the critical outcomes of body weight/BMI, the sub-analysis findings did not differ from the main analysis. Unlike the main analysis, there is no evidence of an increase in quality of life in favour of the active intervention. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 46: Summary of findings table for trials of physical activity and healthy eating interventions compared with any alternative management strategy**

Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Physical activity and healthy eating		
Body mass (weight) - end of treatment	Mean body mass (weight end of treatment) in the intervention groups was 2.8 lower (3.6 to 1.99 lower)	1,111 (14 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Body mass (weight) - up to 6 months' follow-up	Mean body mass-(weight up to 6 months' follow-up) in the intervention groups was 2.33 lower (3.31 to 1.34 lower)	449 (5 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
Body mass (weight) - > 12 months' follow-up	Mean body mass (weight > 12 months' follow-up) in the intervention groups was 3.20 lower (5.17 to 1.23 lower)	247 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Quality of life - end of treatment	Mean quality of life (end of treatment) in the intervention groups was 0.24 standard deviations higher (0.01 to 0.47 higher)	353 (6 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
Satisfaction - end of treatment	Mean satisfaction (end of treatment) in the intervention groups was 0.75 standard deviations higher (0.26 to 1.23 higher)	71 (1 study)	⊕⊕⊕⊖ Moderate <sup>4</sup>
Physical health (exercise) - end of treatment - Clinical Global Impression (CGI): activity Level	Mean physical health (CGI activity level end of treatment) in the intervention groups was 1.04 standard deviations higher (0.28 to 1.81 higher)	34 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
Physical health (exercise) - end of treatment - accelerometry (total minutes of activity)	Mean physical health (total minutes of activity end of treatment) in the intervention groups was 0.56 standard deviations higher (0.03 to 1.09 higher)	57 (1 study)	⊕⊕⊕⊖ low <sup>3,4</sup>
Physical health (exercise) - end of treatment - International Physical Activity Questionnaire-short version (IPAQ-short)	Mean physical health (IPAQ-short score end of treatment) in the intervention groups was 0.01 standard deviations higher (0.34 lower to 0.36 higher)	126 (1 study)	⊕⊕⊕⊕ High
Physical health (exercise) - up to 6 months' follow-up - accelerometry (total minutes of activity)	Mean physical health (total minutes of activity up to 6 months' follow-up) in the intervention groups was 0.22 standard deviations higher (0.33 lower to 0.76 higher)	52 (1 study)	⊕⊕⊕⊖ Low <sup>3</sup>

activity)			
<p>Note. CI = confidence interval.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Most studies included are at moderate risk of bias.</p> <p><sup>2</sup> Evidence of serious heterogeneity of study effect size.</p> <p><sup>3</sup> CI crosses clinical decision threshold.</p> <p><sup>4</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.</p>			

## ***Behavioural interventions to promote physical activity***

### **Physical activity versus any alternative management strategy**

There was no conclusive evidence favouring physical activity over control for reducing weight, quality of life or increasing levels of physical activity as measured by a researcher. However, one trial (N = 53), using a subjective self-report, presented moderate quality evidence of an increase in physical activity for the intervention group at the end of the intervention, but this was not maintained at short-term follow-up.

None of the included trials provided data for the critical outcomes of primary care engagement and user satisfaction.

#### *Sub-analysis (psychosis and schizophrenia only)*

For the critical outcome of physical activity levels, the sub-analysis findings did not differ from the main analysis. No other critical outcome data were available. See Appendix 16 for the related forest plots.

### **Physical activity (yoga) versus physical activity (aerobic)**

One trial (N = 41) presented high quality evidence that yoga when compared with aerobic physical activity improved quality of life at short-term follow-up. No other critical outcomes were reported for this review.

#### *Sub-analysis (psychosis and schizophrenia only)*

For the critical outcome of quality of life, the sub-analysis findings did not differ substantially from the main analysis. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 47: Summary of findings table for physical activity interventions compared with any alternative management strategy**

Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Physical activity		
<i>Physical health (weight/BMI) - end of treatment</i>	Mean physical health (weight end of treatment) in the intervention groups was 0.20 higher (0.20 lower to 0.59 higher)	105 (2 study)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Quality of life - end of treatment</i>	Mean quality of life (end of treatment) in the intervention groups was 0.62 standard deviations higher (0.41 lower to 1.66 higher)	83 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,4,5</sup>
<i>Physical activity (minutes walked) - end of treatment</i>	Mean physical activity (minutes walked end of treatment) in the intervention groups was 0.24 standard deviations higher (0.16 lower to 0.64 higher)	97 (1 study)	⊕⊕⊕⊕ Low <sup>2,6</sup>
<i>Physical activity (IPAQ-short telephone format)</i>	Mean physical activity (IPAQ-short score) in the intervention groups was 0.32 standard deviations higher (0.27 lower to 0.91 higher)	53 (1 study)	⊕⊕⊕⊕ Moderate <sup>6</sup>
<i>Physical activity (minutes walked) - up to 6 months' follow-up</i>	Mean physical activity (minutes walked up to 6 months' follow-up) in the intervention groups was 0.34 standard deviations higher (0.06 lower to 0.74 higher)	97 (1 study)	⊕⊕⊕⊕ Low <sup>2,6</sup>
<p>Note. CI = confidence interval.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Concern as to the applicability of intervention and population.</p> <p><sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p> <p><sup>3</sup> Suspicion of publication bias.</p> <p><sup>4</sup> Most information is from studies at moderate risk of bias.</p> <p><sup>5</sup> Evidence of very serious heterogeneity of study effect size.</p> <p><sup>6</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.</p>			

**Table 48: Summary of findings table for yoga compared with aerobic exercise**

Outcomes	Illustrative comparative risks* (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Corresponding risk		
	Physical activity (yoga)		
<i>Quality of life - up to 6 months' follow-up</i>	Mean quality of life (up to 6 months' follow-up) in the intervention groups was 0.34 standard deviations higher (0.06 lower to 0.74 higher)	41 (1 study)	⊕⊕⊕⊕ High
<p>Note. CI = confidence interval.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p>			

### 7.2.5 Clinical evidence summary

Overall the evidence suggests that behavioural interventions to promote physical activity and healthy eating are effective in reducing body weight/BMI and this effect can be maintained in the short term. As no longer-term data were available, the effects greater than 6 months are not known. There is no consistent evidence (across outcome rater types) of a beneficial effect on the levels of physical activity. In addition, there is evidence that an intervention that combines a behavioural approach to promoting both physical activity and healthy eating can improve quality of life when measured at the end of treatment. However, the longer-term benefits are not known. In sub-analysis including trials with a majority sample of participants with a primary diagnosis of psychosis or schizophrenia, the findings did not differ from the main analysis.

Interventions that aimed to promote physical activity alone were not found to be any more effective than control in reducing weight/BMI, with inconclusive evidence with regards to increased levels of physical activity. Additionally there was no evidence of an increase in quality of life at the end of treatment. Limited evidence suggests that a yoga intervention is more effective than aerobic physical activity in improving quality of life in the short term. These findings did not differ for the psychosis and schizophrenia subgroup.

### 7.2.6 Health economics evidence

No studies assessing the cost effectiveness of behavioural interventions to promote physical health in people with psychosis and schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. One study currently in press (Winterbourne et al., (2013a) was identified following information provided by the GDG. Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are provided in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

Winterbourne and colleagues (2013a) performed a cost-utility analysis comparing a 3-month intervention involving psychoeducation, nutritional and/or exercise counselling with standard care. Standard care involved basic advice on weight and exercise, on the risk of developing a cardiovascular event and/or type 2 diabetes mellitus and life expectancy. A hypothetical cohort of 1000, 30-year old male service users with first episode psychosis was modelled in yearly cycles over their lifetime. In the first cycle, following the weight-gain prevention intervention, these individuals could either remain in a health state where baseline weight gain is unchanged or gain 7% of their initial bodyweight. In addition, in every cycle, the service users can transition to a health state where they have diabetes and/or a



major cardiovascular event. The analysis was performed from the perspective of the UK NHS and adopted a lifetime perspective. Only direct healthcare costs were included in the analysis and the primary outcome measure was the QALY. The expected mean lifetime costs per person were £6,893 and £6,293 for the intervention and standard care groups, respectively. According to the model the mean lifetime QALYs were 14.0 and 13.4 for the intervention and standard care groups, respectively. The cost per QALY associated with the intervention was £960, which is far below NICE's lower cost-effectiveness threshold value of £20,000. Moreover, the cost-effectiveness acceptability analysis showed that at a willingness to pay of £20,000 per QALY, the probability of the intervention being cost effective was 0.95. Deterministic sensitivity analysis found the cost per QALY to be sensitive to the intervention effect, intervention costs and utility values. Using alternative 12-month follow-up data, where transition probability from baseline to weight gain health state increased from 0.26 to 0.78 and the cost of the intervention increased from £856 to £1,288, resulted in the intervention being dominated by standard care. A range of subgroup analyses were performed (that is, changing gender, smoking status, baseline BMI and diagnosis). However, in all of the sub-analyses the cost per QALY was in the range of £705-1,034. Overall the analysis was judged to be partially applicable to this guideline review and the NICE reference case. Even though it excluded costs relevant to the PSS perspective the authors reported that these were expected to account only for a small proportion of the total NHS and social care costs (<10%) for people with psychosis and schizophrenia and so are unlikely to affect the results. Also, it is not clear whether the definition of standard care is applicable to the current practice in the NHS as it was adapted from the studies included in the meta-analyses of the intervention effect. Moreover, diabetes and CVD risk estimates were based on risk algorithms for the general population. Research in people with mental health problems indicate that they are at higher risk than the general population of certain physical health problems including obesity (Hert et al., 2011), which in turn leads to higher risk of cardiovascular disease and diabetes. The authors have partially allowed for higher risk in this population by assuming that people in the cohort were heavy smokers. The utility values were taken from UK population but the EQ-5D ratings were from a mix of UK, German and US patient samples. The resource utilisation was based on RCT data and authors' assumptions, which may limit the generalisability of the findings. As a result, this analysis was judged by the GDG to have potentially serious methodological limitations.

## 7.2.7 Linking evidence to recommendations

### *Relative value placed on the outcomes considered*

The GDG agreed that the main aims of a physical health and/or healthy eating intervention should be to improve health, reduce weight and improve quality of life (Sattelmair et al., 2011; Tuomilehto et al., 2011). The GDG also considered the importance of engaging the service user in the intervention. Therefore, the GDG decided to focus on the following, which were considered to be critical:

- physical health
- BMI/ weight

- levels of physical activity
- service use
- primary care engagement (for example, GP visits)
- quality of life
- user satisfaction (validated measures only).

### *Trade-off between clinical benefits and harms*

A wealth of research in the general population supports the importance of being physically active and having a healthy, balanced diet. For adults with psychosis and schizophrenia, interventions that aim to both increase physical activity and improve healthy eating are effective in reducing weight. Although data assessing benefits in the short and long term were sparse, the evidence suggested benefits are sustained. Furthermore, both improved quality of life and satisfaction with the intervention were observed. The GDG considered this evidence of clinical benefit to be of particular importance in a population with greatly increased risk of mortality.

### *Trade-off between net health benefits and resource use*

The health economic evidence on interventions to promote physical health in adults with psychosis and schizophrenia was limited to one UK study. Despite the study's limitations (for instance, lack of robust long-term clinical evidence and the model not considering the potential savings to the NHS as a consequence of reducing other obesity-related illnesses), the results provide evidence that non-pharmacological interventions that include psychoeducation, nutritional and/or exercise counselling, can be successful in preventing weight gain in the short term in people with psychosis and schizophrenia. The positive economic finding supports the GDG's view that these interventions are not only of important clinical benefit but also are likely to be cost effective within the NICE decision-making context.

### *Quality of the evidence*

The evidence ranged from very low to high across both groups of interventions. For the combined physical health and healthy eating intervention, evidence was of better quality and rated from low to moderate across critical outcomes. Reasons for downgrading included risk of bias, inconsistency (although the direction of effect was consistent across studies) and, for some outcomes, imprecision.

### *Other considerations*

The review of behavioural interventions that promote healthy eating (without a physical activity component) did not identify any studies meeting the review protocol. The evidence suggests that a behavioural intervention to increase physical activity and healthy eating is effective in reducing weight and improving quality of life in adults with psychosis and schizophrenia. The GDG considered the possibility of cross-referring to existing guidance in this area for the general population. However, people with psychosis and schizophrenia are at a high risk of morbidity and mortality because of physical complications such as diabetes, obesity, cardiovascular disease and other related illness. Therefore, the GDG decided it was

important to generate recommendations specifically for this population and felt the available evidence assisted in informing these recommendations. They did, however, see the benefit of making specific reference to NICE guidance on obesity and prevention of diabetes and cardiovascular disease.

Evidence suggests that long periods of mild physical activity, for example walking, is more effective than shorter periods of moderate to vigorous exercise in improving insulin action and plasma lipids for people who are sedentary. The GDG purposefully decided to use the terms 'physical activity' and 'healthy eating' (rather than the potentially stigmatising words 'exercise' and 'diet') in order to take this evidence into consideration and promote a long-term lifestyle change rather than a short-term 'fix' to reduce weight (Duvivier et al., 2013).

The GDG went beyond the evidence of clinical benefit to consider other important issues that can determine the physical health of an adult with psychosis or schizophrenia. These issues relate to when physical health problems should be assessed, how they should be monitored and who should be responsible for both physical and mental health. The GDG considered and discussed the important role of primary care in monitoring physical health (especially current diabetes and cardiovascular disease) and that this should be made explicit in the care plan. The GDG believed that these issues were of equal importance to the service user's health as the interventions themselves.

Finally, two recommendations from the 2009 guideline, which were developed by GDG consensus and originally included in the chapter on service-level interventions (which has been updated for the 2014 guideline), have also been included here.

## **7.2.8 Recommendations**

- 7.2.8.1** People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider. [new 2014]
- 7.2.8.2** If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see [Obesity](#) [NICE clinical guideline 43], [Lipid modification](#) [NICE clinical guideline 67] and [Preventing type 2 diabetes](#) [NICE public health guidance 38]. [new 2014]
- 7.2.8.3** Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia. These should be audited in the annual team report. [new 2014]
- 7.2.8.4** Trusts should ensure compliance with quality standards on the monitoring and treatment of cardiovascular and metabolic disease in people with psychosis or schizophrenia through board-level performance indicators. [new 2014]

- 7.2.8.5** GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia. Include all the checks recommended in 10.11.1.3 and refer to relevant NICE guidance on monitoring for cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist, and put in the secondary care notes. [new 2014]
- 7.2.8.6** Identify people with psychosis or schizophrenia who have high blood pressure, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity following relevant NICE guidance (see [Lipid modification](#) [NICE clinical guideline 67], [Preventing type 2 diabetes](#) [NICE public health guidance 38], [Obesity](#) [NICE clinical guideline 43], [Hypertension](#) [NICE clinical guideline 127], [Prevention of cardiovascular disease](#) [NICE public health guidance 25] and [Physical activity](#) [NICE public health guidance 44]). [new 2014]
- 7.2.8.7** Treat people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance (for example, see [Lipid modification](#) [NICE clinical guideline 67], [Type 1 diabetes](#) [NICE clinical guideline 15], [Type 2 diabetes](#) [NICE clinical guideline 66], [Type 2 diabetes – newer agents](#) [NICE clinical guideline 87]). [2009]
- 7.2.8.8** Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 12.2.5.7, 7.2.8.5–7.2.8.7. [2009]

## **7.2.9 Research recommendation**

- 7.2.9.1** What are the short- and long-term benefits to physical health of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without major risks? [2009]

## **7.3 INTERVENTIONS FOR SMOKING CESSATION AND REDUCTION**

### **7.3.1 Introduction**

A UK community cohort study (Brown et al., 2010) of people with schizophrenia found that 73% smoked, that smoking-related disease accounted for 70% of the excess natural mortality in the cohort, and that the risk of mortality was doubled for those who smoked. These high rates contrast with around only 22% of the general population who currently smoke (The NHS Information Centre & Lifestyles Statistics, 2011).

Interventions for smoking cessation in the general population range from basic advice to more intensive approaches involving pharmacotherapy coupled with either individual or group psychological support; the three main pharmacotherapies are nicotine replacement therapy (NRT), bupropion (antidepressant) and varenicline (a nicotinic receptor partial agonist) (Campion et al., 2008). Banham and Gilbody (Banham & Gilbody, 2010) reviewed eight RCTs of pharmacological and/or psychological interventions for smoking cessation for people with severe mental illness (schizophrenia and bipolar disorder). In their review most cessation interventions showed moderate benefit, some reaching statistical significance. The authors concluded that treating tobacco dependence was effective and those treatments that work in the general population also work for those with severe mental illness and appear approximately equally effective. These trials observed few adverse events, nor were adverse effects on psychiatric symptoms noted, most significant changes favouring the intervention groups over the control groups. Notwithstanding these potential benefits smokers with severe mental illness are rarely referred to smoking cessation services (Campion et al., 2008).

### **7.3.2 Clinical review protocol (interventions for smoking cessation and reduction)**

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 49 (a complete list of review questions and their related protocols can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 49: Clinical review protocol summary for the review of interventions for smoking cessation and reduction**

<b>Component</b>	<b>Description</b>
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of interventions for smoking cessation and reduction?
<i>Objectives</i>	To evaluate the clinical effectiveness of interventions to improve the health of people with psychosis and schizophrenia
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis
<i>Intervention(s)</i>	<p><b>Included interventions</b> Only pharmacological interventions that aim for smoking reduction or cessation will be evaluated. These include:</p> <ul style="list-style-type: none"> <li>• bupropion</li> <li>• varenicline</li> <li>• transdermal nicotine patch.</li> </ul> <p><b>Excluded interventions</b> This review will not evaluate:</p> <ul style="list-style-type: none"> <li>• interventions that report smoking outcomes but the primary aim is not smoking reduction or cessation</li> <li>• non-pharmacological interventions (because they are already addressed in other guidelines)</li> <li>• combined non-pharmacological and pharmacological interventions.</li> </ul>
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Anxiety and depression</li> <li>• Physical health</li> <li>• Smoking (cessation or reduction)</li> <li>• Weight/BMI</li> <li>• Quality of life</li> <li>• User satisfaction (validated measures only)</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	<ul style="list-style-type: none"> <li>• RCT: database inception to June 2013</li> <li>• SR: 1995 to June 2013</li> </ul>
<i>Study design</i>	RCT
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• 6-8 weeks' follow-up (short-term)</li> <li>• Up to 6 months' follow-up (medium-term)</li> <li>• Greater than 6 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><b>Sub-analysis</b> Where the data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>

### 7.3.3 Studies considered<sup>13</sup>

The GDG selected an existing Cochrane review (Tsoi et al., 2013) as the basis for this section of the guideline, with a new search conducted to update the existing review. The existing review included 34 RCTs evaluating a variety of interventions and comparisons. A number of these were outside the scope of this guideline, therefore, only the comparisons relevant to this guideline are reported.

In total, 11 RCTs (N = 498) met the eligibility criteria for this review<sup>14</sup>:

+Akbarpour2010 (Akbarpour et al., 2010), +Bloch 2010 (Bloch et al., 2010), \*Evins 2001 (Evins et al., 2001), \*Evins 2005 (Evins et al., 2005), \*Evins 2007 (Evins et al., 2007), +Fatemi2005 (Fatemi et al., 2005), \*George 2002 (George et al., 2002), \*George 2008 (George et al., 2008), \*Li 2009 (Li et al., 2009), \*Weiner 2011 (Weiner et al., 2011), \*Weiner 2012 (Weiner et al., 2012), \*Williams 2007 (Williams et al., 2007), \*Williams 2012 (Williams et al., 2012a). Two trials meeting eligibility criteria were reported only as letters to the editors or conference proceedings (+Fatemi 2005; \*Williams 2007) and thus findings are described narratively. Nine studies meeting eligibility criteria (+Akbarpour2010, +Bloch 2010, \*Evins 2001, \*Evins 2005, \*Evins2007, \*George 2002, \*George 2008, \*Li 2009, \*Weiner 2012) were published in peer-reviewed journal. All included trials were published between 2001 and 2012. Further information about both included and excluded studies can be found in Tsoi et al. (2013).

Of the included trials, seven (N = 344) involved a comparison of bupropion versus placebo with the aim of smoking cessation. Three trials (N = 103) also compared bupropion with placebo but with the aim of smoking reduction. Two trials (N = 60) compared varenicline with placebo with the aim of smoking cessation. One trial compared high dose (42 mg daily) versus regular dose (21 mg daily) transdermal nicotine patch (TNP) for smoking cessation<sup>15</sup>. Table 50 provides an overview of the trials included in each category.

---

<sup>13</sup>Changes have not been made to the study ID format used in the Cochrane review utilised in this section.

<sup>14</sup> Studies prefixed with an asterisk (\*) indicate interventions for smoking cessation and studies prefixed with a cross (+) indicate interventions for smoking reduction.

<sup>15</sup> This review did not evaluate two trials of TNP where treatment was for only 32 hours (Dalack GW, Meador-Woodruff JH. Acute feasibility and safety of a smoking reduction strategy for smokers with schizophrenia. *Nicotine & Tobacco Research*. 1999;1:53-7.) and 7 hours (Hartman N, Leong GB, Glynn SM, Wilkins JN, Jarvik ME. Transdermal nicotine and smoking behavior in psychiatric patients. *American Journal of Psychiatry*. 1991;148:374-5. Also, patients in both trials had no desire to reduce or stop smoking.

**Table 50: Study information table for trials comparing interventions for smoking cessation and to reduce smoking with any alternative management strategy**

	<b>Bupropion versus placebo (smoking cessation)</b>	<b>Bupropion versus placebo (smoking reduction)</b>	<b>Varenicline versus placebo (smoking cessation)</b>	<b>High dose (42 mg) versus regular dose (21 mg) TNP (smoking cessation)</b>
<i>Total no. of trials (k); participants (N)</i>	k =7; (N = 344)	k =3; (N = 103)	K=2 (N = 137)	k = 1; (N = 51)
<i>Study ID(s)</i>	*Evins 2001 *Evins 2005 *Evins 2007 *George 2002 *George 2008 *Li 2009 *Weiner 2012	+Akbarpour 2010 +Bloch 2010 +Fatemi 2005	*Weiner 2011 *Williams 2012	*Williams 2007
<i>Country</i>	China (k = 1) USA (k = 6)	Iran (k = 1) Israel (k = 1) USA (k = 1)	USA (k = 1) USA & Canada (k = 1)	USA (k = 1)
<i>Year of publication</i>	2001 to 2012	2005 to 2010	2001 to 2012	2007
<i>Mean age of participants (range)</i>	43.46 years (38-48.7 years)	44.5 years (41.6-47.4 years) <sup>2</sup>	41.1 years (not reported k = 1)	N/A <sup>3</sup>
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	100% (100 - 100%)	100% (100 - 100%)	100% (100 - 100%)	100% (100 - 100%)
<i>Mean percentage of women (range)</i>	29.62% (0 - 43.75%) <sup>1</sup>	12.3%(0 - 24.59%) <sup>2</sup>	23% (not reported k = 1)	N/A <sup>3</sup>
<i>Length of treatment</i>	4 to 12 weeks	3 to 14 weeks	12 weeks	8 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> *Weiner 2012  <i>Up to 6 months</i> *Evins 2001 *Evins 2005 *Evins 2007 *Li 2009  <i>6- 12 months</i> *George 2002 *George 2008	<i>End of treatment only</i> +Akbarpour 2010 +Bloch 2010 +Fatemi 2005	<i>End of treatment</i> *Weiner 2011 *Williams 2012  <i>24 weeks</i> *Williams 2012	<i>End of treatment only</i> *Williams 2007
<i>Intervention type</i>	Bupropion (k = 7)	Bupropion (k = 3)	Varenicline (k = 2)	TNP 42 mg daily (k = 1)
<i>Comparisons</i>	Placebo (k = 7)	Placebo (k = 3)	Placebo (k = 2)	TNP 21 mg daily (k = 1)
<p><i>Note.</i> TNP = transdermal nicotine patch.  <sup>1</sup>Evins 2007 did not provide data.  <sup>2</sup>Fatemi 2005 did not provide data.  <sup>3</sup>Williams 2007 did not provide data.</p>				



### **7.3.4 Clinical evidence for interventions for reducing smoking reduction or cessation**

#### ***Bupropion for smoking cessation***

Low to moderate quality evidence from up to seven studies (N = 340) showed that bupropion was more effective than placebo for smoking abstinence at the end of the intervention at up to 6 months' follow-up.

Low to moderate quality evidence from up to four studies (N = 169) showed that bupropion was more effective than placebo for smoking reduction (as measured by exhaled carbon monoxide levels and cigarettes per day) at the end of treatment. No significant difference was observed between groups at 6 months' follow-up. No difference between bupropion and placebo groups was reported for either positive or negative psychosis symptoms or depressive symptoms.

#### ***Bupropion for smoking reduction***

No significant difference between bupropion and placebo was observed for smoking reduction (as measured by exhaled carbon monoxide levels) and positive or negative psychosis symptoms at the end of the intervention.

#### ***Varenicline for smoking cessation***

Low quality evidence from up to two studies (N = 137) showed that varenicline was more effective than placebo for smoking abstinence at up to 6 months' follow-up. No significant difference was observed between groups at the end of the intervention.

#### ***Transdermal nicotine patch for smoking cessation***

The trial evaluating this comparison was reported in a conference paper and could be included in meta-analysis. The authors reported that there was no significant difference between high and regular dose TNP in time to first relapse.

Summary of findings can be found in Table 51 and Table 52. The full GRADE evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

**Table 51: Summary of findings table for bupropion versus placebo for smoking cessation and reduction**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Bupropion versus placebo			
<i>Abstinence - 6 months' follow-up (primary outcome) - bupropion versus placebo</i>	Study population		RR 2.19 (0.5 to 9.63)	104 (3 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	38 per 1000	83 per 1000 (19 to 363)			
	36 per 1000	79 per 1000 (18 to 347)			
<i>Abstinence - 6 months' follow-up (primary outcome) - bupropion + TNP versus placebo + TNP</i>	Study population		RR 3.41 (0.87 to 13.3)	110 (2 studies)	⊕⊕⊕⊖ Moderate <sup>2</sup>
	36 per 1000	124 per 1000 (32 to 484)			
	39 per 1000	133 per 1000 (34 to 519)			
<i>Abstinence - end of treatment (secondary outcome) - bupropion + TNP versus placebo + TNP</i>	Study population		RR 2.92 (0.75 to 11.33)	110 (2 studies)	⊕⊕⊕⊖ Low <sup>2,3</sup>
	109 per 1000	319 per 1000 (82 to 1000)			
	113 per 1000	330 per 1000 (85 to 1000)			
<i>Abstinence - end of treatment (secondary outcome) - bupropion versus placebo</i>	Study population		RR 3.67 (1.66 to 8.14)	230 (5 studies)	⊕⊕⊕⊖ Moderate <sup>4</sup>
	52 per 1000	191 per 1000 (87 to 425)			
	63 per 1000	231 per 1000 (105 to 513)			
<i>Reduction (expired CO level) - end of treatment (secondary outcome) - abstinence studies - studies using final measurements</i>	N/A	Mean reduction (expired CO level at the end of treatment) in the intervention groups was 6.01 lower (10.2 to 1.83 lower)	N/A	150 (3 studies)	⊕⊕⊕⊖ Moderate <sup>5</sup>
<i>Reduction (expired CO level) - the end of treatment (secondary outcome) - abstinence studies - studies using change from baseline</i>	N/A	Mean reduction (expired CO level at the end of treatment) in the intervention groups was 14.8 lower (28.15 to 1.45 lower)	N/A	19 (1 study)	⊕⊕⊕⊖ Low <sup>5</sup>
<i>Reduction (expired CO level) - 6 months' follow-up (secondary outcome) - abstinence studies - studies using final measurements</i>	N/A	Mean reduction (expired CO level at 6 months' follow-up) in the intervention groups was 2.08 lower (17.76 lower to 13.59 higher)	N/A	104 (2 studies)	⊕⊕⊕⊖ Very low <sup>2,6</sup>
<i>Reduction (expired CO level) - 6 months' follow-up (secondary outcome) - abstinence studies - studies using change from baseline</i>	N/A	Mean reduction (expired CO level at 6 months' follow-up) in the intervention groups was 14.3 lower (27.2 to 1.4 lower)	N/A	19 (1 study)	⊕⊕⊕⊖ Low <sup>5</sup>
<i>Reduction (change in number of CPD from baseline) - end of treatment (secondary outcome) - abstinence studies</i>	N/A	Mean reduction (change in number of CPD from baseline at the end of treatment) in the intervention groups was 10.77 lower (16.52 to 5.01 lower)	N/A	184 (3 studies)	⊕⊕⊕⊖ Very low <sup>1,3,5</sup>

<i>Reduction (change in number of CPD from baseline) - 6 months' follow-up (secondary outcome) - abstinence studies</i>	N/A	Mean reduction (change in number of CPD from baseline at 6 months' follow-up) in the intervention groups was 0.4 higher (5.72 lower to 6.53 higher)	N/A	104 (2 studies)	⊕⊕⊕⊕ Low <sup>2,5</sup>
<i>Reduction (change in number of CPD from baseline) - end of treatment (secondary outcome) - reduction studies</i>	N/A	Mean reduction (change in number of CPD from baseline at the end of treatment) in the intervention groups was 2.61 lower (7.99 lower to 2.77 higher)	N/A	93 (2 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>

Note. CI = confidence interval; RR = risk ratio; CO = carbon monoxide; CPD = cigarettes per day.  
 \*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
<sup>1</sup> Most information is from studies at moderate risk of bias.  
<sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).  
<sup>3</sup> Evidence of serious heterogeneity of study effect size.  
<sup>4</sup> Most information is from studies at moderate risk of bias.  
<sup>5</sup> Optimal information size not met.  
<sup>6</sup> Evidence of very serious heterogeneity of study effect size.

**Table 52: Summary of findings table for varenicline versus placebo for smoking cessation**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Bupropion versus placebo			
<i>Abstinence – 6 months' follow-up (primary outcome)</i>	Study population		RR 5.06 (0.67 to 38.24)	128 (1 study)	⊕⊕⊕⊕ low <sup>1,2</sup>
	23 per 1000	118 per 1000 (16 to 889)			
	23 per 1000	116 per 1000 (15 to 880)			
<i>Abstinence - end of treatment (secondary outcome)</i>	Study population		RR 4.74 (1.34 to 16.71)	137 (2 study)	⊕⊕⊕⊕ low <sup>1,2</sup>
	42 per 1000	197 per 1000 (56 to 696)			
	23 per 1000	109 per 1000 (31 to 384)			

Note. CI = confidence interval; RR = risk ratio; CO = carbon monoxide; CPD = cigarettes per day.  
 \*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
<sup>1</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.  
<sup>2</sup> CI crosses the clinical decision threshold.  
<sup>3</sup> Most information is from studies at moderate risk of bias.  
<sup>4</sup> Optimal information size not met.

### 7.3.5 Clinical evidence summary

This review suggests that bupropion is an effective intervention for smoking cessation in adults with psychosis and schizophrenia immediately post-intervention and at longer-term follow-up (up to 6 months). However, the evidence is of poor quality and inconclusive because of the low number of studies, especially for longer-term follow-up, resulting in wide confidence intervals. This review did not find any adverse effects on mental state, suggesting that bupropion is well tolerated in adults with psychosis and schizophrenia. There is no consistent evidence for the effectiveness of bupropion for smoking reduction. There is some evidence that it is effective in reducing smoking at the end of the intervention for both those who attempted abstinence but did not succeed, and those who initially aimed to reduce smoking. However, this effect is not maintained at longer-term follow-up. Limited evidence suggests that varenicline is an effective intervention for smoking cessation in adults with psychosis and schizophrenia at longer-term follow-up (up to 6 months) but this effect was not found immediately post-intervention. Although there was no significant difference between the intervention and control group in psychiatric symptoms, there were reports of suicidal ideation and behaviours from two participants in the varenicline group. Limited evidence suggests that there is no difference between a high and regular dose transdermal nicotine patch for smoking cessation.

### 7.3.6 Health economics evidence

No studies assessing the cost effectiveness of interventions for reducing smoking in people with psychosis and schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. One study currently in press (Winterbourne et al., 2013b) was identified following information provided by the GDG. Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

Winterbourne and colleagues (2013b) conducted a cost-utility analysis comparing bupropion in combination with CBT and NRT with standard care (defined as CBT and NRT only) in service users with psychosis and schizophrenia. In a Markov model, a hypothetical cohort of 1000, 27-year old male smokers, was modelled in 6-monthly cycles over their lifetime. In each cycle, smokers could quit, thus becoming former smokers, or they could remain smokers, or they could die. Former smokers could relapse, thus becoming smokers again, or remain former smokers or die. In each cycle, individuals could have one of four comorbidities: lung cancer, coronary heart disease, stroke and chronic obstructive pulmonary disease (COPD). The analysis was conducted from the perspective of the UK's NHS and the time horizon

of the analysis was lifetime. According to the model, the expected lifetime costs per person were £12,730 for the intervention group and £12,713 for standard care. The expected number of QALYs per person over a lifetime was estimated to be 19.7 for the intervention group and 19.6 for the standard care group. The cost per QALY associated with the intervention was £244, which is far below the lower NICE cost-effectiveness threshold of £20,000. Moreover, the cost-effectiveness acceptability analysis showed that at willingness to pay of £20,000-30,000 per additional QALY the probability of the intervention being cost effective is 0.93-0.94. Overall, the model was found to be robust to estimates of comorbidities, utility values, costs associated with death and intervention costs. However, using the lower estimate of intervention effect resulted in a cost per QALY of £150,609 and using an upper estimate intervention was dominant. This huge variation in the results reflects the lack of clinical evidence pertaining to smoking cessation interventions in this population. Also, using a 10-year time frame resulted in a cost per QALY of £54,446 and the subgroup analysis indicated that the intervention was cost saving for the female cohort. The analysis has excluded costs accruing to the PSS. However, the authors justified this by reporting that PSS costs account for <10% of the total NHS and social care services costs for people with psychosis and schizophrenia and so are unlikely to affect the results. Also, a range of other costs that are relevant to the NHS have been excluded, including psychosis and schizophrenia treatment costs and costs of managing drug-related side effects. Moreover, the standard care definition was adopted from the studies that were included in the meta-analysis of intervention effect. Therefore, it is not clear if the comparator used is a good representation of the current clinical practice in the NHS. The analysis has incorporated the impact of smoking cessation on various comorbidities including lung cancer, COPD, coronary heart disease and stroke. The prevalence data for stroke and coronary heart disease were derived from a Canadian population-based study and for COPD from a US population-based controlled study, which may be different from prevalence rates in the UK. Similarly, EQ-5D ratings for the baseline were from a German patient sample. Also, the treatment effect estimate was based on a meta-analysis and authors' assumptions, and as indicated by the sensitivity analysis, the results are very sensitive to this estimate. The resource use data were derived from various published sources and supplemented with authors' assumptions. Overall this study was judged by the GDG to be partially applicable to this guideline review and the NICE reference case, and it had potentially serious methodological limitations.

### **7.3.7 Linking evidence to recommendations**

#### ***Relative value placed on the outcomes considered:***

The GDG agreed that the main aim of a smoking intervention is to either reduce or stop smoking. Furthermore, satisfaction with services (indicating the likelihood of continuing the intervention) and the service user's quality of life were considered critical outcomes. In addition to this, the GDG felt it was important to assess any adverse effects on psychiatric symptoms as a result of smoking reduction or cessation. Therefore, the outcomes the GDG considered to be critical were:

- anxiety and depression
- physical health
  - smoking (cessation or reduction)
  - weight/BMI
- quality of life
- user satisfaction (validated measures only).

### *Trade-off between clinical benefits and harms*

The physical harm caused by smoking is so palpable that the GDG felt it was important to offer all people with psychosis and schizophrenia who smoke support with smoking cessation or reduction, even if they had previously been unsuccessful in doing so.

The GDG evaluated the evidence presented for efficacy of safety of interventions in a schizophrenia population. Furthermore, evidence from the general population in the NICE smoking cessation public health guideline (PH10) (NICE, 2013b) was also considered by the GDG.

For adults with psychosis and schizophrenia who smoke, the GDG considered there to be reasonable evidence of the benefits of bupropion for smoking cessation and some limited evidence of its effectiveness for smoking reduction. The evidence of smoking reduction or cessation using bupropion did not exacerbate psychosis symptoms, or symptoms of anxiety or depression. However, the GDG was concerned that bupropion is contraindicated in people with bipolar disorder because of the risk of seizures and other neuropsychiatric adverse effects<sup>16</sup>. A large number of people with an initial diagnosis of psychosis prove to have a more specific diagnosis of bipolar disorder. Therefore, the GDG believe that bupropion should not be used for people with psychosis unless a diagnosis of schizophrenia is confirmed.

The GDG considered there was reasonable evidence of a benefit of varenicline for smoking cessation for people with schizophrenia. However, there are concerns about possible neuropsychiatric adverse effects as stated in the Summary of Product Characteristics (SPC)<sup>17</sup>, and found in the evidence from this review. The GDG considered that varenicline should be prescribed cautiously for smoking cessation for an adult with psychosis and schizophrenia, and, bearing in mind guidance from the Royal College of Practitioners and the Royal College of Psychiatrists (Campion et al., 2010) the service user regularly monitored for possible neuropsychiatric adverse effects especially in the first 2-3 weeks. The GDG thought that to promote service user choice, people should be made aware of the possible adverse effects of both varenicline and bupropion.

---

<sup>16</sup> See <http://emc.medicines.org.uk/>

<sup>17</sup> See <http://emc.medicines.org.uk/>

There was a paucity of follow-up data evaluating the long-term efficacy of bupropion or varenicline, however, the GDG believed that the potential negative consequences of continuing smoking outweighed this lack of knowledge.

There was also a lack of data evaluating the efficacy of NRT in this population. The GDG therefore considered the efficacy evidence in the general population for smoking reduction, and the fact that there are no known contraindications (outside of those for the general population as discussed in PH10) specifically for those with psychosis and schizophrenia. The group decided that a transdermal nicotine patch and other forms of NRT should also be offered to encourage smoking cessation and reduction.

The GDG also deliberated about how best to manage smoking in inpatient settings and judged that support should be offered to encourage those who may not want to cease smoking completely to temporarily stop or reduce smoking by using NRT.

### *Trade-off between net health benefits and resource use*

The health economic evidence on smoking cessation was limited to one UK study. Despite study limitations (for instance, poor clinical evidence, the omission of potential cost savings from reducing smoking), the results provide some evidence that providing targeted smoking cessation interventions for adults with psychosis and schizophrenia can be cost effective and a viable approach within the NICE decision-making context. The positive economic finding supports the GDG view that it is important to offer all people with psychosis and schizophrenia who smoke support with smoking cessation.

### *Quality of the evidence*

The evidence ranged from very low to moderate quality across critical outcomes. Reasons for downgrading included risk of bias in the included studies, high heterogeneity and lack of precision in confidence intervals. Wide confidence intervals were a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most and the small number of participants in the included trials could have contributed to the lack of precision.

### *Other considerations*

At the time of drafting this guidance, NICE public health guidance, *Smoking Cessation in Secondary Care: Acute, Maternity and Mental Health Services* was out for public consultation and a final post-consultation draft was not available. As of August 2013, the public health guideline recommends varenicline or bupropion for all people who smoke. However, the GDG thought it was of critical importance that varenicline should only be offered to people with psychosis and schizophrenia cautiously because of concerns about its association with an increased risk of neuropsychiatric events. The GDG also judged it important that bupropion is not offered to people who have a diagnosis of psychosis unless a more specific diagnosis of schizophrenia is confirmed.

Finally, blood levels of some antipsychotics, particularly clozapine and olanzapine, are reduced as the hydrocarbons in cigarette smoke induce the main enzyme system responsible for the metabolism of these drugs. When smoking is stopped, enzyme induction no longer occurs and blood levels of the affected drugs could increase to high levels. The effect of smoking on people taking clozapine is of particular concern and individuals can become ill unless the dose is adjusted. The GDG believes that this should be considered in advance of smoking cessation.

### **7.3.8 Recommendations**

**7.3.8.1** Offer people with psychosis or schizophrenia who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine. [new 2014]

**7.3.8.2** Consider one of the following to help people stop smoking:

- nicotine replacement therapy (usually a combination of transdermal patches with a short-acting product such as an inhalator, gum, lozenges or spray) for people with psychosis or schizophrenia **or**
- bupropion<sup>18</sup> for people with a diagnosis of schizophrenia **or**
- varenicline for people with psychosis or schizophrenia.

Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first 2-3 weeks. [new 2014]

**7.3.8.3** For people in inpatient settings who do not want to stop smoking, offer nicotine replacement therapy to help them to reduce or temporarily stop smoking. [new 2014]

---

<sup>18</sup> At the time of publication (February 2014), bupropion was contraindicated in people with bipolar disorder. Therefore, it is not recommended for people with psychosis unless they have a diagnosis of schizophrenia.



# 8 PEER-PROVIDED AND SELF-MANAGEMENT INTERVENTIONS

## 8.1 INTRODUCTION

This chapter is new for the 2014 guideline and reviews the evidence for peer-provided interventions (see Section 8.2) and self-management interventions (see Section 8.3). The decisions that led to the development of recommendations from both reviews can be found in Section 8.4, and the recommendations themselves in Section 8.5.

## 8.2 PEER-PROVIDED INTERVENTIONS

### 8.2.1 Introduction

Peer support workers have a long history as an informal element of all types of mental health services, dating as far back as the 19<sup>th</sup> century (Basset et al., 2010). More recently, attendees of inpatient wards and day centres have freely provided one another with informal support, finding that contact with others with similar experiences can bring hope and understanding. This capacity for mutual support has been more formally harnessed through third sector and self-help agencies, for example, Mind and the Hearing Voices Network (Hearing Voices Network, 2003), and employing people with lived experience of substance misuse is widely accepted in addiction services, for example, Alcoholics Anonymous. Across North America and Australasia (Repper & Carter, 2010) peer support workers are becoming well established within the mainstream mental health workforce, and access to such support for people with severe mental illness has been widely advocated internationally by service user researchers (Clay et al., 2005; Deegan, 1996; Faulkner & Basset, 2012) and professional organisations (Bradstreet & Pratt, 2010; Halvorson & Whitter, 2009; The Royal College of Psychiatrists Social Inclusion Scoping Group, 2009). Provision of peer support is identified as a fidelity requirement for recovery-orientated services (Armstrong & Steffen, 2009) and commonly promoted in literature on recovery (Scottish Recovery Network, 2005; Slade, 2009). Roles for peer support workers have thus evolved over time, with some continuing to be informal through peer-led groups and others developing as more intentional or formal roles. This chapter is concerned with the latter.

One definition of peer support work is ‘social emotional support, frequently coupled with instrumental support, that is mutually offered or provided by persons having a mental health condition to others sharing a similar mental health condition to bring about a desired social or personal change’ (Solomon, 2004). A key aspect of this definition is that it is explicit about the use that is made of lived experience, or mutuality, of mental illness. In addition, peer support should not be tokenistic (that is, have little real commitment or understanding of the role of peers within the

system), and it should not be a way of undertaking work cheaply that would be better done by professionals.

People who have experienced mental health problems and used services are potentially well placed to support other service users. There is much evidence that people with psychosis or schizophrenia find engagement with mental health services difficult and may avoid contact (NICE, 2011). This may be because of previous bad experiences, especially in inpatient settings, internal and external stigma, discrimination and/or low expectations from mental health professionals about prognosis and potential aspirations. Peers may bring experiential knowledge to help them support others to overcome these barriers, challenge attitudes of clinical staff and contribute to culture change within mental health services (Repper & Watson, 2012). They may also be able to credibly model recovery and coping strategies, thus promoting hope and self-efficacy (Salzer & Shear, 2002). The opportunity to help others may also be of therapeutic value to peers providing support (Skovholt, 1974).

Peer-provided interventions operate in a variety of ways and do not derive from a highly specified theoretical model or have a single, well-defined goal. The critical ingredients of peer support have been conceptualised more in terms of style and process – for example being non-coercive, informal and focused on strengths (Solomon, 2004) – than in terms of content. This creates challenges for the evaluation of peer support programmes because they may differ considerably and may aim to improve different outcomes.

Three broad types of organised peer-provided interventions have been identified (Davidson et al., 1999):

- *Mutual support groups* in which relationships are reciprocal in nature, even if some participants are viewed as more experienced or skilled than others.
- *Peer-support services* in which support is primarily in one direction, with one or more clearly defined peer support worker offering support to one or more programme participant (support is separate from or additional to standard care provided by mental health services).
- *Peer mental health service providers* where people who have used mental health services are employed by a service to provide part or all of the standard care provided by the service.

However, even within these subtypes of peer support, programmes may vary regarding mode of delivery (group or one to one; in person or internet-based), duration, degree of co-location and integration with mental health services, and content (whether highly structured and focusing on self-management or less structured with greater focus on activity and social contact).

### **8.2.2 Clinical review protocol (peer-provided interventions)**

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the

guideline, can be found in Table 53 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 53: Clinical review protocol for the review of peer-provided interventions**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of peer-provided interventions compared with treatment as usual or other intervention?
<i>Sub-question (s)</i>	<ul style="list-style-type: none"> <li>a. Peer support</li> <li>b. Mutual support</li> <li>c. Peer mental health service providers</li> </ul>
<i>Objectives</i>	To evaluate the clinical effectiveness of peer-provided interventions in the treatment of psychosis and schizophrenia.
<i>Population</i>	<b>Included</b> Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Peer-provided interventions
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Empowerment/recovery</li> <li>• Functional disability</li> <li>• Quality of life</li> <li>• Service use <ul style="list-style-type: none"> <li>○ GP visits</li> <li>○ A&amp;E visits</li> <li>○ Hospitalisation (admissions, days)</li> </ul> </li> <li>• User satisfaction (validated measures only)</li> </ul>
<i>Electronic databases</i>	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMEDLINE Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	RCT: database inception to June 2013 SR: 1995 to June 2013
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><b>Sub-analysis</b> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia, schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>

### 8.2.3 Studies considered<sup>19</sup>

Sixteen RCTs (N = 4,778) met the eligibility criteria for this review: BARBIC2009 (Barbic et al., 2009), CHINMAN2013 (Chinman et al., 2013), CLARKE2000 (Clarke et al., 2000), COOK2011 (Cook et al., 2011), COOK2012 (Cook et al., 2012), CRAIG2004A (Craig et al., 2004a), DAVIDSON2004 (Davidson, 2004), EDMUNDSON1982 (Edmundson et al., 1982), GESTEL-TIMMERMANS2012 (Van Gestel-Timmermans et al., 2012), KAPLAN2011 (Kaplan et al., 2011), ROGERS2007 (Rogers et al., 2007), RIVERA2007 (Rivera et al., 2007), SLEDGE2011 (Sledge et al., 2011), SEGAL2011 (Segal et al., 2011), SELLS2006 (Sells et al., 2006), SOLOMON1995 (Solomon & Draine, 1995). All trials were published in peer-reviewed journals between 1982 and 2012. Further information about both included and excluded studies can be found in Appendix 15a.

For the purposes of the guideline, interventions were categorised as:

- peer support
- mutual support
- peer mental health service providers.

Of the 16 included trials, nine involved a comparison between peer-support services and any type of control, four involved a comparison between mutual support and any type of control, and three compared peer mental health service providers with any control. Table 54 provides an overview of the included trials in each category.

Of the eligible trials, three included a large proportion (>75%) of participants with a primary diagnosis of psychosis or schizophrenia. Only one of the included trials was based in the UK/Europe.

---

<sup>19</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

**Table 54: Study information table for trials included in the meta-analysis of peer-provided interventions versus any alternative management strategy**

	Peer-support services versus any control	Mutual-support services versus any control	Peer mental health service providers versus any control
<i>Total no. of trials (k); participants (N)</i>	k = 9; N = 2,466	k = 4; N = 2,369	k = 3; N = 411
<i>Study ID</i>	BARBIC2009 CHINMAN2013 COOK2011 COOK2012 CRAIG2004A DAVIDSON2004 GESTEL-TIMMERMANS2012 RIVERA2007 SLEDGE2011	EDMUNDSON1982 KAPLAN2011 ROGERS2007 SEGAL2011	CLARKE2000 SELLS2006 SOLOMON1995
<i>Country</i>	Canada (k = 1) Netherlands (k = 1) UK (k = 1) USA (k = 6)	USA (k = 4)	USA (k = 3)
<i>Year of publication</i>	2004 to 2012	1982 to 2011	1995 to 2006
<i>Mean age of participants (range)</i>	43.16 years (37.6 to 53.27 years)	42.23 years (37 to 47 years) <sup>1</sup>	39.8 years (36.5 to 41.9 years)
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	52.83% (20.2 to 100%)	37.9% (22.4 to 50.4%) <sup>1</sup>	67.6% (59.5 to 82%)
<i>Mean percentage of women (range)</i>	46.72% (11.46 to 66%)	59.9% (54 to 65.7%) <sup>1</sup>	41.7% (38.7 to 47%)
<i>Length of treatment (range)</i>	8 to 52 weeks	35 to 52 weeks	52 to 104 weeks
<i>Length of follow-up</i>	<i>End of treatment only:</i> BARBIC2009 CHINMAN2013 CRAIG2004A DAVIDSON2004 RIVERA2007 SLEDGE2011  <i>Up to 6 months:</i> COOK2011 COOK2012 GESTEL-TIMMERMANS2012  <i>7-12 months:</i> COOK2011	<i>End of treatment only:</i> EDMUNDSON1982 KAPLAN2011 ROGERS2007 SEGAL2011	<i>End of treatment only:</i> CLARKE2000 SELLS2006 SOLOMON1995
<i>Intervention type</i>	'Recovery Workbook' + TAU (k = 1) 'PEER Simpson Transfer Model' (k = 1)	Community network development (k = 1) Internet peer support email list (k = 1)	Peer-based case management (k = 1) Consumer-provided ACT (k = 1)

	'Building Recovery of Individual Dreams and Goals through Education and Support' (BRIDGES) + TAU (k = 1) 'Wellness Recovery Action Plan' (WRAP) + TAU (k = 1) Peer support + TAU (k = 3) 'The Partnership Project' + TAU (k = 1) 'Recovery Is Up to You' + TAU (k = 1)	Bulletin board (k = 1) Consumer-operated service programmes (k = 2)	Consumer case management (k = 1)
<i>Comparisons</i>	TAU/usual services (k = 6) Case management without peer enhancement (k = 2) Supported socialisation from non-consumer (k = 1)	Outpatient services (k = 3) Waitlist (k = 1)	Case management (k = 2) Professional-led ACT (k = 1)
<i>Note.</i> ACT = assertive community treatment; TAU = treatment as usual. <sup>1</sup> EDMUNDSON1982 does not report data.			

## 8.2.4 Clinical evidence for peer-provided interventions

### *Peer support*

Evidence from each important outcome and overall quality of evidence are presented in Table 55. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Low to very low quality evidence from up to four studies with 1,066 participants showed that peer support had a positive effect on self-rated recovery at the end of the intervention and at short-term follow-up. No difference was observed between peer support and control in empowerment or quality of life at the end of treatment, but up to two studies (N = 639) presented very low quality evidence that peer support was more effective than control in improving these outcomes at short-term follow-up.

Very low quality evidence from one trial with 165 participants favoured control over peer support for the outcome of functional disability.

Three studies (N = 255) provided very low quality evidence of a beneficial effect of peer support on contact with services at the end of the intervention. However, no follow-up data were available. There was no conclusive evidence of any benefit of peer support on hospitalisation or on service user satisfaction outcomes at the end of the intervention and no follow-up data were available.

### *Sub-analysis (psychosis and schizophrenia only)*

For the critical outcomes of hospitalisation, service use, satisfaction with services, recovery and quality of life, the sub-analysis findings did not differ from the main analysis and continued to show a benefit of peer support at the end of the intervention. Unlike the main analysis, the sub-analysis found a large positive effect on empowerment at the end of the intervention. However, because of a discrepancy in the authors' description of the empowerment measure and the data presented, this large effect should be treated with caution.

**Table 55: Summary of findings table for peer support compared with any alternative management strategy**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Peer support					
Comparison: Any alternative management strategy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Peer support			
<i>Recovery - end of treatment</i>	N/A	Mean recovery (end of treatment) in the intervention groups was 0.24 standard deviations higher (0.09 to 0.39 higher)	N/A	1,066 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Recovery, up to 6 months' follow-up</i>	N/A	Mean recovery (up to 6 months' follow-up) in the intervention groups was 0.23 standard deviations higher (0.09 to 0.37 higher)	N/A	439 (2 studies)	⊕⊕⊕⊕ Low <sup>2,3</sup>
<i>Empowerment - end of treatment</i>	N/A	Mean empowerment (end of treatment) in the intervention groups was 2.34 standard deviations lower (7.68 lower to 3.00 higher)	N/A	286 (2 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4,5</sup>
<i>Empowerment - up to 6 months' follow-up</i>	N/A	Mean empowerment (up to 6 months' follow-up) in the intervention groups was 0.25 standard deviations higher (0.07 to 0.43 higher)	N/A	538 (2 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4</sup>
<i>Functioning / disability - end of treatment</i>	N/A	Mean functioning/disability (end of treatment) in the intervention groups was 0.37 standard deviations higher (0.06 to 0.68 higher)	N/A	165 (1 study)	⊕⊕⊕⊕ Very low <sup>2,3,6</sup>
<i>Quality of life - end of treatment</i>	N/A	Mean quality of life (end of treatment) in the intervention groups was 0.04 standard deviations lower (0.24 lower to 0.16 higher)	N/A	1039 (5 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3,4</sup>
<i>Quality of life- up to 6 months' follow-up</i>	N/A	Mean quality of life (up to 6 months' follow-up) in the intervention groups was 0.24 standard deviations higher (0.08 to 0.40 lower)	N/A	639 (2 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4</sup>
<i>Service use, contact - end of treatment</i>	N/A	Mean service use (end of treatment) in the intervention groups was 0.22 standard deviations lower (0.72 lower to 0.28 higher)	N/A	255 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3,4</sup>
<i>Service use, hospitalisation- end of treatment</i>	Study population		RR 1.07 (0.55 to 2.07)	45 (1 study)	⊕⊕⊕ Very low <sup>2,3,6</sup>
	429 per 1000	459 per 1000 (236 to 887)			
	429 per	459 per 1000			



	1000	(236 to 888)			
<i>Satisfaction, questionnaire - end of treatment</i>	N/A	Mean satisfaction (end of treatment) in the intervention groups was 0.02 standard deviations lower (0.23 lower to 0.20 higher)	N/A	332 (3 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4</sup>
<p><i>Note.</i> CI = confidence interval; RR = risk ratio.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Evidence of serious heterogeneity of study effect size.</p> <p><sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p> <p><sup>3</sup> Suspicion of publication bias.</p> <p><sup>4</sup> Most information is from studies at moderate risk of bias.</p> <p><sup>5</sup> Evidence of very serious heterogeneity of study effect size.</p> <p><sup>6</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.</p> <p><sup>7</sup> A single study of 0.00 effect.</p>					

### ***Mutual support***

Evidence from each important outcome and overall quality of evidence are presented in

Table 56. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Very low quality evidence from up to three trials (N = 2,266) provided evidence favouring mutual support for self-rated outcomes of empowerment, quality of life, and contact with services at the end of the intervention. There was no evidence available to assess these outcomes at follow-up. No difference was observed between groups in hospitalisation outcomes at the end of the intervention. No data were available for the critical outcomes of functional disability and service user satisfaction.

### ***Peer mental health service providers***

Evidence from each important outcome and overall quality of evidence are presented in Table 57. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Very low quality evidence from a single trial with 87 participants favoured control for service user satisfaction at the end of the intervention. There was no evidence of a difference between groups in hospitalisation at the end of the intervention. No follow-up data were available for both outcomes and no data were available at all for the other critical outcomes of empowerment/recovery, functional disability or quality of life.

### ***Sub-analysis (psychosis and schizophrenia only)***

No difference between the sub-analysis and the main analysis was found for service user satisfaction. No other data were available.

**Table 56: Summary of findings table for mutual support compared with any alternative management strategy**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Mutual support					
Comparison: Any alternative management strategy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Mutual support			
Recovery - end of treatment	N/A	Mean recovery (end of treatment) in the intervention groups was 0.11 standard deviations higher (0.13 lower to 0.35 higher)	N/A	300 (1 study)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
Empowerment - end of treatment	N/A	Mean empowerment (end of treatment) in the intervention groups was 1.44 standard deviations higher (0.09 to 2.79 higher)	N/A	2266 (3 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4,5</sup>
Quality of life - end of treatment	N/A	Mean quality of life (end of treatment) in the intervention groups was 1.42 standard deviations higher (1.16 to 1.69 higher)	N/A	300 (1 study)	⊕⊕⊕⊕ Very low <sup>1,3,6</sup>
Service use, contact - end of treatment	Study population		RR 0.63 (0.44 to 0.92)	80 (1 study)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	250 per 1000	158 per 1000 (110 to 230)			
	250 per 1000	158 per 1000 (110 to 230)			
Service use, hospitalisation - end of treatment	Study population		RR 0.5 (0.23 to 1.11)	80 (1 study)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	350 per 1000	175 per 1000 (81 to 389)			
	350 per 1000	175 per 1000 (81 to 389)			
Note. CI = confidence interval; RR = risk ratio.					
*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
<sup>1</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.					
<sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).					
<sup>3</sup> Suspicion of publication bias.					
<sup>4</sup> Most information is from studies at moderate risk of bias.					
<sup>5</sup> Evidence of very serious heterogeneity of study effect size.					
<sup>6</sup> Optimal information size not met.					

**Table 57: Summary of findings table for interventions with peer mental health service providers compared with any alternative management strategy**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Peer mental health service providers					
Comparison: Any alternative management strategy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Peer mental health service providers			
Service use, hospitalisation - end of treatment	Study population		RR 0.68 (0.45 to 1.03)	114 (1 study)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	544 per 1000	370 per 1000 (245 to 560)			
	544 per 1000	370 per 1000 (245 to 560)			
Satisfaction, questionnaire - end of treatment	N/A	Mean satisfaction ( end of treatment) in the intervention groups was 0.48 standard deviations higher (0.05 to 0.91 higher)	N/A	87 (1 study)	⊕⊕⊕⊕ Very low <sup>1,3,4</sup>
<i>Note.</i> CI = confidence interval; RR = risk ratio.					
*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
<sup>1</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.					
<sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).					
<sup>3</sup> Suspicion of publication bias.					
<sup>4</sup> Optimal information size not met.					

## 8.2.5 Clinical evidence summary

Overall there is inconclusive evidence concerning the efficacy for peer-provided interventions in both magnitude and direction of the effect. When large effects are observed, there is some concern about the validity of these findings because of the size of the trials and variance observed across studies. Furthermore, due to the limited evidence, no longer-term effects of the intervention can be determined.

## 8.2.6 Health economics evidence

The systematic literature search identified one economic study that assessed peer-provided intervention for people with psychosis and schizophrenia (Lawn, 2008). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and

quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

Lawn and colleagues (2008) conducted a cost analysis in Australia. The analysis was based on a small pre- and post-observational study (n = 49). The study comprised individuals with bipolar affective disorder, schizophrenia, schizoaffective disorder and first episode psychosis. Standard care was defined as psychiatric inpatient care and care by a community-based emergency team and a community mental health team (CMHT). The analysis was conducted from the healthcare payer perspective and considered costs of admissions, community emergency contacts and programme provision. The authors found that peer-provided interventions led to a cost saving of \$AUD 2,308 per participant over 3 months and cost \$AUD 405 to provide, resulting in a net saving of \$AUD 1,901 per participant over 3 months. The analysis was judged to be partially applicable to this guideline review and the NICE reference case. However, the analysis was based on a very small pre- and post-observational study, which was prone to bias due to the inability to control for confounding factors. Moreover, the analysis has not attempted to capture health effects and adopted a very short time horizon that may not be sufficiently long to reflect all important differences in costs. Also, the source of unit costs is unclear. The analysis was therefore judged by the GDG to have very serious methodological limitations.

## **8.3 SELF-MANAGEMENT INTERVENTIONS**

### **8.3.1 Introduction**

Self-management refers to an 'individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent living with a chronic condition' (Barlow et al., 2002). Mental illness self-management has increased in popularity over the past decade, and programmes based on this approach have been now widely recommended as a means of promoting recovery and empowering service users, while simultaneously addressing service capacity issues (Mueser et al., 2002b; Turner et al., 2008). This reflects a broader trend in healthcare of a collaborative rather than a traditional didactic medical approach (Mueser & Gingerich, 2011).

Objectives for self-management include: instilling hope; improving illness management skills; providing information about the nature of the illness and treatment options; developing strategies for self-monitoring of the illness; improving coping strategies; and developing skills to manage life changes (Mueser & Gingerich, 2011). Training in self-management may come from mental health professionals, peer support workers or coaches, or it may be provided partly or wholly through information technology. The philosophical underpinning for such training in self-management skills is one of teaching and learning, fostering active engagement and participation. Central to this approach is also the development of individual strategies so that self-management strategies are rooted in experience – this approach, in turn, supports the validation of services users' experiences, so individuals can apply their own meaning to each topic.

Active service user participation in developing and sustaining self-management programmes may be difficult to achieve where there is a perception of a large power difference between mental health professionals and service users and their carers. A relatively pessimistic view of service users' potential has also been reported among healthcare professionals, which may also impact on the extent to which they promote and engage with collaborative interventions (Hansson et al., 2013). Thus, the belief that people with psychosis or schizophrenia can contribute to their own health management is likely to be an important condition for effective collaboration in self-management programmes.

A number of self-management packages focused on serious mental illness have been developed. They include the Wellness Recovery Action Plan (WRAP) (Copeland & Mead, 2004), the Illness Management and Recovery (IMR) programme (Gingerich & Tornvall, 2005) and the Social and Independent Living Skills (SILS) programme (Lieberman et al., 1994). Means of delivery vary widely, and may be face to face, group-based or via written or digital materials. Professionals, carers and peers are involved to varying extents in supported self-management programmes. Online and other computerised self-management programmes are becoming widespread in other areas of health, though their development for psychosis and schizophrenia has thus far been limited. A prominent UK trend is the setting up in many areas of recovery colleges, in which peers, carers and mental health professionals collaborate in supporting service users in learning about mental health and recovery (Perkins et al., 2012; Perkins & Slade, 2012). Self-management tools are a key element in this approach. Recovery colleges are thought to provide an environment for developing ability and knowledge on condition management and life skills. The culture and structure of the recovery college promote responsibility and can give confidence to 'graduates' to access education and employment.

Several papers (Jones & Riazzi, 2011; Kemp, 2011; Mueser & Gingerich, 2011) have reviewed and summarised the elements of self-management programmes, which include:

- psychoeducation about mental health difficulties and available treatments and services
- relapse prevention approaches, where service users are supported in identifying early warning signs and in developing strategies for avoiding or attenuating the severity of relapse
- management of medication, including identification of side effects and strategies for negotiation with professionals to optimise medication regimes to achieve the best balance of positive and negative effects
- symptom management, including strategies for managing persistent symptoms of psychosis, anxiety and low mood
- setting individual recovery goals and developing strategies for achieving them

- development of life skills important for wellbeing, self-care, productivity and leisure, for example, diet, exercise, smoking cessation, finances, safety, relationships, organisation, home making and communication.

### 8.3.2 Clinical review protocol (self-management interventions)

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 58 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 58: Clinical review protocol summary for the review of self-management interventions**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of self-management interventions compared with treatment as usual or other intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of self-management interventions in the treatment of psychosis and schizophrenia.
<i>Population</i>	<b>Included</b> Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Self-management interventions
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Empowerment/recovery</li> <li>• Functional disability</li> <li>• Hospitalisation (admissions, days)</li> <li>• Contact with secondary services</li> <li>• Quality of life</li> <li>• Symptoms of psychosis <ul style="list-style-type: none"> <li>○ total symptoms</li> <li>○ positive symptoms</li> <li>○ negative symptoms</li> </ul> </li> </ul>
<i>Electronic database</i>	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMEDLINE Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	RCT: database inception to June 2013 SR: 1995 to June 2013
<i>Study design</i>	RCT
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><b>Sub-analysis</b> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia, schizoaffective disorder or psychosis.</p>

	Where data were available, sub-analyses were conducted for UK/Europe studies.
--	---

### 8.3.3 Studies considered<sup>20</sup>

Twenty-five RCTs (N = 3,606) met the eligibility criteria for this review: ANZAI2002 (Anzai et al., 2002), BARBIC2009 (Barbic et al., 2009), BAUER2006 (Bauer et al., 2006), CHAN2007 (Chan et al., 2007), COOK2011 (Cook et al., 2011), COOK2012 (Cook et al., 2012), ECKMAN1992 (Eckman et al., 1992), FARDIG2011 (Färdig et al., 2011), HASSON2007 (Hasson-Ohayon et al., 2007), KOPELOWICZ1998A (Kopelowicz, 1998), KOPELOWICZ1998B (Kopelowicz et al., 1998), LEVITT2009 (Levitt et al., 2009), LIBERMAN1998 (Lieberman et al., 1998), LIBERMAN2009 (Lieberman & Kopelowicz, 2009), MARDER1996 (Marder et al., 1996), NAGEL2009 (Nagel et al., 2009), PATTERSON2003 (Patterson et al., 2003), PATTERSON2006 (Patterson et al., 2006), SALYERS2010 (Salyers et al., 2010), SHON2002 (Shon & Park, 2002), VREELAND2006 (Vreeland et al., 2006), WIRSHING2006 (Wirshing et al., 2006), XIANG2006 (Xiang et al., 2006), XIANG2007 (Xiang et al., 2007), GESTEL-TIMMERMANS2012 (Van Gestel-Timmermans et al., 2012).

All 25 trials were published in peer-reviewed journals between 1992 and 2012. Further information about both included and excluded studies can be found in Appendix 15a.

Of the 25 included trials, there were four evaluating the effectiveness of peer-led self-management, and there were 21 evaluating professional-led self-management. The GDG decided that there was not enough trial evidence to conduct separate reviews based on these categories, therefore all trials were included in a larger review of self-management verses any alternative management strategy.

Of the eligible trials, 18 included a large proportion (>75%) of participants with a primary diagnosis of psychosis or schizophrenia. None of the included trials were based in the UK and only two were based in Europe. Table 59 provides an overview of the trials.

---

<sup>20</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

**Table 59: Study information table for trials included in the meta-analysis of self-management interventions versus any alternative management strategy**

	<b>Self-management versus any alternative management strategy</b>
<i>Total no. of trials (k); participants (N)</i>	k = 25; N = 3606
<i>Study ID</i>	ANZAI2002 BARBIC2009 BAUER2006 CHAN2007 COOK2011 COOK2012 ECKMAN1992 FARDIG2011 GESTEL-TIMMERMANS2012 HASSON2007 KOPELOWICZ1998A KOPELOWICZ1998B LEVITT2009 LIBERMAN1998 LIBERMAN2009 MARDER1996 NAGEL2009 PATTERSON2003 PATTERSON2006 SALYERS2010 SHON2002 VREELAND2006 WIRSHING2006 XIANG2006 XIANG2007
<i>Country</i>	Australia (k = 1) Canada (k = 1) China (k = 3) Israel (k = 1) Japan (k = 1) South Korea (k = 1) Sweden (k = 1) USA (k = 15) Netherlands (k = 1)
<i>Year of publication</i>	1992 to 2012
<i>Mean age of participants (Range)</i>	41.02 years (32.0 to 53.9 years) <sup>1</sup>
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	79.6% (20.2 to 100%)
<i>Mean percentage of women (range)</i>	33% (0 to 66%)
<i>Length of treatment</i>	1 week to 3 years.
<i>Length of follow-up</i>	<i>End of treatment only</i> BARBIC2009 BAUER2006 HASSON2007 KOPELOWICZ1998A



	<p>KOPELOWICZ1998B MARDER1996 PATTERSON2006 SHON2002 VREELAND2006 WIRSHING2006</p> <p><i>Up to 6 months:</i> COOK2011 COOK2012 GESTEL-TIMMERMANS2012 NAGEL2009 PATTERSON2003 XIANG2006 XIANG2007</p> <p><i>7-12 months:</i> ANZAI2002 CHAN2007 ECKMAN1992 FARDIG2011 LEVITT2009 LIBERMAN2009 NAGEL2009</p> <p><i>&gt;12 months:</i> LIBERMAN1998 LIBERMAN2009 NAGEL2009 SALYERS2010 XIANG2007</p>
<i>Intervention type</i>	<p>'Bipolar Disorders Program' (k = 1) 'Transforming Relapse and Instilling Prosperity' (TRIP) (k = 1) 'Wellness Recovery Action Planning' (WRAP) (k = 1) 'Building Recovery of Individual Dreams and Goals through Education and Support' (BRIDGES) (k = 1) 'Illness Management and Recovery' (IMR) program (k = 4) 'Social and Independent Living Skills Program' (k = 10) Motivational care planning + TAU (k = 1) 'Functional Adaptation Skills Training' (FAST) (k = 2) Self-management education programme (k = 1) 'Team Solutions' (k = 1) 'Recovery Is Up to You' (k = 1) 'Recovery Work Book' (k = 1)</p>
<i>Comparison</i>	<p>Occupational therapy (k = 2) Psychoeducation (k = 1) Supportive group therapy (k = 4) Illness education class (k = 1) Traditional ward occupational therapy programme (k = 1) Group discussion (k = 1) TAU (k = 14) No treatment (k = 1)</p>
<p><i>Note.</i> TAU = treatment as usual. <sup>1</sup>VREELAND2006 did not report data.</p>	

### 8.3.4 Clinical evidence for self-management interventions

Evidence from each important outcome and overall quality of evidence are presented in Table 60. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Very low quality evidence from up to ten trials (N = 1050) showed that self-management was more effective than control in the management of positive and negative symptoms of psychosis at the end of treatment. No difference was observed between groups at other follow-up points in both positive and negative symptoms. There was inconclusive evidence for the benefits of self-management on total psychosis symptoms. No evidence of benefit was observed at the end of treatment, but moderate quality evidence from one trial with up to 191 participants found some benefit of self-management over control in psychotic symptoms at medium and long-term follow-up.

Very low to moderate quality evidence from up to five trials (N = 338) showed that self-management was more effective than control in reducing the risk of admission in the short-term, although no difference was observed between groups at the end of the intervention or at medium and long-term follow-up.

One study with 54 participants presented moderate quality evidence favouring self-management in increasing contact with aftercare services.

There was no conclusive evidence of any benefit of self-management on self-rated empowerment at the end of the intervention. However, moderate quality evidence from one study (N = 538) provided evidence of benefit on empowerment at short-term follow-up. Very low quality evidence from up to seven studies with 1,234 participants showed that self-management was more effective than control in improving both self-rated and clinician-rated recovery. No difference between groups was observed for functional disability at any follow-up point.

Low quality evidence from nine trials with 1,337 participants showed that self-management had a positive effect on quality of life at the end of treatment. However, at follow-up assessments, the findings were less conclusive. Low quality evidence from up to three studies (N = 600) found no difference between groups in quality of life at short- and long-term follow-up, but a significant difference favouring the intervention at medium-term follow-up.

Regarding trials not included in the meta-analyses, NAGEL2009 reported the intervention to be effective on the outcomes of interest.

#### *Sub-analysis (psychosis and schizophrenia only)*

For the critical outcomes of total and negative psychosis symptoms, empowerment, hospitalisation and contact with secondary services, the sub-analysis findings did not differ substantially from the main analysis and found no benefit of self-management. The benefit found for quality of life was not as conclusive in sub-

analysis. Unlike the main analysis, there was no evidence of a benefit of self-management for self-rated recovery although the findings still favoured self-management for clinician-rated recovery. The related forest plots can be found in Appendix 16.

**Table 60: Summary of findings table for self-management compared with any alternative management strategy**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Self-management			
<i>Psychosis (total symptoms) - end of treatment</i>	N/A	Mean psychosis (total symptoms - end of treatment) in the intervention groups was 0.40 standard deviations lower (1.02 lower to 0.22 higher)	N/A	283 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Psychosis (positive symptoms) - end of treatment</i>	N/A	Mean psychosis (positive symptoms - end of treatment) in the intervention groups was 0.31 standard deviations lower (0.56 lower to 0.07 lower)	N/A	1145 (10 studies)	⊕⊕⊕⊕ Very low <sup>1,3,4</sup>
<i>Psychosis (negative symptoms) - end of treatment</i>	N/A	Mean psychosis (negative symptoms - end of treatment) in the intervention groups was 0.45 standard deviations lower (0.76 to 0.13 lower)	N/A	527 (7 studies)	⊕⊕⊕⊕ Very low <sup>1,3,4</sup>
<i>Psychosis (total symptoms) - up to 6 months' follow-up</i>	N/A	Mean psychosis (total symptoms - up to 6 months' follow-up) in the intervention groups was 0.23 standard deviations lower (0.66 lower to 0.2 higher)	N/A	84 (1 study)	⊕⊕⊕⊕ Low <sup>3,5</sup>
<i>Psychosis (positive symptoms) - up to 6 months' follow-up</i>	N/A	Mean psychosis (positive symptoms - up to 6 months' follow-up) in the intervention groups was 0.24 standard deviations lower (0.69 lower to 0.21 higher)	N/A	410 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Psychosis (negative symptoms) - up to 6 months' follow-up</i>	N/A	Mean psychosis (negative symptoms - up to 6 months' follow-up) in the intervention groups was 0.33 standard deviations lower (0.88 lower to 0.22 higher)	N/A	410 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Psychosis (total symptoms) - 7-12 months' follow-up</i>	N/A	Mean psychosis (total symptoms - 7-12 months' follow-up) in the intervention groups was 1.49 standard deviations lower (1.96 to 1.01 lower)	N/A	88 (1 study)	⊕⊕⊕⊕ High
<i>Psychosis (positive symptoms) - 7-12 months' follow-up</i>	N/A	Mean psychosis (positive symptoms - 7-12 months' follow-up) in the intervention groups was 0.49 standard deviations	N/A	639 (3 studies)	⊕⊕⊕⊕ Very low <sup>2,3</sup>

		lower (1.28 lower to 0.3 higher)			
<i>Psychosis (negative symptoms) - 7-12 months' follow-up</i>	N/A	Mean psychosis (negative symptoms - 7-12 months' follow-up) in the intervention groups was 0.77 standard deviations lower (2.17 lower to 0.63 higher)	N/A	191 (2 studies)	⊕⊕⊕⊕ Very low <sup>2,3</sup>
<i>Psychosis (total symptoms) - &gt;12 months' follow-up</i>	N/A	Mean psychosis (total symptoms - >12 months' follow-up) in the intervention groups was 1.36 standard deviations lower (2.07 to 0.65 lower)	N/A	38 (1 study)	⊕⊕⊕⊕ Moderate <sup>5</sup>
<i>Psychosis (positive symptoms) - &gt;12 months' follow-up</i>	N/A	Mean psychosis (positive symptoms - >12 months' follow-up) in the intervention groups was 0.72 standard deviations lower (1.06 to 0.37 lower)	N/A	141 (2 studies)	⊕⊕⊕⊕ Moderate <sup>1</sup>
<i>Psychosis (negative symptoms) - &gt;12 months' follow-up</i>	N/A	Mean psychosis (negative symptoms - >12 months' follow-up) in the intervention groups was 0.92 standard deviations lower (1.93 lower to 0.09 higher)	N/A	141 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Global state - functioning, disability - end of treatment</i>	N/A	Mean global state (functioning, disability - end of treatment) in the intervention groups was 0.07 standard deviations lower (0.33 lower to 0.2 higher)	N/A	526 (7 studies)	⊕⊕⊕⊕ Low <sup>1,4</sup>
<i>Global state - functioning, disability - up to 6 months' follow-up</i>	N/A	Mean global state (functioning, disability - up to 6 months' follow-up) in the intervention groups was 0.37 standard deviations lower (1.05 lower to 0.32 higher)	N/A	315 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,3,4</sup>
<i>Global state - functioning, disability - 7-12 months' follow-up</i>	N/A	Mean global state (functioning, disability - 7-12 months' follow-up) in the intervention groups was 0.44 standard deviations lower (0.83 to 0.05 lower)	N/A	103 (1 study)	⊕⊕⊕⊕ Low <sup>3,5</sup>
<i>Global state - functioning, disability - &gt;12 months' follow-up</i>	N/A	Mean global state (functioning, disability - >12 months' follow-up) in the intervention groups was 0.56 standard deviations lower (1.99 lower to 0.87 higher)	N/A	183 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Quality of life - end of treatment</i>	N/A	Mean quality of life (end of treatment) in the intervention groups was 0.24 standard deviations higher (0.14 to 0.35 higher)	N/A	1337 (9 studies)	⊕⊕⊕⊕ Low <sup>3,4</sup>
<i>Quality of life - up to 6 months' follow-up</i>	N/A	Mean quality of life (up to 6 months' follow-up) in the intervention groups was 0.24 standard deviations higher (0.01 lower to 0.50 higher)	N/A	240 (2 studies)	⊕⊕⊕⊕ Low <sup>3,5</sup>
<i>Quality of life - 7-12 months' follow-up</i>	N/A	Mean quality of life (7-12 months' follow-up) in the intervention	N/A	600 (3 studies)	⊕⊕⊕⊕ Low <sup>3,4</sup>

		groups was 0.34 standard deviations higher (0.09 to 0.60 higher)			
<i>Quality of life - &gt;12 months' follow-up</i>	N/A	Mean quality of life (>12 months' follow-up) in the intervention groups was 0.23 standard deviations higher (0.13 lower to 0.60 higher)	N/A	118 (2 studies)	⊕⊕⊕⊕ Low <sup>1</sup>
<i>Empowerment - end of treatment</i>	N/A	Mean empowerment (end of treatment in the intervention groups) was 1.44 standard deviations higher (0.08 lower to 2.97 higher)	N/A	538 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,2</sup>
<i>Empowerment - up to 6 months' follow-up</i>	N/A	Mean empowerment (up to 6 months' follow-up) in the intervention groups was 0.25 standard deviations higher (0.07 to 0.43)	N/A	318 (1 study)	⊕⊕⊕⊕ Moderate
<i>Recovery (self-rated) - end of treatment</i>	N/A	Mean recovery (self-rated - end of treatment) in the intervention groups was 0.27 standard deviations lower (0.49 to 0.05 lower)	N/A	1234 (7 studies)	⊕⊕⊕⊕ Very low <sup>1,4</sup>
<i>Recovery (clinician-rated) - end of treatment</i>	N/A	Mean recovery (clinician-rated - end of treatment) in the intervention groups was 0.67 standard deviations lower (0.88 to 0.45 lower)	N/A	354 (3 studies)	⊕⊕⊕⊕ Moderate <sup>1</sup>
<i>Recovery (self-rated) - up to 12 months' follow-up</i>	N/A	Mean recovery (self-rated - up to 12 months' follow-up) in the intervention groups was 0.22 standard deviations lower (0.36 to 0.09 lower)	N/A	883 (4 studies)	⊕⊕⊕⊕ Low <sup>1</sup>
<i>Recovery (clinician-rated) - up to 12 months' follow-up</i>	N/A	Mean recovery (clinician-rated - up to 12 months' follow-up) in the intervention groups was 0.57 standard deviations lower (0.92 to 0.21 lower)	N/A	129 (2 studies)	⊕⊕⊕⊕ Moderate <sup>1</sup>
<i>Service use, contact - end of treatment</i>	Study population		RR 0.24 (0.09 to 0.61)	54 (1 study)	⊕⊕⊕⊕ Moderate <sup>5</sup>
	630 per 1000	151 per 1000 (57 to 384)			
<i>Service use - hospitalisation - end of treatment - days hospitalised</i>	N/A	The mean service use (hospitalisation, end of treatment - days hospitalised) in the intervention groups was 0.03 standard deviations lower (0.39 lower to 0.34 higher)	N/A	122 (1 study)	⊕⊕⊕⊕ Moderate <sup>5</sup>
<i>Service use - hospitalisation - end of treatment</i>	Study population		RR 1.06 (0.61 to 1.85)	122 (1 study)	⊕⊕⊕⊕ Low <sup>1</sup>
	288 per 1000	305 per 1000 (175 to 532)			
<i>Service use - hospitalisation - up to 6 months' follow-up</i>	Study population		RR 0.23 (0.08 to 0.7)	269 (3 studies)	⊕⊕⊕⊕ Moderate <sup>5</sup>
	118 per	27 per 1000			

up	1000	(9 to 82)			
Service use - hospitalisation - 7-12 months' follow-up	Study population		RR 0.77 (0.43 to 1.39)	238 (3 studies)	⊕⊕⊕⊖ Low <sup>1</sup>
	181 per 1000	139 per 1000 (78 to 252)			
Service use - hospitalisation - >12 months' follow-up	Study population		RR 0.66 (0.23 to 1.92)	338 (4 studies)	⊕⊕⊕⊖ Very low <sup>1,4</sup>
	192 per 1000	127 per 1000 (44 to 369)			
Service use - hospitalisation - >12 months' follow-up - days hospitalised	N/A	Mean service use (hospitalisation - >12 months' follow-up - days hospitalised) in the intervention groups was 0.15 standard deviations higher (0.21 lower to 0.51 higher)	N/A	122 (1 study)	⊕⊕⊕⊖ Moderate <sup>5</sup>

### 8.3.5 Clinical evidence summary

Overall, the evidence suggests that self-management interventions are effective for reducing symptoms of psychosis. However, this benefit was less conclusive for reducing the risk of hospitalisation. Self-management was effective at improving quality of life at the end of the intervention, with some less certain evidence of long-term benefit. Self-management was also found to be beneficial for aiding recovery in both self-and clinician-rated outcomes. This effect was sustained at long-term follow-up. There was no conclusive evidence of a beneficial effect of self-management on functional disability.

### 8.3.6 Health economics evidence

No studies assessing the cost effectiveness of self-management interventions for adults with psychosis and schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

## 8.4 LINKING EVIDENCE TO RECOMMENDATIONS

### *Relative value placed on the outcomes considered*

The GDG judged that the aim of peer-provided and self-management interventions were to manage symptoms and thus reduce the risk of hospitalisation because of relapse. The GDG also thought that self-management interventions aimed to empower the service user and improve quality of life and day-to-day functioning. Therefore, the GDG decided that the critical outcomes were:

For self-management:

- empowerment/recovery
- functional disability
- quality of life
- hospitalisation (admissions, days)
- contact with secondary services
- symptoms of psychosis

- total symptoms
- positive symptoms
- negative symptoms.

For peer-provided interventions:

- empowerment/ recovery
- functional disability
- quality of life
- service use
  - GP visits
  - A&E visits
  - hospitalisation (admissions, days)
- user satisfaction (validated measures only).

### *Trade-off between clinical benefits and harms*

The GDG considered the benefits of peer-provided interventions and self-management for symptom management. Although there was some evidence of improvement in symptoms at the end of the intervention for self-management (not for peer-provided interventions), data were limited at any further follow-up point. The GDG thought that self-management and peer support were likely to be beneficial for people with psychosis and schizophrenia, but should not be provided as the sole intervention because they were not designed as stand-alone treatments. However, the GDG considered that both interventions should be provided as additional support for people throughout all phases of the illness.

### *Trade-off between net health benefits and resource use*

There was only one economic study that attempted to assess the cost savings associated with peer-provided interventions for adults with psychosis and schizophrenia; however the GDG judged it to have very serious limitations. No studies assessing the cost effectiveness of self-management interventions for adults with psychosis and schizophrenia were identified by the systematic review of the economic literature. Due to the lack of clinical data it was decided that formal economic modelling of peer-provided or self-management interventions in this area would not be useful in decision-making. Nevertheless, the GDG judged that the costs of providing such interventions are justified by the expected clinical benefits, that is, aiding recovery in both self- and clinician-rated outcomes. Moreover, it is likely that the costs of providing such interventions will be offset, at least partially, by cost savings in health services resulting from improvements in symptoms of psychosis.

### *Quality of the evidence*

For both peer-provided and self-management interventions, the quality of the evidence ranged from very low to high. The evidence for peer support was of particular poor quality and ranged from very low to low across critical outcomes. Reasons for downgrading concerned risk of bias, high heterogeneity or lack of precision in confidence intervals, which crossed clinical decision thresholds.

Heterogeneity was a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most studies. Furthermore, wide confidence intervals were also of concern to the GDG. This problem was particularly found for outcomes with low numbers of included studies and participants. The GDG considered these quality issues when discussing possible recommendations.

### ***Other considerations***

The GDG considered it important to define the components of peer support and self-management interventions. The components included in the reviews were generally well specified and therefore the GDG used this information as a basis of discussion when developing a recommendation.

## **8.5 RECOMMENDATIONS**

### **8.5.1 Clinical practice recommendations**

- 8.5.1.1** Consider peer support for people with psychosis or schizophrenia to help improve service user experience and quality of life. Peer support should be delivered by a trained peer support worker who has recovered from psychosis or schizophrenia and remains stable. Peer support workers should receive support from their whole team, and support and mentorship from experienced peer workers. [new 2014]
- 8.5.1.2** Consider a manualised self-management programme delivered face-to-face with service users, as part of the treatment and management of psychosis or schizophrenia. [new 2014]
- 8.5.1.3** Peer support and self-management programmes should include information and advice about:
- psychosis and schizophrenia
  - effective use of medication
  - identifying and managing symptoms
  - accessing mental health and other support services
  - coping with stress and other problems
  - what to do in a crisis
  - building a social support network
  - preventing relapse and setting personal recovery goals. [new 2014]

### **8.5.2 Research recommendations**

- 8.5.2.1** What is the clinical and cost effectiveness of peer support interventions in people with psychosis and schizophrenia? (see Appendix 10 for further details) [2014]



## 9 PSYCHOLOGICAL THERAPY AND PSYCHOSOCIAL INTERVENTIONS

This chapter has been partially updated for the 2014 guideline. Most sections remain unchanged from the 2009 guideline, however some of the recommendations have been updated to bring them in line with the recommendations from *Psychosis and Schizophrenia in Children and Young People*. This was considered necessary to avoid discrepancies between the child and adult guidelines, particularly regarding early intervention. Consequently new sections have been added to the evidence to recommendations section. In addition some recommendations from the 2009 guideline have been amended to improve the wording and structure with no important changes to the context and meaning of the recommendation. In addition, a new review was conducted for the psychological management of trauma (section 9.11) because of the inclusion of people with psychosis for this update and the association of trauma with the development of psychosis.

Sections of the guideline where the evidence has not been updated since 2002 are marked as **\*\*2002\*\*\_\*\*2002\*\*** and where the evidence has not be updated since 2009, marked by asterisks (**\*\*2009\*\*\_\*\*2009\*\***).

Please note that all references to study IDs in sections that have not been updated in this chapter can be found in Appendix 22c.

### 9.1 INTRODUCTION

**\*\* 2009\*\***Psychological therapies and psychosocial interventions in the treatment of schizophrenia have gained momentum over the past 3 decades. This can be attributed to at least two main factors. First, there has been growing recognition of the importance of psychological processes in psychosis, both as contributors to onset and persistence, and in terms of the negative psychological impact of a diagnosis of schizophrenia on the individual's well-being, psychosocial functioning and life opportunities. Psychological and psychosocial interventions for psychosis have been developed to address these needs. Second, although pharmacological interventions have been the mainstay of treatment since their introduction in the 1950s, they have a number of limitations. These include limited response of some people to antipsychotic medication, high incidence of disabling side effects and poor adherence to treatment. Recognition of these limitations has paved the way for acceptance of a more broadly-based approach, combining different treatment options tailored to the needs of individual service users and their families. Such treatment options include psychological therapies and psychosocial interventions. Recently, emphasis has also been placed on the value of multidisciplinary formulation and reflective practice, particularly where psychologists and allied

mental health professionals operate within multidisciplinary teams (British Psychological Society, 2007).

The 'New Ways of Working' report (British Psychological Society, 2007) details the increasing demand by both service users and carers to gain access to psychological interventions, and the increasing recognition of these interventions in the treatment and management of serious mental illnesses including schizophrenia. The report proposes that a large expansion of training of psychologists and psychological therapists is needed to increase the workforce competent in the provision of psychological therapies. This chapter addresses the evidence base for the application of psychological and psychosocial treatments, generally in combination with antipsychotic medication, in the treatment of schizophrenia, for individuals, groups and families.

### **9.1.1 The stress-vulnerability model**

Although the rationales for medical, psychological and psychosocial interventions are derived from a variety of different biological, psychological and social theories, the development of the stress-vulnerability model (Nuechterlein, 1987; Zubin & Spring, 1977) has undoubtedly facilitated the theoretical and practical integration of disparate treatment approaches (see Chapter 2). In this model, individuals develop vulnerability to psychosis attributable to biological, psychological and/or social factors; treatments, whether pharmacological or psychological, then aim to protect a vulnerable individual and reduce the likelihood of relapse, reduce the severity of the psychotic episode and treat the problems associated with persisting symptoms. Psychological interventions may, in addition, aim to improve specific psychological or social aspects of functioning and to have a longer-term effect upon an individual's vulnerability.

### **9.1.2 Engagement**

A prerequisite for any psychological or other treatment is the effective engagement of the service user in a positive therapeutic or treatment alliance (Roth et al., 1996). Engaging people effectively during an acute schizophrenic illness is often difficult and demands considerable flexibility in the approach and pace of therapeutic working. Moreover, once engaged in a positive therapeutic alliance, it is equally necessary to maintain this relationship, often over long periods, with the added problem that such an alliance may wax and wane, especially in the event of service users becoming subject to compulsory treatment under the Mental Health Act. Special challenges in the treatment of schizophrenia include social withdrawal, cognitive and information-processing problems, developing a shared view with the service user about the nature of the illness, and the impact of stigma and social exclusion.

### **9.1.3 Aims of psychological therapy and psychosocial interventions**

The aims of psychological and psychosocial interventions in the treatment of a person with schizophrenia are numerous. Particular treatments may be intended to

improve one or more of the following outcomes: to decrease the person's vulnerability; reduce the impact of stressful events and situations; decrease distress and disability; minimise symptoms; improve quality of life; reduce risk; improve communication and coping skills; and/or enhance treatment adherence. As far as possible, research into psychological interventions needs to address a wide range of outcomes.

#### 9.1.4 Therapeutic approaches identified

The following psychological therapies and psychosocial interventions were reviewed:

- adherence therapy
- arts therapies
- cognitive behavioural therapy
- cognitive remediation
- counselling and supportive therapy
- family intervention
- psychodynamic and psychoanalytic therapies
- psychoeducation
- social skills training\*\*2009\*\*
- psychological management of trauma.

\*\*2009\*\* The primary clinical questions addressed in this chapter can be found in Box 1.

#### Box 1: Primary clinical questions addressed in this chapter

##### *Initial treatment*

For people with first-episode or early schizophrenia, what are the benefits and downsides of psychological/ psychosocial interventions when compared with alternative management strategies at initiation of treatment?

##### *Acute treatment*

For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of psychological/ psychosocial interventions when compared with alternative management strategies?

##### *Promoting recovery in people with schizophrenia that is in remission*

For people with schizophrenia that is in remission, what are the benefits and downsides of psychological/ psychosocial interventions when compared with alternative management strategies?

##### *Promoting recovery in people with schizophrenia who have had an inadequate or no response to treatment*

For people with schizophrenia who have an inadequate or no response to treatment, what are the benefits and downsides of psychological/ psychosocial interventions when compared with alternative management strategies? \*\*2009\*\*

*Psychological management of trauma*

For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of psychological management strategies for previous trauma compared with treatment as usual or another intervention?

### 9.1.5 Multi-modal interventions

\*\*2009\*\* Some researchers have combined two psychological and/or psychosocial interventions to attempt to increase the effectiveness of the intervention. For example, a course of family intervention may be combined with a module of social skills training. The combinations are various and thus these multi-modal interventions do not form a homogenous group of interventions that can be analysed together. Therefore, multi-modal interventions that combined psychological and psychosocial treatments within the scope of this review were included in the primary analysis for each intervention review. Sensitivity analyses were conducted to test the effect, if any, of removing these multi-modal interventions. Where papers reported more than two treatment arms (for example, family intervention only versus social skills training only versus family intervention plus social skills training), only data from the single intervention arms was entered into the appropriate analysis (for example, family intervention only versus social skills training only). Papers assessing the efficacy of psychological treatments as adjuncts to discrete treatments outside the scope of the 2009 guideline (for example, supported employment and pre-vocational training) were excluded from the analysis.

It is, however, worth noting that although some of the papers included in the 2002 guideline can be classed as multi-modal treatments because they systematically combine elements such as, for example, family intervention, social skills training and CBT, this needs to be understood in the context of the standard care available at the time. In particular, there has been a recent emphasis on incorporating active elements, particularly psychoeducation, into a more comprehensive package of standard care. Elements included in the experimental arms of older studies may now be considered routine elements of good standard care. It should also be noted that standard care differs across countries.

#### *Definition*

To be classified as multi-modal, an intervention needed to be composed of the following:

- a treatment programme where two or more specific psychological interventions (as defined above) were combined in a systematic and programmed way; and

- the intervention was conducted with the specific intention of producing a benefit over and above that which might be achieved by a single intervention alone.
- In addition, multi-modal treatments could provide specific interventions, either concurrently or consecutively.

### **9.1.6 Competence to deliver psychological therapies**

For the purpose of implementing the guideline, it is important to have an understanding of the therapists' level of competence in the psychological therapy trials that were included. Each of the psychological therapy papers was reviewed for details of training or level of competence of the therapists delivering the intervention<sup>21</sup>.

## **9.2 ADHERENCE THERAPY**

### **9.2.1 Introduction**

Pharmacological interventions have been the mainstay of treatment since their introduction in the 1950s; however, about 50% of people with schizophrenia and schizophreniform disorder are believed to be non-adherent to (or non-compliant with) their medication (Nose et al., 2003). It is estimated that non-adherence to medication leads to a higher relapse rate, repeated hospital admissions, and therefore increased economic and social burden for the service users themselves as well as for mental health services (Gray et al., 2006; Robinson et al., 1999).

Against this background, 'compliance therapy' was first developed by Kemp and colleagues (1996; 1998) to target service users with schizophrenia and psychosis. The therapy aims to improve service users' attitude to medication and treatment adherence, and thus hypothetically enhance their clinical outcomes, and prevent potential and future relapse (Kemp et al., 1996; Kemp et al., 1998). Recently, the terms 'adherence' and 'concordance' have been used synonymously to denote 'compliance therapy' and its major aim (that is, adherence to medication), as reflected in emerging literature (McIntosh et al., 2006). Overall, 'adherence therapy' is the commonly accepted term used contemporarily.

Adherence therapy is designed as a brief and pragmatic intervention, borrowing techniques and principles from motivational interviewing (Miller & Rollnick, 1991), psychoeducation and cognitive therapy (Kemp et al., 1996). A typical adherence therapy course offered to a service user with psychosis usually comprises four to eight sessions, each lasting from roughly 30 minutes to 1 hour (Gray et al., 2006; Kemp et al., 1996). The intervention uses a phased approach to:

- assess and review the service user's illness and medication history
- explore his or her ambivalence to treatment, maintenance medication and stigma

---

<sup>21</sup>Training and competency reviews are presented only for recommended interventions.

- conduct a medication problem-solving exercise to establish the service user's attitude to future medication use.

### **Definition**

Adherence therapy was defined as:

- any programme involving interaction between service provider and service user, during which service users are provided with support, information and management strategies to improve their adherence to medication and/or with the specific aim of improving symptoms, quality of life and preventing relapse.

To be considered as well defined, the strategy should be tailored to the needs of individuals.

## **9.2.2 Clinical review protocol**

The review protocol, including information about the databases searched and the eligibility criteria can be found in Table 61. The primary clinical questions can be found in Appendix 21. A new systematic search for relevant studies was conducted for the 2009 guideline. The search identified an existing Cochrane review (McIntosh et al., 2006) which was used to identify papers prior to 2002 (further information about the search strategy can be found in Appendix 20).

**Table 61: Clinical review protocol for the review of adherence therapy**

<i>Electronic databases</i>	CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT (≥10 participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Adherence therapy
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Adherence to antipsychotic treatment Insight Quality of life Leaving the study early for any reason Adverse events

### **9.2.3 Studies considered for review<sup>22</sup>**

Five RCTs (N = 649) met the inclusion criteria for the 2009 guideline review. Although broadly based on a cognitive behavioural approach, KEMP1996 was reclassified as an adherence therapy paper because the primary aim of the intervention was to improve adherence and attitudes towards medication. All of the trials were published in peer-reviewed journals between 1996 and 2007. In addition, two studies were excluded from the analysis because they failed to meet the intervention definition (further information about both included and excluded studies can be found in Appendix 22c).

### **9.2.4 Adherence therapy versus control**

For the 2009 guideline, five RCTs of adherence therapy versus any type of control were included in the meta-analysis (see Table 62 for a summary of the study characteristics). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### **9.2.5 Clinical evidence summary**

The limited evidence from KEMP1996 regarding improvements in measures of compliance and insight has not been supported by new studies, including those with follow-up measures. Although there is limited and inconsistent evidence of improved attitudes towards medication, adherence therapy did not have an effect on symptoms, quality of life, relapse or rehospitalisation.

### **9.2.6 Health economic evidence**

The systematic search of the economic literature identified one study that assessed the cost effectiveness of adherence therapy for people with acute psychosis treated in an inpatient setting in the UK (Healey et al., 1998). The study was conducted alongside the RCT described in KEMP1996. The comparator of adherence therapy was supportive counselling. The study sample consisted of 74 people with schizophrenia, affective disorders with psychotic features or schizoaffective disorder who were hospitalised for psychosis. The time horizon of the economic analysis was 18 months (RCT period plus naturalistic follow-up). Costs consisted of those to the NHS (inpatient, outpatient, day-hospital care, accident and emergency services, primary and community care) and criminal justice system costs incurred by arrests, court appearances, probation, and so on. Outcomes included relapse rates, BPRS and GAF scores, Drug Attitude Inventory (DAI) scores, Insight scale scores and levels of compliance with antipsychotic medication. Adherence therapy was reported to have a significant positive effect over supportive counselling in terms of relapse, GAF, DAI and Insight scale scores as well as compliance at various follow-up time points. The two interventions were associated with similar costs: mean weekly cost per person over 18 months was £175 for adherence therapy and £193 for supportive

---

<sup>22</sup>Here and elsewhere in this chapter, each study considered for review is referred to by a study ID, with studies included in the previous guideline in lower case and new studies in upper case (primary author and date). References for included studies denoted by study IDs can be found in Appendix 22c.

counselling in 1995/96 prices ( $p = 0.92$ ). Because of high rates of attrition, the sample size at endpoint ( $N = 46$ ) was adequate to detect a 30% difference in costs at the 5% level of significance. The authors suggested that adherence therapy was a cost-effective intervention in the UK because it was more effective than supportive counselling at a similar cost.

**Table 62: Summary of study characteristics for adherence therapy**

<b>Adherence therapy versus any control</b>	
<i>K (total N)</i>	5 (649)
<i>Study ID</i>	GRAY2006 KEMP1996 MANEESAKORN2007 ODONNELL2003 TSANG2005
<i>Diagnosis</i>	58–100% schizophrenia or other related diagnoses (DSM-III or IV)
<i>Baseline severity</i>	BPRS total: Mean (SD)~45 (13) GRAY2006 Mean (SD)~58 (14) KEMP1996 Mean (SD)~69 (20) ODONNELL2003 Mean (SD)~44 (8) TSANG2005 PANSS total: Mean (SD)~59 (13) MANEESAKORN2007
<i>Number of sessions</i>	Range: 4–8
<i>Length of treatment</i>	Range: Maximum 3–20 weeks (GRAY2006, KEMP1996; MANEESAKORN2007)
<i>Length of follow-up</i>	Up to 12 months: GRAY2006, ODONNELL2003, TSANG2005 Up to 18 months: KEMP1996
<i>Setting</i>	Inpatient: KEMP1996, MANEESAKORN2007, ODONNELL2003, TSANG2005 Inpatient and outpatient: GRAY2006

Details on the methods used for the systematic search of the economic literature are described in Appendix 28. References to included/excluded studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in the form of evidence tables in Appendix 25.

### 9.2.7 Linking evidence to recommendations

The 2009 guideline review found no consistent evidence to suggest that adherence therapy is effective in improving the critical outcomes of schizophrenia when compared with any other control. Although one UK-based study (KEMP1996) reported positive results for measures of adherence and drug attitudes, these findings have not been supported in recent, larger-scale investigations. It is also noteworthy that a proportion of participants in the KEMP1996 study had a primary diagnosis of a mood disorder and that, in an 18-month follow-up paper, the authors stated that ‘subgroup analyses revealed the following: patients with schizophrenia



tended to have a less favourable outcome in terms of social functioning, symptom level, insight and treatment attitudes’.

One economic analysis, conducted alongside KEMP1996, suggested that adherence therapy could be a cost-effective option for people experiencing acute psychosis in the UK because it was more effective than its comparator at a similar total cost. In addition to the aforementioned limitations of the KEMP1996 study, because of high attrition rates the sample was very small, making it difficult to establish such a hypothesis.

Based on the limited health economic evidence and lack of clinical effectiveness, the GDG therefore concluded that there is no robust evidence for the use of adherence therapy as a discrete intervention.

## **9.2.8 Recommendations**

**9.2.8.1** Do not offer adherence therapy (as a specific intervention) to people with psychosis or schizophrenia. [2009]

## **9.3 ARTS THERAPIES**

### **9.3.1 Introduction**

The arts therapy professions in the US and Europe have their roots in late 19th and early 20th century hospitals, where involvement in the arts was used by patients and interested clinicians as a potential aid to recovery. This became more prevalent after the influx of war veterans in the 1940s, which led to the emergence of formal training and professional bodies for art, music, drama and dance movement therapies. These treatments were further developed in psychiatric settings in the latter half of the 20th century (Bunt, 1994; Wood, 1997).

While the four modalities use a variety of techniques and arts media, all focus on the creation of a working therapeutic relationship in which strong emotions can be expressed and processed. The art form is also seen as a safe way to experiment with relating to others in a meaningful way when words can be difficult. A variety of psychotherapeutic theories are used to understand the interactions between patient(s) and therapist but psychodynamic models (see Section 9.8) tend to predominate in the UK (Crawford & Patterson, 2007).

More recently, approaches to working with people with psychosis using arts therapies have begun to be more clearly defined, taking into consideration the phase and symptomatology of the illness (Gilroy & McNeilly, 2000; Jones, 1996). The arts therapies described in the studies included in this review have predominantly emphasised expression, communication, social connection and self-awareness through supportive and interactive experiences, with less emphasis on the use of ‘uncovering’ psycho-analytic approaches (Green et al., 1987; Rohricht & Priebe, 2006; Talwar et al., 2006; Ulrich et al., 2007; Yang et al., 1998).

Art, music, drama and dance movement therapists<sup>23</sup> practising in the UK are state registered, regulated by the Health Professions Council, which requires specialist training at Master's level.

### **Definition**

Arts therapies are complex interventions that combine psychotherapeutic techniques with activities aimed at promoting creative expression. In all arts therapies:

- the creative process is used to facilitate self-expression within a specific therapeutic framework
- the aesthetic form is used to 'contain' and give meaning to the service user's experience
- the artistic medium is used as a bridge to verbal dialogue and insight-based psychological development if appropriate
- the aim is to enable the patient to experience him/herself differently and develop new ways of relating to others.

Arts therapies currently provided in the UK comprise: art therapy or art psychotherapy, dance movement therapy, body psychotherapy, drama therapy and music therapy.

### **9.3.2 Clinical review protocol**

The review protocol, including information about the databases searched and the eligibility criteria, can be found in Table 63. The primary clinical questions can be found in Box 1 (further information about the search strategy can be found in Appendix 20).

**Table 63: Clinical review protocol for the review of arts therapies**

<i>Electronic databases</i>	CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	Database inception to 30 July 2008
<i>Study design</i>	RCT ( $\geq 10$ participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Arts therapies
<i>Comparator</i>	Any alternative management strategy

---

<sup>23</sup>Registration pending.

<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Leaving the study early for any reason Adverse events
--------------------------	--

### 9.3.3 Studies considered for review

Seven RCTs (N = 406) met the inclusion criteria for the 2009 guideline review. All trials were published in peer-reviewed journals between 1974 and 2007 (further information about both included and excluded studies can be found in Appendix 22c).

### 9.3.4 Arts therapies versus any control

For the 2009 guideline review, six out of the seven RCTs were included in the meta-analysis of arts therapies versus any type of control (see Table 64 for a summary of the study characteristics). One of the included studies (NITSUN1974) did not provide any useable data for any of the critical outcomes listed in the review protocol. Sub-analyses were used to examine treatment modality and setting. Forest plots and/or data tables for each outcome can be found in Appendix 23d.

**Table 64: Summary of study characteristics for arts therapies**

<b>Arts therapies versus any control</b>	
<i>K (totalN)</i>	6 (382)
<i>StudyID</i>	GREEN1987 RICHARDSON2007 ROHRICHT2006 TALWAR2006 ULRICH2007 YANG1998
<i>Diagnosis</i>	50–100%schizophrenia or other related diagnoses (DSM-III or IV)
<i>Baseline severity</i>	BPRS total: Mean (SD): ~16 ( 9) RICHARDSON2007 Mean (SD): ~40 (8) YANG1998 PANSS total: Mean (SD): ~78 (18) ROHRICHT2006 Mean (SD): ~72 (13) TALWAR2006
<i>Treatment modality</i>	Art: GREEN1987, RICHARDSON2007 Body-orientated: ROHRICHT2006 Music: TALWAR2006, ULRICH2007, YANG1998
<i>Length of treatment</i>	Range: 5–20 weeks
<i>Length of follow-up</i>	Up to 6 months: RICHARDSON2007, ROHRICHT2006

Setting	Inpatient: TALWAR2006, ULRICH2007, YANG1998 Outpatient: GREEN1987, RICHARDSON2007, ROHRICHT2006
---------	--

### 9.3.5 Clinical evidence summary

The review found consistent evidence that arts therapies are effective in reducing negative symptoms when compared with any other control. There was some evidence indicating that the medium to large effects found at the end of treatment were sustained at up to 6 months' follow-up. Additionally, there is consistent evidence to indicate a medium effect size regardless of the modality used within the intervention (that is, music, body-orientated or art), and that arts therapies were equally as effective in reducing negative symptoms in both inpatient and outpatient populations.

### 9.3.6 Health economic considerations

No evidence on the cost effectiveness of arts therapies for people with schizophrenia was identified by the systematic search of the economic literature. Details on the methods used for the systematic search of the economic literature are described in Appendix 11.

The clinical studies on arts therapies included in the guideline systematic literature review described interventions consisting of 12 sessions on average. These programmes are usually delivered by one therapist to groups of six to eight people in the UK and have an average duration of 1 hour.

Arts therapies are provided by therapists with a specialist training at Master's level. The unit cost of a therapist providing arts therapies was not available. The salary scale of an arts therapist lies across bands 7 and 8a, which is comparable to the salary level of a clinical psychologist. The unit cost of a clinical psychologist is £67 per hour of client contact in 2006/07 prices (Curtis, 2007). This estimate has been based on the mid-point of Agenda for Change salaries band 7 of the April 2006 pay scale according to the National Profile for Clinical Psychologists, Counsellors and Psychotherapists (NHS Employers, 2006). It includes salary, salary oncosts, overheads and capital overheads, but does not take into account qualification costs because the latter are not available for clinical psychologists.

Based on the estimated staff time associated with an arts therapy programme (as described above) and the unit cost of a clinical psychologist, the average cost of arts therapy per person participating in such a programme would range between £100 and £135 in 2006/07 prices.

Using the lower cost-effectiveness threshold of £20,000 per QALY set by NICE (NICE, 2008b), a simple threshold analysis indicated that arts therapies are cost effective if they improve the HRQoL of people with schizophrenia by 0.005 to 0.007 annually, on a scale of 0 (death) to 1 (perfect health). Using the upper cost-

effectiveness threshold of £30,000 per QALY, the improvement in HRQoL of people in schizophrenia required for arts therapies to be cost effective fell by 0.003 to 0.004 annually.

### 9.3.7 Linking evidence to recommendations

The clinical review indicated that arts therapies are effective in reducing negative symptoms across a range of treatment modalities, and for both inpatient and outpatient populations. The majority of trials included in the review utilised a group-based approach. It is noteworthy that in all of the UK-based studies the therapists conducting the intervention were all Health Professions Council (HPC) trained and accredited, with the equivalent level of training occurring in the non-UK based studies.

The cost of arts therapies was estimated at roughly £100 to £135 per person with schizophrenia (2006/07 prices); a simple threshold analysis showed that if arts therapies improved the HRQoL of people with schizophrenia by approximately 0.006 annually (on a scale of 0 to 1) then they would be cost effective, according to the lower NICE cost-effectiveness threshold. Using the upper NICE cost-effectiveness threshold, improvement in HRQoL would need to approximate 0.0035 annually for the intervention to be considered cost effective. Use of this upper cost-effectiveness threshold can be justified because arts therapies are the only interventions demonstrated to have medium to large effects on negative symptoms in people with schizophrenia. The GDG estimated that the magnitude of the improvement in negative symptoms associated with arts therapies (SMD -0.59 with 95% CIs -0.83 to -0.36) could be translated into an improvement in HRQoL probably above 0.0035, and possibly even above 0.006 annually, given that the therapeutic effect of arts therapies was shown to last (and was even enhanced) at least up to 6 months following treatment (SMD -0.77 with 95% CIs -1.27 to -0.26).

At present, the data for the effectiveness of arts therapies on other outcomes, such as social functioning and quality of life, is still very limited and infrequently reported in trials. Consequently, the GDG recommends that further large-scale investigations of arts therapies should be undertaken to increase the current evidence base. Despite this small but emerging evidence base, the GDG recognise that arts therapies are currently the only interventions (both psychological and pharmacological) to demonstrate consistent efficacy in the reduction of negative symptoms. This, taken in combination with the economic analysis, has led to the following recommendations.

### 9.3.8 Recommendations

#### *Subsequent acute episodes*

- 9.3.8.1** Consider offering arts therapies to all people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings. [2009]

**9.3.8.2** Arts therapies should be provided by a Health and Care Professions Council registered arts therapist with previous experience of working with people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the service user. Aims of arts therapies should include:

- enabling people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others
- helping people to express themselves and to organise their experience into a satisfying aesthetic form
- helping people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to the person. [2009]

**9.3.8.3** When psychological treatments, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption. [2009]

### *Promoting recovery*

**9.3.8.4** Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms. [2009]

## **9.3.9 Research recommendations**

**9.3.9.1** An adequately powered RCT should be conducted to investigate the clinical and cost effectiveness of arts therapies compared with an active control (for example, sham music therapy) in people with schizophrenia.[2009]

**9.3.9.2** An adequately powered RCT should be conducted to investigate the most appropriate duration and number of sessions for arts therapies in people with schizophrenia.[2009]

## **9.4 COGNITIVE BEHAVIOURAL THERAPY**

### **9.4.1 Introduction**

CBT is based on the premise that there is a relationship between thoughts, feelings and behaviour. Although Albert Ellis first developed CBT (which he called rational emotive behaviour therapy) in the 1960s, most CBT practiced in the present day has its origins in the work of Aaron T. Beck. Beck developed CBT for the treatment of depression in the 1970s (Beck, 1979), but since then it has been found to be an effective treatment in a wide range of mental health problems including anxiety disorders, obsessive-compulsive disorder, bulimia nervosa and PTSD. In the early 1990s, following an increased understanding of the cognitive psychology of

psychotic symptoms (Frith, 1992; Garety & Hemsley, 1994; Slade & Bentall, 1988), interest grew in the application of CBT for people with psychotic disorders. Early CBT trials tended to be particularly symptom focused, helping service users develop coping strategies to manage hallucinations (Tarrier et al., 1993). Since then, however, CBT for psychosis (CBTp) has evolved and now tends to be formulation based.

As with other psychological interventions, CBT depends upon the effective development of a positive therapeutic alliance (Roth et al., 1996). On the whole, the aim is to help the individual normalise and make sense of their psychotic experiences, and to reduce the associated distress and impact on functioning. CBTp trials have investigated a range of outcomes over the years; these include symptom reduction (positive, negative and general symptoms) (Rector et al., 2003), relapse reduction (Garety et al., 2008), social functioning (Startup et al., 2004), and insight (Turkington et al., 2002). More recently, researchers have shown an interest in the impact of CBTp beyond the sole reduction of psychotic phenomena and are looking at changes in distress and problematic behaviour associated with these experiences (Trower et al., 2004). Furthermore, the populations targeted have expanded, with recent developments in CBTp focusing on the treatment of first episode psychosis (Jackson et al., 2005; Jackson et al., 2008), and people with schizophrenia and comorbid substance use disorders (Barrowclough et al., 2001).

### ***Definition***

CBT was defined as a discrete psychological intervention where service users:

- establish links between their thoughts, feelings or actions with respect to the current or past symptoms, and/or functioning, and
- re-evaluate their perceptions, beliefs or reasoning in relation to the target symptoms.

In addition, a further component of the intervention should involve the following:

- service users monitoring their own thoughts, feelings or behaviours with respect to the symptom or recurrence of symptoms, and/or
- promotion of alternative ways of coping with the target symptom, and/or
- reduction of distress, and/or
- improvement of functioning.

### **9.4.2 Clinical review protocol**

The review protocol, including information about the databases searched and the eligibility criteria, can be found in Table 65. The primary clinical questions can be found in Box 1. For the 2009 guideline, a new systematic search was conducted for relevant RCTs published since the 2002 guideline (further information about the search strategy can be found in Appendix 20 and information about the search for health economic evidence can be found in Section 9.4.8).

### 9.4.3 Studies considered for review

In the 2002 guideline, 13 RCTs (N = 1,297) of CBT were included. One RCT from the 2002 guideline (KEMP1996) was removed from the 2009 guideline analysis and re-classified by the GDG as adherence therapy and a further three studies were removed because of inadequate numbers of participants (Garety1994; Levine1996; Turkington2000). The search for the 2009 guideline identified six papers providing follow-up data to existing RCTs and 22 new RCTs, including those with CBT as part of a multi-modal intervention. In total, 31 RCTs (N = 3,052) met the inclusion criteria for the update. Of these, one was currently unpublished and 30 were published in peer-reviewed journals between 1996 and 2008 (further information about both included and excluded studies can be found in Appendix 22c).

**Table 65: Clinical review protocol for the review of CBT**

<i>Electronic databases</i>	CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT (≥ 10 participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	CBT
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Adherence to antipsychotic treatment Insight Quality of life Leaving the study early for any reason Adverse events

### 9.4.4 Cognitive behavioural therapy versus control

For the 2009 guideline review, 31 RCTs of CBT versus any type of control were included in the meta-analysis (see Table 66 for a summary of the study characteristics). However this comparison was only used for outcomes in which there were insufficient studies to allow for a separate standard care and other active treatment arms.



For the primary analysis, 19 RCTs were included comparing CBT with standard care, 14 comparing CBT with other active treatments and three comparing CBT with non-standard care. Forest plots and/or data tables for each outcome can be found in Appendix 23d.

In addition to the primary analyses, subgroup analyses were used to explore certain characteristics of the trials<sup>24</sup> (see Table 67 for a summary of the studies included in each subgroup comparison). Five RCTs were included in the analysis comparing CBT with any control in participants experiencing a first episode of schizophrenia; eight compared CBT with any control in participants experiencing an acute-episode; 11 compared CBT with any control in participants during the promoting recovery phase; six compared group CBT with any control; and 19 compared individual CBT with any control. Multi-modal trials were not included in the subgroup analyses. Forest plots and/or data tables for each outcome can be found in Appendix 23d.

---

<sup>24</sup>Existing subgroup comparisons assessing the country of the trial, number of treatment sessions and duration of treatment were also updated. However, there was insufficient data to draw any conclusions based on these subgroups. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted.

**Table 66: Summary of study characteristics for CBT**

	CBT versus any control <sup>a</sup>	CBT versus standard care	CBT versus other active treatments	CBT versus non-standard care
<i>k</i> (total N)	31 (3052)	19 (2118)	14 (1029)	3 (136)
<i>Study ID</i>	BACH2002 BARROW-CLOUGH2006 BECHDOLF2004 Bradshaw2000 CATHER2005 Drury1996 DURHAM2003 ENGLAND2007 GARETY2008 <sup>b</sup> GRANHOLM2005 <sup>c</sup> GUMLEY2003 Haddock1999 Hogarty1997 <sup>e</sup> JACKSON2005 JACKSON2007 JENNER2004 <sup>c</sup> Kuipers1997 LECLERC2000 LECOMTE2008 Lewis2002 <sup>d</sup> MCLEOD2007	BACH2002 BARROW-CLOUGH2006 DURHAM2003 ENGLAND2007 GARETY2008 GRANHOLM2005 <sup>c</sup> GUMLEY2003 JACKSON2005 JENNER2004 <sup>c</sup> Kuipers1997 LECLERC2000 LECOMTE2008 Lewis2002 MCLEOD2007 STARTUP2004 Tarrier1998 TROWER2004 Turkington2002 WYKES2005	BECHDOLF2004 CATHER2005 DURHAM2003 GARETY2008 Haddock1999 Hogarty1997 JACKSON2007 LECOMTE2008 Lewis2002 PENADES2006 PINTO1999 <sup>c</sup> Sensky2000 Tarrier1998 VALMAGGIA2005	Drury1996 Bradshaw2000 RECTOR2003

	PENADES2006 PINTO1999 <sup>c</sup> RECTOR2003 Sensky2000 STARTUP2004 Tarrier1998 TROWER2004 Turkington2002 VALMAGGIA2005 WYKES2005			
<i>Diagnosis</i>	58–100% Schizophrenia or other related diagnoses (DSM or ICD-10)	58–100% Schizophrenia or Other related diagnoses (DSM or ICD-10)	64–100% Schizophrenia or Other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)
<i>Baseline severity</i>	<i>BPRS total:</i> Mean (SD) range: ~17 (7) to ~82 (21)  <i>PANSS total:</i> Mean (SD) range: ~25 (7) to ~96 (16)  <i>CPRS total:</i> Mean (SD) ~24 (14) to ~36 (14)	<i>BPRS total:</i> Mean (SD) range: ~17 (7) to ~82 (21)  <i>PANSS total:</i> Mean (SD) range: ~25 (7) to ~96 (16)  <i>CPRS total:</i> Mean (SD) range: ~24 (14)	<i>PANSS total:</i> Mean (SD) range: ~51 (13) to ~96 (16)  <i>CPRS total:</i> Mean (SD) ~36 (14)	Not reported

*Continued*

	<b>CBT versus any control<sup>a</sup></b>	<b>CBT versus standard care</b>	<b>CBT versus other active treatments</b>	<b>CBT versus non-standard care</b>
<i>Number of sessions</i>	<i>Range: 4–156</i>	<i>Range: 4–24</i>	<i>Range: 10–156</i>	<i>Range: 20–156</i>
<i>Length of treatment</i>	<i>Range: 2–156 weeks</i>	<i>Range: 2–52 weeks</i>	<i>Range: 8–156 weeks</i>	<i>Range: 24–156 weeks</i>
<i>Length of follow-up (only including papers reporting follow-up measures)</i>	<i>Range: 3–60 months</i>	<i>Range: 3–60 months</i>	<i>Range: 3–60 months</i>	<i>Range: 6–24 months</i>
<i>Setting</i>	<i>Inpatient:</i> BECHDOLF2004 Bradshaw2000 Drury1996 Haddock1999 Hogarty1997 <sup>e</sup> Lewis2002 <sup>f</sup> STARTUP2004 VALMAGGIA2005  <i>Outpatient:</i> BARROW-CLOUGH2006 CATHER2005 ENGLAND2007 GRANHOLM2005 <sup>c</sup> GUMLEY2003	<i>Inpatient:</i> Lewis2002 <sup>f</sup> STARTUP2004         <i>Outpatient:</i> BARROW-CLOUGH2006 ENGLAND2007 GRANHOLM2005 <sup>c</sup> GUMLEY2003 JACKSON2005	<i>Inpatient:</i> BECHDOLF2004 Haddock1999 Hogarty1997 <sup>e</sup> Lewis2002 <sup>f</sup> VALMAGGIA2005         <i>Outpatient:</i> CATHER2005 LECOMTE2008 Sensky2000 Tarrier1998	<i>Inpatient:</i> Bradshaw2000 Drury1996         <i>Outpatient:</i> RECTOR2003

**Table 66: (Continued)**

	CBT versus any control <sup>a</sup>	CBT versus standard care	CBT versus other active treatments	CBT versus non-standard care
<i>k</i> (total N)	31 (3052)	19 (2118)	14 (1029)	3 (136)
<i>Study ID</i>	BACH2002 BARROW-CLOUGH2006 BECHDOLF2004 Bradshaw2000 CATHER2005 Drury1996 DURHAM2003 ENGLAND2007 GARETY2008b GRANHOLM2005c GUMLEY2003 Haddock1999 Hogarty1997e JACKSON2005 JACKSON2007 JENNER2004c Kuipers1997 LECLERC2000 LECOMTE2008 Lewis2002d MCLEOD2007	BACH2002 BARROW-CLOUGH2006 DURHAM2003 ENGLAND2007 GARETY2008 GRANHOLM2005c GUMLEY2003 JACKSON2005 JENNER2004c Kuipers1997 LECLERC2000 LECOMTE2008 Lewis2002 MCLEOD2007 STARTUP2004 Tarrier1998 TROWER2004 Turkington2002 WYKES2005	BECHDOLF2004 CATHER2005 DURHAM2003 GARETY2008 Haddock1999 Hogarty1997 JACKSON2007 LECOMTE2008 Lewis2002 PENADES2006 PINTO1999c Sensky2000 Tarrier1998 VALMAGGIA2005	Drury1996 Bradshaw2000 RECTOR2003

JACKSON2005 JENNER2004 <sup>c</sup> Kuipers1997 LECOMTE2008 RECTOR2003 Sensky2000 Tarrier1998 WYKES2005	JENNER2004 <sup>c</sup> Kuipers1997 LECOMTE2008 Sensky2000 Tarrier1998 WYKES2005	
<i>Inpatient and outpatient:</i> BACH2002 DURHAM2003 GARETY2008 LECLERC2000 MCLEOD2007 PINTO1999 <sup>c</sup> TROWER2004 Turkington2002 <i>EIS setting:</i> JACKSON2007	<i>Inpatient and outpatient:</i> BACH2002 DURHAM2003 GARETY2008 LECLERC2000 MCLEOD2007 TROWER2004 Turkington2002	<i>Inpatient and outpatient:</i> DURHAM2003 GARETY2008 PINTO1999 <sup>c</sup>  <i>EIS setting:</i> JACKSON2007

### 9.4.5 Training

The inconsistency in reporting what training the therapists in the trials had received meant it was impossible to determine the impact of level of training on the outcomes of the trial. Less than half (15/31) of the included CBT papers made reference to specific CBT-related training. In early CBTp trials this is not surprising because the researchers were at the forefront of the development of the therapy and no specific psychosis-related CBT training would have been available. In studies where training was mentioned, it was often vague in terms of the length of training therapists had received and whether the training had been specifically focused on CBT for psychosis. Moreover, where details of training programmes associated with the trial were provided, previous experience and training did not always appear to have been controlled for. This means that therapists could have entered the study with different levels of competence, making it impossible to determine the impact of the specified training programme. Of the 25 trials reporting the professional conducting the intervention, the majority utilised clinical psychologists (14/25). However, a proportion of trials utilised different professionals including psychiatrists (3/25), psychiatric nurses (7/25), social workers (2/25), Master's level psychology graduates and/or interns (1/25), occupational therapists (1/24) and local mental health workers (2/25). Within some trials, a number of professionals may have delivered the intervention (for example, two psychologists and one psychiatrist). Often, where the professional conducting the intervention was not a clinical psychologist, reference was made to specific training in CBTp or extensive experience working with people with psychosis.

**Table 67: Summary of study characteristics for CBT subgroup analyses**

	CBT versus any control- first episode <sup>a</sup>	CBT versus any control- acute episode	CBT versus any control- promoting recovery	Group CBT versus any control	Individual CBT versus any control
K (total N)	5 (618)	8 (695)	11 (1093)	6 (534)	19 (2082)
Study ID	Haddock1999 JACKSON2005 JACKSON2007 LECOMTE2008 Lewis2002	BACH2002 BECHDOLF2004 Bradshaw2000 Drury1996 ENGLAND2007 GARETY2008 MCLEOD2007 STARTUP2004	BARROW- CLOUGH2006 CATHER2005 DURHAM2003 Kuipers1997 PENADES2006 Sensky2000 Tarrier1998 TROWER2004 Turkington2002 VALMAGGIA2005 WYKES2005	BARROW- CLOUGH2006 BECHDOLF2004 LECOMTE2008 LECLERC2000 MCLEDO2007 WYKES2005	BACH2002 Bradshaw1999 CATHER2005 DURHAM2003 ENGLAND2007 GARETY2008 GUMLEY2003 Haddock1999 JACKSON2005 JACKSON2007 Kuipers1997 Lewis2002 PENADES2006 Sensky2000 STARTUP2004 Tarrier1998 TROWER2004 Turkington2002 VALMAGGIA2005
<p><i>Note.</i> Studies were categorised as short (&lt;12 weeks), medium (12–51 weeks) and long (52 weeks or more).</p> <p><sup>a</sup>A number of trials included participants in all phases of illness (for example, 20% first episode, 60% acute and 20% promoting recovery) and hence could not be included in the subgroup analysis.</p>					



Competence does not appear to be directly correlated with training and a number of additional variables play a part. The Durham and colleagues' (2003) study indicated that training in general CBT did not necessarily produce proficient CBTp therapists. Although the therapists in the study had undergone CBT training, when their practice was assessed on a CBTp fidelity measure, they did not appear to be using specific psychosis-focused interventions. A number of studies included in the CBTp meta-analyses used CBT fidelity measures to determine the quality of the therapy that was being delivered. Again, there were inconsistencies between studies. Three different fidelity measures were used and there was no agreed standard as to what the cut-off score for demonstrating competence should be. Moreover, Durham and colleagues (2003) used two of these scales in their trial and found that therapy ratings did not correlate.

With regard to the use of treatment manuals, however, there was more consistent reporting across the trials, with the majority of papers (24/31) making reference to either a specific treatment manual or to a manualised approach. Reporting of supervision was also more consistent, with both peer- and senior-supervision evident in over two-thirds of the trials.

#### **9.4.6 Ethnicity**

Only one follow-up paper (Rathod et al., 2005) assessed changes in insight and compliance in the Black Caribbean and African-Caribbean participants included in the Turkington 2002 study. The subgroup analysis indicated a higher dropout rate among both black and ethnic minority groups. Additionally, compared with their white counterparts, the black and minority ethnic participants demonstrated significantly smaller changes in insight. Although these are potentially interesting findings, it must be noted that black and minority ethnic participants comprised only 11% of the study population, with Black African and African-Caribbean participants representing 3 and 5% of the sample, respectively. With regard to the other studies included in the review, there was a paucity of information on the ethnicity of participants. Because of the lack of information, the GDG were unable to draw any conclusions from the data or make any recommendations relating to practice. However, the GDG acknowledge that this is an area warranting further research and formal investigation.

#### **9.4.7 Clinical evidence summary**

The review found consistent evidence that, when compared with standard care, CBT was effective in reducing rehospitalisation rates up to 18 months following the end of treatment. Additionally, there was robust evidence indicating that the duration of hospitalisation was also reduced (8.26 days on average). Consistent with the 2002 guideline, CBT was shown to be effective in reducing symptom severity as measured by total scores on items, such as the PANSS and BPRS, both at end of treatment and at up to 12 months' follow-up. Robust small to medium effects ( $SMD \sim 0.30$ ) were also demonstrated for reductions in depression when comparing CBT with both standard care and other active treatments. Furthermore, when compared with any control, there was some evidence for improvements in social functioning up to 12 months.

Although the evidence for positive symptoms was more limited, analysis of PSYRATS data demonstrated some effect for total hallucination measures at the end of treatment. Further to this, there was some limited but consistent evidence for symptom-specific measures including voice compliance, frequency of voices and believability, all of which demonstrated large effect sizes at both end of treatment and follow-up. However, despite these positive effects for hallucination-specific measures, the evidence for there being any effect on delusions was inconsistent. Although no RCTs directly compared group-based with individual CBT, indirect comparisons indicated that only the latter had robust effects on rehospitalisation, symptom severity and depression. Subgroup analyses also demonstrated additional effects for people with schizophrenia in the promoting recovery phase both with and without persistent symptoms. In particular, when compared with any other control, studies recruiting people in the promoting recovery phase demonstrated consistent evidence for a reduction in negative symptoms up to 24 months following the end of treatment.

#### **9.4.8 Health economic evidence**

##### *Systematic literature review*

The systematic literature search identified two economic studies that assessed the cost effectiveness of CBT for people with schizophrenia (Kuipers et al., 1998; Startup et al., 2005). Both studies were undertaken in the UK. Details on the methods used for the systematic search of the economic literature are described in Appendix 11. References to included/excluded studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in the form of evidence tables in Appendix 25.

Kuipers and colleagues (1998) evaluated the cost effectiveness of CBT added to standard care compared with standard care alone in 60 people with medication-resistant psychosis participating in an RCT conducted in the UK (KUIPERS1997). The time horizon of the analysis was 18 months (RCT period plus naturalistic follow-up). The study estimated NHS costs (inpatient, outpatient, day hospital, primary and community services) and costs associated with specialist, non-domestic accommodation. Medication costs were not considered. The primary outcome of the analysis was the mean change in BPRS score. CBT was shown to be significantly more effective than its comparator in this respect, with the treatment effect lasting 18 months after the start of the trial ( $p < 0.001$ ). The costs between the two treatment groups were similar: the mean monthly cost per person over 18 months was £1,220 for CBT added to standard care and £1,403 for standard care alone ( $p = 0.416$ , 1996 prices). The study had sufficient power to detect significant differences in costs. The authors suggested that CBT might be a cost-effective intervention in medication-resistant psychosis, as the clinical benefits gained during the 9 months of CBT were maintained and even augmented 9 months later, while the extra intervention costs seemed to be offset by reduced utilisation of health and social care services.

Startup and colleagues (2005) conducted a cost-consequence analysis to measure the cost effectiveness of CBT on top of treatment as usual versus treatment as usual alone in 90 people hospitalised for an acute psychotic episode participating in an RCT in North Wales (STARTUP2004). The time horizon of the analysis was 2 years; the perspective was that of the NHS and Personal Social Services (PSS). Costs included hospital, primary, community and residential care and medication. Health outcomes were measured using the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Social Functioning Scale (SFS) and the GAF scale. CBT showed a significant effect over control in SANS and SFS scores, at no additional cost: the mean cost per person over 24 months was £27,535 for the CBT group and £27,956 for the control group ( $p = 0.94$ ). The study had insufficient power for economic analysis.

The above results indicate that CBT is potentially a cost-effective intervention for people with acute psychosis or medication-resistant schizophrenia. However, the study samples were very small in both studies and insufficient to establish such a hypothesis with certainty.

### *Economic modelling*

#### **Objective**

The guideline systematic review and meta-analysis of clinical evidence demonstrated that provision of CBT to people with schizophrenia results in clinical benefits and reduces the rates of future hospitalisation. A cost analysis was undertaken to assess whether the costs to the NHS of providing CBT in addition to standard care to people with schizophrenia are offset by future savings resulting from reduction in hospitalisation costs incurred by this population.

#### **Intervention assessed**

According to the guideline systematic review and meta-analysis of clinical evidence, group-based CBT is not an effective intervention. Therefore, the economic analysis compared individually-delivered CBT added to standard care versus standard care alone.

#### **Methods**

A simple economic model estimated the net total costs (or cost savings) to the NHS associated with provision of individual CBT in addition to standard care to people with schizophrenia. Two categories of costs were assessed: intervention costs of CBT, and cost savings resulting from the expected reduction in hospitalisation rates in people with schizophrenia receiving CBT, estimated based on the guideline meta-analysis of respective clinical data. Standard care costs were not estimated, because these were common to both arms of the analysis.

#### **Cost data**

##### *Intervention costs (costs of providing CBT)*

The clinical studies on individual CBT included in the guideline systematic review described programmes of varying numbers of sessions. The resource use estimate

associated with provision of CBT in the economic analysis was based on the average resource use reported in these studies, confirmed by the GDG expert opinion to be consistent with clinical practice in the UK. According to the reported resource use data, CBT in the economic analysis consisted of 16 individually-delivered sessions lasting 60 minutes each.

CBT can be delivered by a variety of mental health professionals with appropriate training and supervision. The salary level of a mental health professional providing CBT was estimated by the GDG to range between bands 6 and band 8. This is comparable with the salary level of a clinical psychologist. Therefore, the unit cost of clinical psychologists was used to estimate an average intervention cost. The unit cost of a clinical psychologist has been estimated at £67 per hour of client contact in 2006/07 prices (Curtis, 2007). This estimate has been based on the mid-point of Agenda for Change salary band 7 of the April 2006 payscale according to the National Profile for Clinical Psychologists, Counsellors and Psychotherapists (NHS Employers, 2006). It includes salary, salary oncosts, overheads and capital overheads but does not take into account qualification costs because the latter are not available for clinical psychologists. The same source of national health and social care unit costs reports the cost of CBT as £67 per hour of face-to-face contact ((Curtis, 2007); 2006/07 price). This latter unit cost has been estimated on the basis that CBT is delivered by a variety of health professionals, including specialist registrars, clinical psychologists and mental health nurses, and is equal to the unit cost of a clinical psychologist per hour of client contact.

Based on the above resource use estimates and the unit cost of clinical psychologists, the cost of providing a full course of CBT to a person with schizophrenia was estimated at £1,072 in 2006/07 prices.

*Costs of hospitalisation / cost savings from reduction in hospitalisation rates* The average cost of hospitalisation for a person with schizophrenia was estimated by multiplying the average duration of hospitalisation for people with schizophrenia, schizotypal and delusional disorders in England in 2006/07 (NHS The Information Centre, 2008b) by the national average unit cost per bed-day in an inpatient mental health acute care unit for adults for 2006/07 (NHS Reference Costs, (Department of Health, 2008)). Hospital Episode Statistics (HES) is a service providing national statistical data of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere in England (NHS The Information Centre, 2008b). With respect to inpatient data, HES records episodes (periods) of continuous admitted patient care under the same consultant. In cases where responsibility for a patient's care is transferred to a second or subsequent consultant, there will be two or more episodes recorded relating to the patient's stay in hospital. This means that, for any condition leading to hospital admission, the average length of inpatient stay as measured and reported by HES may be an underestimation of the actual average duration of continuous hospitalisation. Based on HES, the average duration of hospitalisation for people with schizophrenia, schizotypal and delusional disorders (F20-F29 according to ICD-10) in England was 110.6 days in 2006/07. Based on the annually collected

NHS Reference Costs (NHS The Information Centre, 2008b) the cost per bed-day in a mental health acute care inpatient unit was £259 in 2006/07. By multiplying these figures, the average cost of hospitalisation per person with schizophrenia was estimated at £28,645 in 2006/07 prices.

*Clinical data on hospitalisation rates following provision of cognitive behavioural therapy*

The guideline meta-analysis of CBT data on hospitalisation rates showed that providing CBT in addition to standard care to people with schizophrenia significantly reduces the rate of future hospitalisations compared with people receiving standard care alone. Table 68 shows the CBT studies included in the meta-analysis of hospitalisation-rate data up to 18 months following treatment (whether these studies were conducted in the UK or not), the hospitalisation rates for each treatment arm reported in the individual studies and the results of the meta-analysis.

The results of meta-analysis show that CBT, when added to standard care, reduces the rate of future hospitalisations in people with schizophrenia (RR of hospitalisation of CBT added to standard care versus standard care alone: 0.74). This result was statistically significant at the 0.05 level (95% CIs of RR: 0.61 to 0.94).

The baseline rate of hospitalisation in the economic analysis was taken from the overall rate of hospitalisation under standard care alone as estimated in the guideline meta-analysis of CBT data on hospitalisation rates; that is, a 29.98% baseline hospitalisation rate was used. The rate of hospitalisation when CBT was added to standard care was calculated by multiplying the estimated RR of hospitalisation of CBT plus standard care versus standard care alone by the baseline hospitalisation rate.

Details on the clinical studies considered in the economic analysis are available in Appendix 22c. The forest plots of the respective meta-analysis are provided in Appendix 23d.

**Table 68: Studies considered in the economic analysis of CBT in addition to standard care versus standard care alone and results of meta-analysis**

Study ID	Country	Total events (n) in each treatment arm (N)	
		CBT plus standard care (n/N)	Standard care alone (n/N)
TARRIER1998	UK	16/33	9/28
BACH2002	Non-UK	12/40	19/40
LEWIS2002	UK	33/101	37/102
TURKINGTON2002	UK	36/257	38/165
GUMLEY2003	UK	11/72	19/72
Total		108/503 (21.47%)	122/407 (29.98%)
Meta-analysis results		RR: 0.74 95% CI: 0.61–0.94	

## *Sensitivity analysis*

One-way sensitivity analyses were undertaken to investigate the robustness of the results under the uncertainty characterising some of the input parameters and the use of different data and assumptions in the estimation of total net costs (or net savings) associated with provision of CBT to people with schizophrenia. The following scenarios were explored:

- use of the 95% CIs of the RR of hospitalisation of CBT added to standard care versus standard care alone
- exclusion of TARRIER1998 from the meta-analysis. TARRIER1998 was carried out before the National Service Framework was implemented, and therefore the way the study was conducted in terms of hospitalisation levels may have been different from current clinical practice. The baseline rate of hospitalisation used in the analysis was the pooled, weighted, average hospitalisation rate of the control arms of the remaining studies
- exclusion of BACH2002 from the meta-analysis as this was a non-UK study and clinical practice regarding hospital admission levels may have been different from that in the UK. The baseline rate of hospitalisation used in the analysis was the pooled, weighted, average hospitalisation rate of the control arms of the remaining studies
- exclusion of both TARRIER1998 and BACH2002 from the meta-analysis. The baseline rate of hospitalisation used in the analysis was the pooled, weighted, average hospitalisation rate of the control arms of the remaining studies
- change in the number of CBT sessions (16 in the base-case analysis) to a range between 12 and 20
- change in the baseline rate of hospitalisation (that is, the hospitalisation rate for standard care which was 29.98% in the base-case analysis) to a range between 20 and 40%
- use of a more conservative value of duration of hospitalisation. The average duration of hospitalisation for people with schizophrenia (ICD F20-F29) reported by HES (NHS The Information Centre, 2008b) was 110.6 days, which was deemed high by the GDG. Indeed, HES reported a median duration of hospitalisation for this population of 36 days. HES data were highly skewed, apparently from a number of people with particularly long hospital stays. An alternative, lower length of hospitalisation of 69 days was tested, taken from an effectiveness trial of clozapine versus SGAs in people with schizophrenia with inadequate response or intolerance to current antipsychotic treatment conducted in the UK (CUtLASS Band 2, (Davies et al., 2008)).

## *Results*

### **Base-case analysis**

The reduction in the rates of future hospitalisation achieved by offering CBT to people with schizophrenia in addition to standard care yielded cost savings

equalling £2,061 per person. Given that provision of CBT costs £1,072 per person, CBT results in an overall net saving of £989 per person with schizophrenia. Full results of the base-case analysis are reported in Table 69.

**Table 69: Results of cost analysis comparing CBT in addition to standard care versus standard care alone per person with schizophrenia**

Costs	CBT plus standard care	Standard care alone	Difference
CBT cost	£1,072	0	£1,072
Hospitalisation cost	£6,526	£8,587	-£2,061
Total cost	£7,598	£8,587	-£989

### Sensitivity analysis

The results of the base-case analysis were overall robust to the different scenarios explored in sensitivity analysis. When the 95% CIs of the RR of hospitalisation were used, then the total net cost of providing CBT ranged from -£2,277 (that is a net saving) to £557 per person. When the more conservative value of 69 days length of hospitalisation (instead of 110.6 days used in the base-case analysis) was tested, the net cost of providing CBT ranged between -£1,017 (net saving) to £751 per person. In all scenarios, using the relevant mean RR of hospitalisation taken from the guideline meta-analysis, addition of CBT to standard care resulted in overall cost savings because of a substantial reduction in hospitalisation costs. It must be noted that when BACH2002 was excluded from analysis, then the results of meta-analysis were insignificant at the 0.05 level; consequently, when the upper 95% CI of RR of hospitalisation was used, CBT added to standard care incurred higher hospitalisation costs relative to standard care alone.

Full results of sensitivity analysis are presented in Table 70.

### Discussion

The economic analysis showed that CBT is likely to be an overall cost-saving intervention for people with schizophrenia because the intervention costs are offset by savings resulting from a reduction in the number of future hospitalisations associated with this therapy. The net cost of providing CBT was found to lie between -£2,277 (overall net saving) and £557 per person with schizophrenia (for a mean duration of hospitalisation of 110.6 days) or -£1,017 to £751 per person (for a mean duration of hospitalisation of 69 days), using the 95% CIs of RRs of hospitalisation, as estimated in the guideline meta-analysis. It must be noted that possible reduction in other types of health and social care resource use and subsequent cost savings to the NHS and social services, as well as broader financial implications to society (for example, potential increased productivity) associated with the provision of CBT to people with schizophrenia, have not been estimated in this analysis. In addition, clinical benefits associated with CBT, affecting both people with schizophrenia and their families/carers, such as symptom improvement and enhanced HRQoL following reduction in future inpatient stays, should also be considered when the

cost effectiveness of CBT is assessed. Taking into account such benefits, even a (conservative) net cost of £751 per person can be probably justified.

**Table 70: Results of sensitivity analysis of offering CBT in addition to standard care to people with schizophrenia**

Scenario	Total net cost (negative cost implies net saving)
Use of 95% CIs of RR of hospitalisation	–£2,277 (lower CI) to £557 (upper CI)
Exclusion of TARRIER1998 from meta-analysis	–£1,490 (–£2,771 to £47 using the 95% CIs of RR of hospitalisation)
Exclusion of BACH2002 (non-UK study) from meta-analysis	–£375 (–£2,465 to £2,599 using the 95% CIs of RR of hospitalisation)
Exclusion of TARRIER1998 and BACH2002 from meta-analysis	–£1,231 (–£2,502 to £437 using the 95% CIs of RR of hospitalisation)
CBT sessions between 12 and 20	–£1,257 to –£721, respectively
Hospitalisation rate under standard care between 40 and 20%	–£1,678 to –£303, respectively
Mean length of hospitalisation 69 days	–£214 (–£1,017 to £751 using the 95% CIs of RR of hospitalisation)

### 9.4.9 Linking evidence to recommendations

The conclusions drawn in the 2002 guideline regarding the efficacy of CBT have been supported by the 2009 systematic review. The data for the reduction in rehospitalisation rates and duration of admission remains significant even when removing non-UK and pre-National Service Framework for Mental Health (Department of Health, 1999) papers in a sensitivity analysis, suggesting that these findings may be particularly robust within the current clinical context. The effectiveness of CBT has been corroborated by the evidence for symptom severity, which included reductions in hallucination-specific measures and depression in addition to total symptom scores. However, it must be noted that despite general confirmation of the 2002 recommendations, following the reclassification and subsequent removal of KEMP1996, there was no robust evidence for the efficacy of CBT on measures of compliance or insight. Consequently, the GDG concluded that there is insufficient evidence to support the 2002 recommendation about the use of CBT to assist in the development of insight or in the management of poor treatment adherence.

The systematic review of economic evidence showed that provision of CBT to people with schizophrenia in the UK improved clinical outcomes at no additional cost. This finding was supported by economic modelling undertaken for this guideline, which suggested that provision of CBT might result in net cost savings to the NHS, associated with a reduction in future hospitalisation rates. The results of both the systematic literature review and the economic modelling indicate that providing



individual CBT to people with schizophrenia is likely to be cost effective in the UK setting, especially when clinical benefits associated with CBT are taken into account.

Although the GDG were unable to draw any firm conclusions from subgroup analyses assessing the impact of treatment duration and number of sessions, they did note that the evidence for CBT is primarily driven by studies that included at least 16 planned sessions. To incorporate the current state of evidence and expert consensus, the GDG therefore modified the 2002 recommendation relating to the duration and number of treatment sessions.

There was, however, more reliable evidence to support the provision of CBT as an individual-based therapy, a finding largely consistent with current therapeutic practice within the UK.

From the CBTp studies included in the meta-analyses, it is not possible to make any recommendations on the specific training requirements or competencies required to deliver effective CBTp. In particular, papers varied widely in the degree to which they reported details about the training and experience of the person delivering the intervention. However, the GDG felt that this is an important area for future development and have made a research recommendation. Despite not being able to make any specific recommendations for the types of training required at this stage, it was noted that, overall, the majority of trials used either clinical psychologists or registered and/or accredited psychological therapists to deliver the CBTp. In addition, regular clinical supervision was provided in two thirds of the trials and treatment manuals utilised in nearly all of the trials. From this evidence, and based upon expert opinion, the GDG included a number of recommendations relating to the delivery of CBT for people with schizophrenia.

Both the consistency with which CBT was shown to be effective across multiple critical outcomes and the potential net cost-savings to the NHS support the 2002 recommendations regarding the provision of CBT to people with schizophrenia.

**\*\*2009\*\***

For the 2014 guideline the GDG took the view that, following the publication of *Psychosis and Schizophrenia in Children and Young People*, the 2014 guideline should be consistent where appropriate, including changing the population from 'people with schizophrenia' to 'people with psychosis and schizophrenia'. Therefore the GDG saw the value in advising practitioners of the equivocal evidence regarding psychological interventions when compared with antipsychotic medication and recommended that if a person wished to try a psychological intervention alone, this could be trialled over the course of 1 month or less. The GDG also wished to make it explicit that the options for first episode psychosis and for an acute exacerbation or recurrence of psychosis or schizophrenia should be psychological interventions (individual CBT and family intervention) combined with oral antipsychotic medication.

## 9.4.10 Recommendations

### *Treatment options for first episode psychosis*

**9.4.10.1** For people with first episode psychosis offer:

- oral antipsychotic medication (see recommendations 10.11.1.2–10.11.1.13) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]

**9.4.10.2** Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try psychological interventions alone:

- offer family intervention and CBT
- agree a time (1 month or less) to review treatment options, including introducing antipsychotic medication
- continue to monitor symptoms, distress, impairment and level of functioning (including education, training and employment) regularly. [new 2014]

### *How to deliver psychological interventions*

**9.4.10.3** CBT should be delivered on a one-to-one basis over at least 16 planned sessions and:

- follow a treatment manual<sup>25</sup> so that:
  - people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning
  - the re-evaluation of people's perceptions, beliefs or reasoning relates to the target symptoms
- also include at least one of the following components:
  - people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms
  - promoting alternative ways of coping with the target symptom
  - reducing distress
  - improving functioning. [2009]

### *Subsequent acute episodes*

**9.4.10.4** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:

- oral antipsychotic medication (see recommendations 10.11.1.2–10.11.1.13) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]

---

<sup>25</sup> Treatment manuals that have evidence for their efficacy from clinical trials are preferred.

**9.4.10.5** Offer CBT to all people with psychosis or schizophrenia (delivered as described in recommendation 9.4.10.3). This can be started either during the acute phase or later, including in inpatient settings. [2009]

### *Promoting recovery*

**9.4.10.6** Offer CBT to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission. Deliver CBT as described in recommendation 9.4.10.3. [2009]

## **9.4.11 Research recommendation**

**9.4.11.1** An adequately powered RCT should be conducted to investigate the most appropriate duration and number of sessions for CBT in people with schizophrenia.[2009]

**9.4.11.2** An adequately powered RCT should be conducted to investigate CBT delivered by highly trained therapists and mental health professionals compared with brief training of therapists in people with schizophrenia.[2009]

**9.4.11.3** Research is needed to identify the competencies required to deliver effective CBT to people with schizophrenia.[2009]

## **9.5 COGNITIVE REMEDIATION**

### **9.5.1 Introduction**

**\*\*2009\*\*** The presence of cognitive impairment in a proportion of people with schizophrenia has been recognised since the term ‘schizophrenia’ was first coined (Bleuler, 1911). The precise cause of these deficits (such as structural brain changes, disruptions in neuro-chemical functions or the cognitive impact of the illness and/or of medication) remains contentious, whereas progress on characterising the cognitive problems that arise in schizophrenia has been substantial. Major domains identified include memory problems (Brenner, 1986), attention deficits (Oltmanns & Neale, 1975) and problems in executive function, such as organisation and planning (Weinberger et al., 1988). A recent initiative to promote standardisation of methods for evaluating research on cognitive outcomes (the Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus panel [MATRICS; (Nuechterlein et al., 2004)]) has identified eight more specific domains: attention/vigilance; speed of processing; working memory; verbal learning and memory; visual learning and memory; reasoning and problem solving; verbal comprehension; and social cognition. Few studies as yet examine changes in all these domains. Cognitive impairment is strongly related to functioning in areas such as work, social relationships and independent living (McGurk et al., 2007). Because of the importance of cognitive impairment in terms of functioning, it has been identified as an appropriate target for interventions.

Currently available pharmacological treatments have limited effects on cognitive impairments (see Chapter 10). Cognitive remediation programmes have therefore

been developed over the past 40 years with the goal of testing whether direct attempts to improve cognitive performance might be more effective (McGurk et al., 2007). The primary rationale for cognitive remediation is to improve cognitive functioning, with some papers also stating improved functioning as an additional aim (Wykes & Reeder, 2005). Approaches adopted have ranged from narrowly defined interventions, which involve teaching service users to improve their performance on a single neuropsychological test, to the provision of comprehensive remediation programmes, increasingly using computerised learning (Galletly et al., 2000). The programmes employ a variety of methods, such as drill and practice exercises, teaching strategies to improve cognition, suggesting compensatory strategies to reduce the effects of persistent impairments and group discussions (McGurk et al., 2007).

Because the use of these methods in the treatment of schizophrenia is still developing and early studies had mixed results (Pilling et al., 2002), there remains uncertainty over which techniques should be used (Wykes & van der Gaag, 2001) and whether the outcomes are beneficial, both in terms of sustained effects on cognition and for improving functioning. Reports of combinations of cognitive remediation with other psychosocial interventions, such as social skills training, or vocational interventions, such as supported employment programmes, have been increasing in the literature. In this review, the focus is on cognitive remediation as a single-modality intervention except where it has been combined with another of the psychological or psychosocial interventions. In these cases, the intervention has been classified as multi-modal intervention and subjected to sensitivity analyses (see Section 9.1.5).<sup>\*\*2009\*\*</sup> A review of cognitive remediation combined with any vocational rehabilitation interventions can be found in Chapter 13.

### ***Definition***

<sup>\*\*2009\*\*</sup>Cognitive remediation was defined as:

- an identified procedure that is specifically focused on basic cognitive processes, such as attention, working memory or executive functioning, and
- having the specific intention of bringing about an improvement in the level of performance on that specified cognitive function or other functions, including daily living, social or vocational skills.

## **9.5.2 Clinical review protocol**

The review protocol, including information about the databases searched and the eligibility criteria can be found in

Table 71. The primary clinical questions can be found in Box 1. For the 2009 guideline, a new systematic search was conducted for relevant RCTs published since the 2002 guideline (further information about the search strategy can be found in Appendix 20). It must be acknowledged that some cognitive remediation studies cite improvements to cognition/cognitive measures as their primary outcome. However, it is the view of the GDG that only sustained improvements in cognition, as

measured at follow-up, should be considered as clinically important. The rationale for this is that only sustained improvement would be likely to have an impact on other critical outcomes, such as mental state, psychosocial functioning, hospitalisation and relapse.

### **9.5.3 Studies considered for review**

In the 2002 guideline, seven RCTs of cognitive remediation were included. Two trials (Bellack2001 and Tompkins1995) were removed from the 2009 guideline analysis as the GDG felt that they did not meet the definition of cognitive remediation. The search for the 2009 guideline identified 15 papers providing follow-up data to existing trials and 15 new trials. A recent meta-analysis (McGurk et al., 2007) identified three additional trials and a number of other studies that did not meet inclusion criteria. The cognitive remediation studies included in the trials employed a variety of different methods and in some cases applied cognitive remediation in combination with a variety of other psychological or psychosocial interventions<sup>26</sup>. In total, 25 trials (N = 1,390) met the inclusion criteria. All of the trials were published in peer-reviewed journals between 1994 and 2008 (further information about both included and excluded studies can be found in Appendix 22c).

### **9.5.4 Cognitive remediation versus control**

For the 2009 guideline review, six of the included studies (Benedict1994; BURDA1994; EACK2007; KURTZ2007; SATORY2005; VOLLEMA1995) did not provide useable data for any of the critical outcomes listed in

Table 71. Consequently, 20 RCTs of cognitive remediation versus any type of control were included in the meta-analysis (see Table 72 for a summary of the study characteristics). Where there was sufficient data, sub-analyses were used to examine cognitive remediation versus standard care and versus other active treatment. Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### **9.5.5 Clinical evidence summary**

In the six RCTs (out of 17 included in the meta-analysis) that reported cognitive outcomes at follow-up, there was limited evidence that cognitive remediation produced sustained benefits in terms of cognition. However, these effects were driven primarily by two studies (HOGARTY2004; PENADES2006); therefore, sensitivity analyses were used to explore how robust the findings were. Removal of these studies led to the loss of effects for all but one cognitive domain (reasoning and problem solving). There was limited evidence suggesting that cognitive remediation when compared with standard care may improve social functioning. However, this effect was driven by a range of studies conducted by Velligan and colleagues (VELLIGAN2000, 2002, 2008A, 2008B), in which the intervention was more

---

<sup>26</sup>Trials assessing the efficacy of cognitive remediation as an adjunct to non-psychological or psychosocial interventions were outside the scope of the review. However, a review of cognitive remediation with vocational rehabilitation interventions can be found in Chapter 13.

comprehensive than typical cognitive remediation programmes in the UK, and included the use of individually tailored environmental supports to ameliorate areas in addition to basic cognitive functions. The UK-based studies, although well-conducted, did not report evidence of improvement in social or vocational functioning or symptoms at either end of treatment or follow-up.

**Table 71: Clinical review protocol for the review of cognitive remediation**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	Data base inception to 30July2008
<i>Study design</i>	RCT (≥10 participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Cognitive remediation
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Cognitive outcomes (at follow-up only) <sup>a</sup> Leaving the study early for any reason Adverse events

<sup>a</sup>Cognitive measures were categorised into the following cognitive domains based upon Nuechterlein and colleagues, 2004: attention/vigilance, speed of processing, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, verbal comprehension, and social cognition. The effect sizes for each individual measure were pooled to produce one effect size per domain for each study.

**Table 72: Summary of study characteristics for cognitive remediation**

	Cognitive remediation versus any control	Cognitive remediation versus standard care	Cognitive remediation versus other active treatments
k (total N)	17 (1084)	10 (522)	9 (605)
Study ID	BELLUCCI2002 Hadaslidor2001 HOGARTY2004 Medalia1998 Medalia2000 PENADES2006 SILVERSTEIN2005 <sup>a</sup> SPAULDING1999 TWAMLEY2008 VANDERGAAG2002 VELLIGAN2000 VELLIGAN2002 VELLIGAN2008A VELLIGAN2008B Wykes1999 WYKES2007A WYKES2007B	BELLUCCI2002 Medalia2000 SILVERSTEIN2005 <sup>a</sup> TWAMLEY2008 VELLIGAN2000 VELLIGAN2002 VELLIGAN2008A VELLIGAN2008B WYKES2007A WYKES2007B	Hadaslidor2001 HOGARTY2004 Medalia1998 PENADES2006 SPAULDING1999 VANDERGAAG2002 VELLIGAN2008A VELLIGAN2008B Wykes1999

*Continued*

**Table 72: (Continued)**

	<b>Cognitive remediation versus any control</b>	<b>Cognitive remediation versus standard care</b>	<b>Cognitive remediation versus other active treatments</b>
<i>Diagnosis</i>	83–100%schizophrenia Or other related diagnoses (DSM or ICD-10)	95–100% schizophrenia Or other related diagnoses (DSM or ICD-10)	83–100% schizophrenia Or other related diagnoses (DSM or ICD-10)
<i>Baseline severity</i>	<i>BPRS total:</i> Mean (SD) ~30 (4) Medalia1998 Mean (SD) ~37 (9) WYKES2007B <i>PANSS total:</i> Mean (SD)~60 (15) WYKES2007A	<i>BPRS total:</i> Mean (SD) ~37 (9) WYKES2007B  <i>PANSS total:</i> Mean (SD) ~ 60 (15) WYKES2007A	<i>BPRS total:</i> Mean (SD)~30 (4) Medalia1998
<i>Length of treatment</i>	<i>Range:</i> 5–104 weeks	<i>Range:</i> 5–104 weeks	<i>Range:</i> 6–104 weeks
<i>Length of follow-up</i>	<i>Up to 3 months:</i> TWAMLEY2008 WYKES2007B <i>Up to 6 months:</i> PENADES2006 Wykes1999 WYKES2007A <i>Up to 12 months:</i> HOGARTY2004	<i>Up to 3 months:</i> TWAMLEY2008 WYKES2007B <i>Up to 6 months:</i> WYKES2007A	<i>Up to 6 months:</i> PENADES2006 Wykes1999  <i>Up to 12 months:</i> HOGARTY2004



<i>Setting</i>	<i>Inpatient<sup>b</sup>:</i> Medalia1998 Medalia2000 SILVERSTEIN2005 SPAULDING1999 VANDERGAAG2002 WYKES2007B <i>Outpatient:</i> BELLUCCI2002 HOGARTY2004 VELLIGAN2000 <sup>c</sup> VELLIGAN2002 VELLIGAN2008A VELLIGAN2008B Wykes1999 WYKES2007A <i>Day rehabilitation centre:</i> Hadaslidor2001	<i>Inpatient<sup>b</sup>:</i> Medalia2000 SILVERSTEIN2005 WYKES2007B  <i>Outpatient:</i> BELLUCCI2002 VELLIGAN2000 <sup>c</sup> VELLIGAN2002 VELLIGAN2008A VELLIGAN2008B WYKES2007A	<i>Inpatient<sup>b</sup>:</i> Medalia1998 SPAULDING1999 VANDERGAAG2002  <i>Outpatient:</i> HOGARTY2004 VELLIGAN2008A VELLIGAN2008B Wykes1999  <i>Day rehabilitation centre:</i> Hadaslidor2001
<i>Note.</i> <sup>a</sup> The study included an attentional module for both cognitive remediation and waiting list control participants. The attentional module started after the completion of the cognitive remediation intervention and after testing at time point two. Only data from time point two were used in the analysis as this represented cognitive remediation versus standard care alone. <sup>b</sup> Included inpatient rehabilitation units. <sup>c</sup> Participants in the Velligan papers were recruited following discharge from an inpatient setting.			

Overall, there was no consistent evidence that cognitive remediation alone is effective in improving the critical outcomes, including relapse rates, rehospitalisation, mental state and quality of life. Furthermore, where effects of treatment were found, the evidence is difficult to interpret as many studies report non-significant findings without providing appropriate data for the meta-analysis. Thus, the magnitude of the effect is likely to be overestimated for all outcomes.

### **9.5.6 Linking evidence to recommendation**

The 2002 guideline found no consistent evidence for the effectiveness of cognitive remediation versus standard care or any other active treatment in improving targeted cognitive outcomes or other critical outcomes, such as symptom reduction. It is noteworthy that although the McGurk and colleagues' (2007) review suggested positive effects for symptoms and functioning, this may be, in part, attributed to the fact that their review included a number of studies that failed to meet the inclusion criteria set out by the GDG (for example, minimum number of participants or cognitive remediation as an adjunct to vocational rehabilitation).

Although limited evidence of efficacy has been found in a few recent well-conducted studies, there is a distinct lack of follow-up data and various methodological problems in the consistency with which outcomes are reported. Where studies comprehensively reported outcomes at both ends of treatment and follow-up, there was little consistent advantage of cognitive remediation over standard care and attentional controls. Consequently, although there are some positive findings, the variability in effectiveness suggests that the clinical evidence as a whole is not robust enough to change the 2002 guideline.

The GDG did note, however, that a number of US-based studies have shown sustained improvements in vocational and psychosocial outcomes when cognitive remediation is added to vocational training and/or supported employment services. Despite the emerging evidence within this context, the effectiveness of psychological and psychosocial interventions as adjuncts to supported employment services was outside the scope of the 2009 guideline and, therefore, has not been reviewed systematically. Given this finding and the variability in both the methodological rigour and effectiveness of cognitive remediation studies, it was the opinion of the GDG that further UK-based research is required. In particular, RCTs of cognitive remediation should include adequate follow-up periods to comprehensively assess its efficacy as a discrete and/or adjunctive intervention.

### **9.5.7 Research recommendation**

- 9.5.7.1** An adequately powered RCT with longer-term follow-up should be conducted to investigate the clinical and cost effectiveness of cognitive remediation compared with an appropriate control in people with schizophrenia.[2009]

## 9.6 COUNSELLING AND SUPPORTIVE THERAPY

### 9.6.1 Introduction

In the 1950s Carl Rogers, a pioneering US psychologist influenced by Alfred Adler and Otto Rank, devised 'client-centred' and later 'person-centred' counselling. This was a reaction against the behaviourist and psychodynamic schools that had emerged from late 19th century Freudian psychoanalysis. Unlike the early behaviourists, Rogers accepted the importance of a client's internal emotional world, but this centred on the lived experience of the person rather than empirically untestable psychoanalytic theories of unconscious drives and defences of unconscious processes (Thorne, 1992). Rogerian counselling has since been the starting point for newer therapies, such as humanistic counselling, psychodynamic counselling, psychodrama and Gestalt psychotherapy. In the UK, counselling is most likely to be offered to people with common mental illnesses within a primary care setting.

Supportive therapy has been cited as the individual psychotherapy of choice for most patients with schizophrenia (Lamberti & Herz, 1995). It is notable that most trials involving this intervention have used it as a comparison treatment for other more targeted psychological approaches, rather than investigating it as a primary intervention. This may be because supportive therapy is not a well-defined unique intervention, has no overall unifying theory and is commonly used as an umbrella term describing a range of interventions from befriending to a type of formal psychotherapy (Buckley et al., 2007). More formal supportive therapy approaches tend to be flexible in terms of frequency and regularity of sessions, and borrow some components from Rogerian counselling (namely an emphasis on empathic listening and 'non-possessive warmth'). These may be called 'supportive psychotherapy' and also tend to rely on an active therapist who may offer advice, support and reassurance with the aim of helping the patient adapt to present circumstances (Crown, 1988). This differs from the dynamic psychotherapist, who waits for material to emerge and retains a degree of opacity to assist in the development of a transference relationship.

Undoubtedly there are overlaps between counselling, supportive therapy and the other psychotherapies; known as 'non-specific factors', these are necessary for the development of a positive treatment alliance and are a prerequisite for any psychological intervention to stand a chance of success (Roth et al., 1996). Many of these factors are also part of high-quality 'standard care', as well as forming the key elements of counselling and supportive therapy. Fenton and McGlashan (1997) reported that a patient's feeling of being listened to and understood is a strong predictor of, for example, medication compliance. Also, according to McCabe and Priebe (McCabe & Priebe, 2004), the therapeutic relationship is a reliable predictor of patient outcome in mainstream psychiatric care.

## Definition

Counselling and supportive therapy were defined as discrete psychological interventions that:

- are facilitative, non-directive and/or relationship focused, with the content largely determined by the service user, and
- do not fulfil the criteria for any other psychological intervention.

## 9.6.2 Clinical review protocol

The review protocol, including information about the databases searched and the eligibility criteria used for this section of the guideline, can be found in Table 73. The primary clinical questions can be found in Box 1. A new systematic search for relevant RCTs published since the 2002 guideline was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).

**Table 73: Clinical review protocol for the review of counselling and supportive therapy**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT (≥10 participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Counselling and supportive therapy
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Leaving the study early for any reason Adverse events

## 9.6.3 Studies considered for review

In the 2002 guideline, 14 RCTs (N = 1,143) of counselling and supportive therapy were included. Two studies included in the 2002 guideline (Levine1998; Turkington2000) were excluded from the 2009 guideline review because of inadequate numbers of participants. The search for the 2009 guideline identified four papers providing follow-up data to existing trials and six new trials. In total, 18

RCTs (N = 1,610) met the inclusion criteria for the 2009 guideline. All were published in peer-reviewed journals between 1973 and 2007 (further information about both included and excluded studies can be found in Appendix 22c).

### **9.6.4 Counselling and supportive therapy versus control**

For the 2009 guideline review, 17 RCTs of counselling and supportive therapy versus any type of control were included in the meta-analysis. One included trial (Donlon1973) did not provide any useable data for the analysis. Sub-analyses were then used to examine counselling and supportive therapy versus standard care, versus other active treatment and versus CBT<sup>27</sup> (see Table 74 for a summary of the study characteristics). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### **9.6.5 Clinical evidence summary**

In 17 RCTs comprising 1,586 participants there was evidence to suggest that counselling and supportive psychotherapy do not improve outcomes in schizophrenia when compared with standard care and other active treatments, most notably CBT. A subgroup analysis of counselling and supportive therapy versus CBT favoured CBT for a number of outcomes including relapse. However, it must be noted that in these studies, counselling and supportive therapy was used as comparators to control primarily for therapist time and attention, and thus were not the focus of the research.

---

<sup>27</sup>Existing subgroup comparisons exploring the format of the intervention (group versus individual sessions) was also updated. However, there was insufficient data to draw any conclusions based on this subgroup. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted

**Table 74: Summary of study characteristics for counselling and supportive therapy**

	Counselling and supportive therapy versus any control	Counselling and supportive therapy versus standard care	Counselling and supportive therapy versus other active treatment	Counselling and supportive therapy versus CBT
<i>K (total N)</i>	17 (1586)	2 (262) <sup>e</sup>	17 (1452)	9 (678)
<i>Study ID</i>	Eckman1992 Falloon1981 Haddock1999 Herz2000 Hogarty1997 JACKSON2007 Kemp1996 Lewis2002 <sup>a</sup> Marder1996 PATTERSON2006 PINTO1999 ROHRICHT2006 Sensky2000 SHIN2002 Stanton1984 Tarrier1998 VALMAGGIA2005	Tarrier1998 Lewis2002 <sup>a</sup>	Eckman1992 Falloon1981 Haddock1999 Herz2000 Hogarty1997 JACKSON2007 Kemp1996 Lewis2002 <sup>a</sup> Marder1996 PATTERSON2006 PINTO1999 ROHRICHT2006 Sensky2000 SHIN2002 Stanton1984 Tarrier1998 VALMAGGIA2005	Haddock1999 Hogarty1997 Kemp1996 JACKSON2007 Lewis2002 <sup>a</sup> PINTO1999 Sensky2000 Tarrier1998 VALMAGGIA2005
<i>Diagnosis</i>	58–100% schizophrenia or other related diagnoses (DSM or ICD-10)	88–98% schizophrenia or other related diagnoses (DSM or ICD-10)	58–100% schizophrenia or other related diagnoses (DSM or ICD-10)	58–100% schizophrenia or other related diagnoses (DSM or ICD-10)

<i>Baseline severity</i>	<i>BPRS total:</i> Mean (SD) range: ~32 (8) to ~92 (8)  <i>PANSS total:</i> Mean (SD) range: ~61 (27) to ~87 (17)  <i>CPRS total:</i> Mean (SD) ~36 (14) Sensky2000	<i>PANSS total:</i> Mean (SD) ~87 (17) Lewis2000	<i>BPRS total:</i> Mean (SD) range: ~32 (8) to ~92 (8)  <i>PANSS total:</i> Mean (SD) range: ~61 (27) to ~87 (17)  <i>CPRS total:</i> Mean (SD) ~36 (14) Sensky2000	<i>BPRS total:</i> Mean (SD) range: ~32 (8) to ~92 (8)  <i>PANSS total:</i> Mean (SD) range: ~61 (27) to ~87 (17)  <i>CPRS total:</i> Mean (SD) ~36 (14) Sensky2000
<i>Length of treatment</i>	<i>Range: 5 to 156 weeks</i>	<i>Range: 5 to 10 weeks</i>	<i>Range: 5 to 156 weeks</i>	<i>Range: 5 to 156 weeks</i>
<i>Length of follow-up (only including papers reporting follow-up measures)</i>	<i>Range: 4 to 24 months</i>	<i>Range: up to 24 months</i>	<i>Range: 4 to 156 months</i>	<i>Range: 4 to 24 months</i>

*Continued*

**Table 74:(Continued)**

	Counselling and supportive therapy versus any control	Counselling and supportive therapy versus standard care	Counselling and supportive therapy versus other active treatment	Counselling and supportive therapy versus CBT
<i>Setting</i>	<i>Inpatient:</i> Haddock1999 Hogarty1997 <sup>b</sup> Kemp1996 Lewis2002 <sup>c</sup> Stanton1984 VALMAGGIA2005  <i>Outpatient:</i> Falloon1981 Herz2000 Marder1996 ROHRICHT2006 SHIN2002 Sensky2000 Tarrier1998	<i>Inpatient:</i> Lewis2002 <sup>c</sup>       <i>Outpatient:</i> Tarrier1998	<i>Inpatient:</i> Haddock1999 Hogarty1997 <sup>b</sup> Kemp1996 Lewis2002 <sup>c</sup> Stanton1984 VALMAGGIA2005  <i>Outpatient:</i> Falloon1981 Herz2000 Marder1996 ROHRICHT2006 SHIN2002 Sensky2000 Tarrier1998	<i>Inpatient:</i> Haddock1999 Hogarty1997 <sup>b</sup> Lewis2002 <sup>c</sup> VALMAGGIA2005  <i>Outpatient:</i> Sensky2000 Tarrier1998
	<i>Inpatient and outpatient:</i> Eckmann1992 PINTO1999 <i>Other<sup>d</sup>:</i> JACKSON2007 PATTERSON2006		<i>Inpatient and outpatient:</i> Eckmann1992 PINTO1999 <i>Other<sup>d</sup>:</i> JACKSON2007 PATTERSON2006	<i>Inpatient and outpatient:</i> PINTO1999  <i>Other<sup>d</sup>:</i> JACKSON2007
<p><i>Note.</i> <sup>a</sup>Follow-up papers to Lewis2002 report the data separately for the three study sites, hence in the analysis Lewis2002 appears as LEWIS2002L (Liverpool), LEWIS2002M (Manchester) and LEWIS2002N (Nottingham).</p> <p><sup>b</sup>Participants were recruited in the inpatient setting with the interventions starting shortly before discharge.</p> <p><sup>c</sup>Participants were recruited from inpatient wards and day hospitals.</p> <p><sup>d</sup>Other settings included Board and Care facilities and EIS settings.</p> <p><sup>e</sup>Both studies included multiple treatment arms; only the numbers in the counselling and supportive therapy and standard care arms have been included in this count.</p>				



### **9.6.6 Linking evidence to recommendations**

In the 2002 guideline, the GDG found no clear evidence to support the use of counselling and supportive therapy as a discrete intervention. The limited evidence found for the 2009 guideline does not justify changing this recommendation. The GDG does, however, acknowledge the preference that some service users and carers may have for these interventions, particularly when other more efficacious psychological treatments are not available in the local area. Furthermore, the GDG recognise the importance of supportive elements in the provision of good quality standard care.

### **9.6.7 Recommendation**

**9.6.7.1** Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to people with psychosis or schizophrenia. However, take service user preferences into account, especially if other more efficacious psychological treatments, such as CBT, family intervention and arts therapies, are not available locally. [2009]

## **9.7 FAMILY INTERVENTION**

### **9.7.1 Introduction**

Family intervention in the treatment of schizophrenia has evolved from studies of the family environment and its possible role in affecting the course of schizophrenia (Vaughn & Leff, 1976) after an initial episode. It should be noted that in this context, 'family' includes people who have a significant emotional connection to the service user, such as parents, siblings and partners. Brown and colleagues (Brown et al., 1962; Brown & Rutter, 1966) developed a measure for the level of 'expressed emotion' within families and were able to show that the emotional environment within a family was an effective predictor of relapse in schizophrenia (Bebbington & Kuipers, 1994; Butzlaff & Hooley, 1998). The importance of this work lay in the realisation that it was possible to design psychological methods (in this case, family intervention) that could change the management of the illness by service users and their families, and influence the course of schizophrenia.

Family intervention in schizophrenia derives from behavioural and systemic ideas, adapted to the needs of families of those with psychosis. More recently, cognitive appraisals of the difficulties have been emphasised. Models that have been developed aim to help families cope with their relatives' problems more effectively, provide support and education for the family, reduce levels of distress, improve the ways in which the family communicates and negotiates problems, and try to prevent relapse by the service user. Family intervention is normally complex and lengthy (usually more than ten sessions) but delivered in a structured format with the individual family, and tends to include the service user as much as possible.

## Definition

Family intervention was defined as discrete psychological interventions where:

- family sessions have a specific supportive, educational or treatment function and contain at least one of the following components:
  - problem solving/crisis management work, or
  - intervention with the identified service user.

### 9.7.2 Clinical review protocol

The review protocol, including information about the databases searched and the eligibility criteria used for this section of the guideline, can be found in Table 75. The primary clinical questions can be found in Box 1. A new systematic search for relevant RCTs published since the 2002 guideline was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20 and information about the search for health economic evidence can be found in Section 9.7.8).

**Table 75: Clinical review protocol for the review of family intervention**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT (≥10 participants per arm and ≥ 6 weeks' duration)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Family intervention
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation,) Mental state (total symptoms, depression) Psychosocial functioning Family outcomes (including burden) Quality of life Leaving the study early for any reason Adverse events

### 9.7.3 Studies considered for review

In the 2002 guideline, 18 RCTs (N = 1,458) of family intervention were included. One study (Posner1992) included in the 2009 guideline was re-classified as 'psychoeducation' for the 2009 guideline and two previous trials were classified as having family intervention as part of a multi-modal treatment (Herz2000 and

Lukoff1986). The search for the 2009 guideline identified five papers providing follow-up data to existing trials and 19 new trials. In total, 38 trials (N = 3,134) met the inclusion criteria for the 2009 guideline review. All were published in peer-reviewed journals between 1978 and 2008 (further information about both included and excluded studies can be found in Appendix 22c).

#### **9.7.4 Family intervention versus control**

For the 2009 guideline, one of the included studies (CHENG2005) did not provide useable data for any of the critical outcomes listed in Table 75, thus 32 RCTs of family intervention versus any type of control were included in the meta-analysis. Of these, 26 trials compared family intervention with standard care and eight compared family intervention with other active treatments. Additionally, five trials directly compared a multiple family intervention with a single family intervention (see Table 76 for a summary of the study characteristics). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

Subgroup analyses were also used to examine whether the format of the family intervention had an impact on outcome (ten trials were included in the analysis of multiple family interventions versus any control and 11 trials were included in the analysis of single family interventions versus any control). Additional subgroup analyses were used to explore certain characteristics of the trials, such as the inclusion of the person with schizophrenia, patient characteristics and the length of the intervention<sup>28</sup> (see Table 77 for a summary of the studies included in each subgroup comparison).

#### **9.7.5 Training**

Although there was a paucity of information on training and/or competence of the therapists in the RCTs of family intervention, 28 trials reported the profession of the therapist. In these trials, the professional background varied, with the most commonly reported professions being clinical psychologist (14/28) or psychiatric nurse (12/28). In addition, the following professionals also conducted the intervention in a number of papers: psychiatrist (10/28), social workers (3/28), Masters' level psychology graduates (2/28) and local mental health workers (1/28). In many trials a number of therapists, often across different disciplines, conducted the interventions, with some trials emphasising collaboration between the therapists and the participant's key worker.

---

<sup>28</sup>Existing subgroup comparisons exploring the country of the trial, the number of treatment sessions, and the family characteristics (high emotional expression versus everything) were also updated. However, there was insufficient data to draw any conclusions based on these subgroups. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted.

**Table 76: Summary of study characteristics for family intervention**

	<b>Family intervention versus any control</b>	<b>Family intervention versus standard care</b>	<b>Family intervention versus other active treatments</b>	<b>Multiple family versus single family intervention (direct format comparison)</b>
<i>K (total N)</i>	32 (2429)	26 (1989)	8 (417)	5 (641)
<i>Study ID</i>	Barrowclough1999 Bloch1995 BRADLEY2006 BRESSI2008 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 Falloon1981 GARETY2008 <sup>a</sup> Glynn1992 Goldstein1978 Herz2000 <sup>b</sup> Hogarty1997	Barrowclough1999 Bloch1995 BRADLEY2006 BRESSI2008 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 GARETY2008 <sup>a</sup> Glynn1992 Goldstein1978 JENNER2004 <sup>b</sup> KOPELOWICZ2003 LEAVEY2004	CARRA2007 Falloon1981 GARETY2008 <sup>a</sup> Herz2000 <sup>b</sup> Hogarty1997 LINSZEN1996 <sup>b</sup> Lukoff1986 <sup>b</sup> SZMUKLER2003	Leff1989 McFarlane1995a McFarlane1995b MONTERO2001 Schooler1997

**Table 76:(Continued)**

	Family intervention versus any control	Family intervention versus standard care	Family intervention versus other active treatments	Multiple family versus single family intervention (direct format comparison)
	JENNER2004 <sup>b</sup> KOPELOWICZ2003 LEAVEY2004 Leff1982 LI2005 LINSZEN1996 <sup>b</sup> Lukoff1986 <sup>b</sup> MAGLIANO2006 RAN2003 SO2006 SZMUKLER2003 Tarrier1988 VALENCIA2007 <sup>b</sup> Vaughan1992 Xiong1994 Zhang1994	Leff1982 LI2005 MAGLIANO2006 RAN2003 SO2006 Tarrier1988 VALENCIA2007 <sup>b</sup> Vaughan1992 Xiong1994 Zhang1994		
<i>Diagnosis</i>	93–100% schizophrenia or other related diagnoses (DSM or ICD-10)	93–100% schizophrenia or other related diagnoses (DSM or ICD-10)	98–100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)

<i>Baseline severity</i>	<i>BPRS total:</i> Mean (SD) range: ~27 (3) to ~48 (10)  <i>PANSS total:</i> Mean (SD) range: ~53 (1) To 112 (26)	<i>BPRS total:</i> Mean (SD) range: ~27 (3) to ~48 (10)  <i>PANSS total:</i> Mean (SD) range: ~60 (14) to 112 (26)	   <i>PANSS total:</i> Mean (SD) range: ~53 (17) to ~67 (14)	<i>BPRS total:</i> Mean (SD): 29 (7) Schooler1997
<i>Length of treatment</i>	Range: 6–156 weeks	Range: 12–104 weeks	Range: 6–156 weeks	Range: 52–104 weeks
<i>Length of follow-up (only including papers reporting follow-up measures)</i>	Range: 3–60 months	Range: 3–60 months	Range: 12–60 months	Range: 24–60 months
<i>Setting</i>	<i>Inpatient:</i> Bloch1995 <sup>c</sup> BRESSI2008 Glynn1992 Hogarty1997 <sup>d</sup> LINSZEN1996 <sup>b</sup> Lukoff1986 <sup>b</sup> Vaughan1992	<i>Inpatient:</i> Bloch1995 <sup>c</sup> BRESSI2008 Glynn1992 Vaughan1992	<i>Inpatient:</i> Hogarty1997 <sup>d</sup> LINSZEN1996 <sup>b</sup> Lukoff1986 <sup>b</sup>	<i>Inpatient:</i> Leff1989 McFarlane1995a

**Table 76: (Continued)**

	<b>Family intervention versus any control</b>	<b>Family intervention versus standard care</b>	<b>Family intervention versus other active treatments</b>	<b>Multiple family versus single family intervention (direct format comparison)</b>
	<i>Outpatient:</i> Barrowclough1999 BRADLEY2006 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 Falloon1981 Goldstein1978 <sup>e</sup> Herz2000 <sup>b</sup> JENNER2004 <sup>b</sup> KOPELOWICZ2003	<i>Outpatient:</i> Barrowclough1999 BRADLEY2006 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 Goldstein1978 <sup>e</sup> JENNER2004 <sup>b</sup> KOPELOWICZ2003 Leff1982 MAGLIANO2006	<i>Outpatient:</i> CARRA2007 Falloon1981 Herz2000 <sup>b</sup> SZMUKLER2003	<i>Outpatient:</i> McFarlane1995b MONTERO2001 Schooler1997

Leff1982 MAGLIANO2006 RAN2003 SO2006 SZMUKLER2003 Tarrier1998 VALENCIA2007 <sup>b</sup> Xiong1994 Zhang1994  <i>Inpatient and outpatient:</i> GARETY2008 <sup>a</sup> LEAVEY2004 LI2005	RAN2003 SO2006 Tarrier1998 VALENCIA2007 <sup>b</sup> Xiong1994 Zhang1994  <i>Inpatient and outpatient:</i> GARETY2008 <sup>a</sup> LEAVEY2004 LI2005	<i>Inpatient and outpatient:</i> GARETY2008 <sup>a</sup>	
<p><i>Note.</i> Studies were categorised as short (12weeks or fewer), medium (12–51weeks) and long (52 weeks or more).</p> <p><sup>a</sup>Only the carer pathway was included in the present analysis.</p> <p><sup>b</sup>Multi-modal interventions.</p> <p><sup>c</sup>Carers of patients admitted to the ward were recruited to take part in the study.</p> <p><sup>d</sup>Participants were recruited in the inpatient setting with the intervention starting shortly before discharge.</p> <p><sup>e</sup>Participants were recruited following discharge to an after care outpatient programme</p>			



**Table 77: Summary of study characteristics for family intervention subgroup comparisons**

	<b>Single family intervention versus any control</b>	<b>Multiple family intervention versus any control</b>	<b>Family intervention including service user versus any control</b>	<b>Family intervention excluding service user Versus any control</b>
<i>K (total N)</i>	11 (864)	10 (651)	18 (1319)	9 (622)
<i>Study ID</i>	Barrowclough1999 Bloch1995 BRESSI2008 Falloon1981 GARETY2008 Glynn1992 Hogarty1997 LEAVEY2004 MAGLIANO2006 RAN2003 Vaughan1992	BRADLEY2006 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 KOPELOWICZ2003 SO2006 Xiong1994	Barrowclough1999 BRADLEY2006 BRESSI2008 CHIEN2004B CHIEN2007 Falloon1981 GARETY2008 Glynn1992 Goldstein1978 Hogarty1997 KOPELOWICZ2003 Leff1982 LI2005 MAGLIANO2006 RAN2003 Tarrier1988 Xiong1994 Zhang1994	Bloch1995 Buchkremer1995 CARRA2007 CHIEN2004A Dyck2000 LEAVEY2004 SO2006 SZMUKLER2003 Vaughan1992

**Table 77: (Continued)**

	<b>Short-term family intervention versus any control</b>	<b>Medium-term family intervention versus any control</b>	<b>Long-term family intervention versus any control</b>
<i>K (total N)</i>	4 (248)	12 (1056)	10 (660)
<i>Study ID</i>	Bloch1995 Goldstein1978 SO2006 Vaughan1992	Barrowclough1999 CHIEN2004A CHIEN2004B CHIEN2007 GARETY2008 KOPELOWICZ2003 LEAVEY2004 Leff1982 MAGLIANO2006 RAN2003 SZMUKLER2003 Tarrier1988	BRADLEY2006 BRESSI2008 Buchkremer1995 CARRA2007 Dyck2000 Falloon1981 Glynn1992 Hogarty1997 Xiong1994 Zhang1994
	<b>Family intervention versus any control-first episode<sup>a</sup></b>	<b>Family intervention versus any control-acute episode</b>	<b>Family intervention versus any control-promoting recovery</b>
<i>K (total N)</i>	4 (333)	12 (673)	9 (702)
<i>Study ID</i>	Goldstein1978 LEAVEY2004 SO2006 Zhang1994	Bloch1995 BRADLEY2006 BRESSI2008 Falloon1981 GARETY2008 Glynn1992 Hogarty1997 KOPELOWICZ2003 Leff1982 Tarrier1988 Vaughan1992 Xiong1994	Barrowclough1999 Buchkremer1995 CARRA2007 CHIEN2004A CHIEN2004B CHIEN2007 Dyck2000 LI2005 MAGLIANO2006
<i>Note.</i> <sup>a</sup> A number of trials included participants across different phases of illness (for example, first episode, acute and promoting recovery) and hence could not be included in the subgroup analysis.			

### 9.7.6 Ethnicity

Although the data on ethnicity was limited, a subgroup analysis looking at the efficacy of family intervention in an ethnically diverse population was conducted (see Chapter 6 for definition of ethnically diverse sample). For critical outcomes including relapse, rehospitalisation and symptoms, family intervention was shown to have clinically significant benefits within studies including an ethnically diverse sample. One UK study (LEAVEY2004) assessed the impact of a brief family intervention for families of patients with first episode psychosis. Participants were drawn from a multicultural and ethnically diverse population, with the researchers attempting to match the ethnicity of the family worker with the ethnicity of the carer. LEAVEY2004 failed to demonstrate any significant impact on either patient outcomes or carer level of satisfaction. However, the authors note that the high proportion failing to take up the intervention may have had a detrimental impact upon the results.

A number of papers have assessed the effectiveness of adapting a Western family intervention approach to better suit non-Western populations. For example, both RAN2003 and LI2005 adapted the content of the intervention to better match the cultural needs and family structures of people living in different communities in mainland China. Further to this, researchers have started to assess the impact of cultural modifications aimed at tailoring an intervention to better suit the cultural and ethnic needs of minority populations. For instance, BRADLEY2006 assessed the effectiveness of a modified intervention approach that included the use of language matching and ethno-specific explanatory models in a sample of Vietnamese speaking migrants living in Australia. Although both types of cultural modifications were shown to be effective across critical outcomes, none of the RCTs was conducted with black and minority ethnic participants from the UK; therefore the generalisability of such findings is limited. Furthermore, at present little research exists that directly compares the efficacy and acceptability of culturally and non-culturally modified approaches.

### 9.7.7 Clinical evidence summary

In 32 RCTs including 2,429 participants, there was robust and consistent evidence for the efficacy of family intervention. When compared with standard care or any other control, there was a reduction in the risk of relapse with numbers needed to treat (NNTs) of 4 (95% CIs 3.23 to 5.88) at the end of treatment and 6 (95% CIs 3.85 to 9.09) up to 12 months following treatment. In addition, family intervention also reduced hospital admission during treatment and the severity of symptoms both during and up to 24 months following the intervention. Family intervention may also be effective in improving additional critical outcomes, such as social functioning and the patient's knowledge of the disorder. However, it should be noted that evidence for the latter is more limited and comes from individual studies reporting multiple outcomes across a range of scale-based measures.

The subgroup analyses conducted for the 2009 guideline to explore the variation in terms of intervention delivery consistently indicated that where practicable the service user should be included in the intervention. Although direct format comparisons did not indicate any robust evidence for single over multiple family intervention in terms of total symptoms, single family intervention was seen as more acceptable to service users and carers as demonstrated by the numbers leaving the study early. Additionally, subgroup comparisons that indirectly compared single with multiple family intervention demonstrated some limited evidence to suggest that only the former may be efficacious in reducing hospital admission.

### 9.7.8 Health economic evidence

#### *Systematic literature review*

No studies evaluating the cost effectiveness of family intervention for people with schizophrenia met the set criteria for inclusion in the guideline systematic review of economic literature. However, the 2002 guideline, using more relaxed inclusion criteria, had identified a number of economic studies on family intervention for people with schizophrenia. Details on the methods used for the systematic search of the economic literature in the 2009 guideline are described in Appendix 11. The following text marked by asterisks is derived from the 2002 guideline.

**\*\*2002\*\*** The economic review identified five eligible studies, and a further two studies were not available. All five included studies were based on RCTs. Three papers adapted simple costing methods (Goldstein, 1996; Leff, 2001; Tarrier et al., 1991), while two studies were economic evaluations (Lieberman et al., 1987; McFarlane et al., 1995). Of these, two economic analyses were conducted in the UK (Leff, 2001; Tarrier et al., 1991) and two others were based on clinical data from the UK, but the economic analyses were conducted within a US context (Goldstein, 1996; Lieberman et al., 1987). Most of these studies are methodologically weak, with the potential for a high risk of bias in their results. Another common problem was the low statistical power of the studies to show cost differences between the comparators. All studies focused narrowly on direct medical costs. As such, economic evaluation of family interventions from a broader perspective is impossible.

One study (Tarrier et al., 1991) compared family intervention with standard care and concluded that family intervention is significantly less costly than standard care. Two analyses compared family intervention with individual supportive therapy (Goldstein, 1996; Lieberman et al., 1987). Both studies used clinical data from the same RCT, but their evaluation methodology differed. They concluded that the treatment costs of family intervention are higher than those of individual supportive therapy, but cost savings relating to other healthcare costs offset the extra treatment costs. One study (Leff, 2001) showed economic benefits of family intervention combined with two psychoeducational sessions over psychoeducation alone. However, the difference was not significant. One study (McFarlane et al., 1995) demonstrated that

multi-family group intervention is more cost effective than single-family intervention.

The quality of the available economic evidence is generally poor. The evidence, such as it is, suggests that providing family interventions may represent good 'value for money'. There is limited evidence that multi-family interventions require fewer resources and are less costly than single-family interventions. \*\*2002\*\*

The evidence table for the above studies as it appeared in the 2002 guideline is included in Appendix 25.

### *Economic modelling*

#### **Objective**

\*\*2009\*\* The guideline systematic review and meta-analysis of clinical evidence demonstrated that provision of family intervention is associated with a reduction in relapse and hospitalisation rates of people with schizophrenia. A cost analysis was undertaken to assess whether the costs of providing family intervention for people with schizophrenia are offset by cost savings to the NHS following this decrease in relapse and hospitalisation rates.

#### **Intervention assessed**

Family intervention can be delivered to single families or in groups. The guideline meta-analysis included all studies of family intervention versus control in its main analysis, irrespective of the mode of delivery, because it was difficult to distinguish between single and multiple programmes. The majority of studies described family intervention programmes that were predominantly single or multiple, but might have some multiple or single component, respectively; some of the interventions combined single and multiple sessions equally.

Apart from the main meta-analysis, studies of family intervention versus control were included in additional sub-analyses in which studies comparing (predominantly) single family intervention versus control were analysed separately from studies comparing (predominantly) multiple family intervention versus control. These sub-analyses demonstrated that single family intervention significantly reduced the rates of hospital admission of people with schizophrenia up to 12 months into therapy, whereas multiple family intervention was not associated with a statistically significant respective effect. On the other hand, single and multiple family intervention had a significant effect of similar magnitude in reducing the rates of relapse.

A small number of studies compared directly (exclusively) single with (exclusively) multiple family intervention. Meta-analysis of these studies showed that single and multiple family intervention had no significant difference in clinical outcomes. However, participants showed a clear preference for single interventions, as expressed in dropout rates.

It was decided that the economic analysis would utilise evidence from the main meta-analysis of all studies on family intervention versus control (irrespective of the model of delivery) but, in terms of intervention cost, would consider single family intervention; this would produce a conservative cost estimate per person with schizophrenia, given that in multiple family intervention the intervention cost is spread over more than one family.

## **Methods**

A simple economic model estimated the total net costs (or cost savings) to the NHS associated with provision of single family therapy, in addition to standard care, to people with schizophrenia and their families/carers. Two categories of costs were assessed: costs associated with provision of family intervention, and cost savings from the reduction in relapse and hospitalisation rates in people with schizophrenia receiving family intervention, estimated based on the guideline meta-analysis of respective clinical data. Standard care costs were not estimated because these were common to both arms of the analysis.

## **Cost data**

*Intervention costs (costs of providing family intervention)* The single family intervention programmes described in the clinical studies included in the guideline systematic review were characterised by a wide variety in terms of number of sessions and duration of each session. The resource use estimate associated with provision of single family intervention in the economic analysis was based on the expert opinion of the GDG regarding optimal clinical practice in the UK, and was consistent with average resource use reported in these studies. Single family intervention in the economic analysis consisted of 20 hours and was delivered by two therapists.

As with CBT, the GDG acknowledge that family intervention programmes can be delivered by a variety of mental health professionals with appropriate training and supervision. The salary level of a mental health professional providing family intervention was estimated to be similar to that of a mental health professional providing CBT, and comparable with the salary level of a clinical psychologist. Therefore, the unit cost of a clinical psychologist was used to estimate an average intervention cost. The unit cost of a clinical psychologist is estimated at £67 per hour of client contact in 2006/07 prices (Curtis, 2007). This estimate is based on the mid-point of Agenda for Change salaries Band 7 of the April 2006 pay scale, according to the National Profile for Clinical Psychologists, Counsellors and Psychotherapists (NHS Employers, 2006). It includes salary, salary oncosts, overheads and capital overheads, but does not take into account qualification costs because the latter are not available for clinical psychologists.

Based on the above resource use estimates and the unit cost of a clinical psychologist, the cost of providing a full course of family intervention was estimated at £2,680 per person with schizophrenia in 2006/07 prices.

*Costs of hospitalisation/cost-savings from reduction in hospitalisation rates* As described in Section 9.4.8, the average cost of hospitalisation per person with schizophrenia was estimated at £28,645 in 2006/07 prices, based on national statistics on the mean length of hospitalisation for people with schizophrenia (NHS, The Information Centre, 2008a) and the NHS reference cost per bed-day of an inpatient mental health acute care unit for adults, in 2006/07 prices (Department of Health, 2008).

### **Clinical data on hospitalisation rates following provision of family intervention**

The guideline meta-analysis provided pooled data on both hospitalisation and relapse rates associated with provision of family intervention in addition to standard care versus standard care alone. The analyses showed that adding family intervention to standard care significantly reduced the rates of both hospitalisation and relapse in people with schizophrenia. The vast majority of these data came from studies conducted outside the UK. The GDG expressed the view that hospitalisation levels may differ significantly across countries, depending on prevailing clinical practice, and therefore data on hospitalisation rates derived from non-UK countries might not be applicable to the UK setting. On the other hand, the definition of relapse was more consistent across studies (and countries). For this reason, it was decided to use pooled data on relapse rather hospitalisation rates for the economic analysis; these data would be used, subsequently, to estimate hospitalisation rates relevant to people with schizophrenia in the UK to calculate cost savings from reducing hospital admissions following provision of family intervention.

The guideline meta-analysis of family intervention data on relapse rates included two analyses: one analysis explored the effect on relapse rates during treatment with family intervention, and another analysis estimated the effect on relapse rates at follow-up, between 4 and 24 months after completion of family intervention. Ideally, both analyses should be taken into account at the estimation of total savings associated with family intervention. However, follow-up data were not homogeneous: some studies reported relapse data during treatment separately from respective data after treatment, but other studies included events that occurred during treatment in the reported follow-up data. Taking into account both sets of data might therefore double-count events occurring during treatment and would consequently overestimate the value of cost savings associated with family intervention. It was decided to use relapse data during treatment in the analysis, because these data were homogeneous and referred to events that occurred within the same study phase. It is acknowledged, however, that the cost savings estimated using data exclusively reported during treatment are probably underestimates of the true cost savings because the beneficial effect of family intervention on relapse remains for a substantial period after completing treatment.

Table 78 shows the family intervention studies included in the meta-analysis of relapse rate data for 1 to 12 months into treatment, the relapse rates for each treatment arm reported in the individual studies and the results of the meta-analysis.

The results of the meta-analysis show that family intervention, when added to standard care, reduces the rate of relapse in people with schizophrenia during the intervention period (the RR of relapse of family intervention added to standard care versus standard care alone is 0.52). This result was significant at the 0.05 level (95% CIs of RR: 0.42 to 0.65). It must be noted that the meta-analysis of relapse follow-up data showed that this beneficial effect remains significant up to at least 24 months after the end of therapy (respective RR up to 24 months following provision of family intervention 0.63, with 95% CIs 0.52 to 0.78).

**Table 78: Studies considered in the economic analysis of family intervention added to standard care versus standard care alone and results of the meta-analysis (1 to 12 months into treatment)**

Study ID	Total events (n) in each treatment arm (N)	
	Family intervention plus standard care (n/N)	Standard care alone (n/N)
GOLDSTEIN1978	7/52	12/52
LEFF1982	1/12	6/12
TARRIER1988	13/32	20/32
GLYNN1992	3/21	11/20
XIONG1994	12/34	18/29
BARROWCLOUGH1999	9/38	18/39
RAN2003	22/57	32/53
BRADLEY2006	8/30	13/29
BRESSI2008	3/20	13/20
TOTAL	78/296 (26.35%)	143/286 (50.00%)
Meta-analysis results	RR: 0.52 95% CI: 0.42–0.65	

The baseline rate of relapse in the economic analysis was taken from the overall rate of relapse under standard care alone, as estimated in the guideline meta-analysis of family intervention data on relapse; that is, a 50% baseline relapse rate was used. The rate of relapse when family intervention was added to standard care was calculated by multiplying the estimated RR of relapse of family intervention plus standard care versus standard care alone by the baseline relapse rate.

Details on the studies considered in the economic analysis are available in Appendix 22c. The forest plots of the respective meta-analysis are provided in Appendix 23d.

### **Association between relapse and hospitalisation rates**

In the UK, people with schizophrenia experiencing a relapse are mainly treated either as inpatients or by CRHTTs. Glover and colleagues (2006) examined the reduction in hospital admission rates in England following the implementation of



CRHTTs. They reported that the introduction of CRHTTs was followed by a 22.7% reduction in hospital admission levels. Based on this data, the economic analysis assumed that 77.3% of people with schizophrenia experiencing a relapse would be admitted in hospital, and the remaining 22.7% would be seen by CRHTTs.

### Sensitivity analysis

One- and two-way sensitivity analyses were undertaken to investigate the robustness of the results under the uncertainty characterising some of the input parameters and the use of different assumptions in the estimation of total net costs (or net savings) associated with provision of family intervention for people with schizophrenia. The following scenarios were explored:

- Use of the 95% CIs of the RR of relapse of family intervention added to standard care versus standard care alone.
- Change in the total number of hours of a course of family intervention (20 hours in the base-case analysis) to between a range of 15 and 25 hours.
- Change in the baseline rate of relapse (that is, the relapse rate for standard care) from 50% (that is, the baseline relapse rate in the base-case analysis) to a more conservative value of 30%.
- Change in the rate of hospitalisation following relapse (77.3% in base-case analysis) to 61.6% (based on the upper 95% CI of the reduction in hospital admission levels following the introduction of CRHTTs which, according to Glover and colleagues (2006), was 38.4%).
- Simultaneous use of a 30% relapse rate for standard care and a 61.6% hospitalisation rate following relapse.
- Use of a lower value for duration of hospitalisation. A value of 69 days was tested, taken from an effectiveness trial of clozapine versus SGAs conducted in the UK (CUtLASS Band 2, (Davies et al., 2008).

### Results

*Base-case analysis* Providing family intervention cost £2,680 per person. The reduction in the rates of relapse in people with schizophrenia during treatment with family intervention in addition to standard care resulted in cost savings equaling £5,314 per person. Thus, family intervention resulted in an overall net saving of £2,634 per person with schizophrenia. Full results of the base-case analysis are reported in Table 79.

**Table 79: Results of cost analysis comparing family intervention in addition to standard care with standard care alone per person with schizophrenia**

Costs	Family intervention plus standard care	Standard care alone	Difference
Family intervention cost	£2,680	0	£2,680
Hospitalisation cost	£5,757	£11,071	-£5,314
Total cost	£8,437	£11,071	-£2,634

*Sensitivity analysis* The results of the base-case analysis were overall found to be robust to the different scenarios explored in sensitivity analysis. Family intervention remained cost saving when the 95% CIs of the RR of relapse during treatment were used. In most scenarios, using the mean RR of relapse taken from the guideline meta-analysis, the addition of family intervention to standard care resulted in overall cost savings because of a substantial reduction in relapse and subsequent hospitalisation costs. The only scenario in which family intervention was not cost saving (instead incurring a net cost of £139 per person) was when a 30% baseline relapse rate was assumed, combined with a 61.6% rate of hospitalisation following relapse (in this scenario, the overall cost ranged between a net saving of £390 and a net cost of £827 when the 95% CIs of RR of relapse were used). Full results of sensitivity analysis are presented in Table 80.

## Discussion

The economic analysis showed that family intervention for people with schizophrenia is likely to be an overall cost-saving intervention because the intervention costs are offset by savings resulting from a reduction in the rate of relapses experienced during therapy. The net cost saving of providing family intervention ranged between £1,195 and £3,741 per person with schizophrenia, using a mean duration of hospitalisation of 110.6 days and the 95% CIs of RRs of relapse, as estimated in the guideline meta-analysis. When a mean length of hospital stay of 69 days was used, the net cost of providing family intervention was found to lie between –£1,326 (overall net saving) and £263 per person with schizophrenia.

**Table 80: Results of sensitivity analysis of providing family intervention in addition to standard care for people with schizophrenia**

Scenario	Total net cost (negative cost implies net saving)
Use of 95% CIs of RR of relapse	–£3,741 (lower CI) to –£1,195 (upper CI)
Family intervention hours between 15 and 25	–£3,304 to –£1,964 respectively
Relapse rate under standard care 30%	–£509 (–£1,173 to £355 using the 95% CIs of RR of relapse)
Rate of hospitalisation following relapse 61.6%	–£1,555 (–£2,437 to –£408 using the 95% CIs of RR of relapse)
Relapse rate under standard care 30% and rate of hospitalisation following relapse 61.6%	£139 (–£390 to £827 using the 95% CIs of RR of relapse)
Mean length of hospitalisation 69 days	–£635 (–£1,326 to £263 using the 95% CIs of RR of relapse)

The economic analysis estimated cost savings related exclusively to a decrease in hospitalisation costs following reduction in relapse rates associated with family intervention. Consideration of further potential cost savings, such as savings resulting from an expected reduction in contacts with CRHTTs following reduction in relapse rates, would further increase the cost savings associated with family intervention. Moreover, meta-analysis of follow-up data demonstrated that the beneficial effect of family intervention on relapse rates observed in people with schizophrenia remains significant for a period at least 24 months following treatment. This means that the cost savings associated with family intervention are even higher. Finally, the expected improvement in HRQoL of people with schizophrenia and their carers following a reduction in relapse rates further strengthens the argument that family intervention is likely to be a cost-effective option for people with schizophrenia in the UK.

### **9.7.9 Linking evidence to recommendations**

There was sufficient evidence in the 2002 guideline for the GDG to recommend family intervention in the treatment of schizophrenia. Recent studies have corroborated these conclusions and have consistently shown that family intervention may be particularly effective in preventing relapse.

Further analyses undertaken for the 2009 guideline continue to support the evidence demonstrated in the 2002 guideline with regard to the duration of treatments and the inclusion of the person with schizophrenia, where practicable. Although the evidence is more limited for the advantages of single compared with multiple family interventions, this must be considered in the context of current practice as well as service user and carer preferences. Furthermore, the GDG noted that the majority of UK-based studies were conducted as single family interventions, with the non-UK studies contributing more to the multiple family intervention evidence base. Thus, the evidence for single family intervention may additionally be more generalisable to UK settings.

Existing economic evidence on family intervention is poor. A simple economic analysis undertaken for this guideline demonstrated that, in the UK setting, family intervention is associated with net cost savings when offered to people with schizophrenia in addition to standard care, owing to a reduction in relapse rates and subsequent hospitalisation. The findings of the economic analysis used data on relapse that referred to the period during treatment with family intervention. However, there is evidence that family intervention also reduces relapse rates for a period after completion of the intervention. Therefore, net cost savings from family intervention are probably higher than those estimated in the guideline economic analysis.

With regard to the training and competencies required by the therapist to deliver family intervention to people with schizophrenia and their carers, there was a paucity of information reported throughout the trials. Consequently, the GDG were unable to form any conclusions or make any recommendations relating to practice.

However, the GDG acknowledges that the training and competencies of the therapist is an important area, and one that warrants further research.

The robust evidence presented in the current clinical and health economic evaluation of family intervention further supports the conclusions and recommendations in the 2002 guideline. Although there was a lack of evidence for the use of culturally adapted family interventions within the UK, the GDG acknowledges that this is an important area warranting further investigation given the evidence previously discussed relating to inequality of access for people from black and minority ethnic groups (see Chapter 6).\*\*2009\*\*

Following the publication of *Psychosis and Schizophrenia in Children and Young People* (NCCMH, 2013 [full guideline]; NICE, 2013a), for the 2014 guideline the GDG took the view that the recommendations should be consistent where appropriate. Therefore the GDG saw the value in advising practitioners of the equivocal evidence regarding psychological interventions when compared with antipsychotic medication and recommended that if person wished to try a psychological intervention alone, this could be trialled over the course of a month or less. Following *Psychosis and Schizophrenia in Children and Young People* the GDG also wished to make it explicit that the options for first episode psychosis should be oral antipsychotic medication combined with psychological interventions (family intervention and individual CBT).

## 9.7.10 Recommendations

### *Treatment options for first episode psychosis*

#### 9.7.10.1 For people with first episode psychosis offer:

- oral antipsychotic medication (see recommendations 10.11.1.2–10.11.1.13) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]

**9.7.10.2** If the person wishes to try psychological interventions (family intervention and individual CBT) alone without antipsychotic medication, advise that psychological interventions are more effective when delivered in conjunction with antipsychotic medication. If the person still wishes to try psychological interventions alone, then offer family intervention and CBT. Agree a time (1 month or less) for reviewing treatment options, including introducing antipsychotic medication. Continue to monitor symptoms, level of distress, impairment and level of functioning, (including education, training and employment), regularly. [new 2014]

## *How to deliver psychological interventions*

### **9.7.10.3** Family intervention should:

- include the person with psychosis or schizophrenia if practical
- be carried out for between 3 months and 1 year
- include at least 10 planned sessions
- take account of the whole family's preference for either single-family intervention or multi-family group intervention
- take account of the relationship between the main carer and the person with psychosis or schizophrenia
- have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work. [2009]

## *Subsequent acute episodes*

### **9.7.10.4** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:

- oral antipsychotic medication (see recommendations 10.11.1.2- 10.11.1.13) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]

### **9.7.10.5** Offer family intervention to all families of people with psychosis or schizophrenia who live with or are in close contact with the service user (delivered as described in recommendation 9.7.10.3). This can be started either during the acute phase or later, including in inpatient settings. [2009]

## *Promoting recovery*

### **9.7.10.6** Offer family intervention to families of people with psychosis or schizophrenia who live with or are in close contact with the service user. Deliver family intervention as described in recommendation 9.7.10.3. [2009]

### **9.7.10.7** Family intervention may be particularly useful for families of people with psychosis or schizophrenia who have:

- recently relapsed or are at risk of relapse
- persisting symptoms. [2009]

## **9.7.11 Research recommendations**

### **9.7.11.1** For people with schizophrenia from black and minority ethnic groups living in the UK, does ethnically adapted family intervention for schizophrenia (adapted in consultation with black and minority ethnic groups to better suit different cultural and ethnic needs) enable more people in black and minority ethnic groups to engage with this therapy, and show concomitant reductions in patient relapse rates and carer distress? [2009]

**9.7.11.2** Research is needed to identify the competencies required to deliver effective family intervention to people with schizophrenia and their carers. [2009]

## **9.8 PSYCHODYNAMIC AND PSYCHOANALYTICAL THERAPIES**

### **9.8.1 Introduction**

**\*\*2009\*\*** Psychoanalysis and its derivatives, often termed psychoanalytic and psychodynamic psychotherapies, originate from the work of Freud in the first quarter of the 20th century. These approaches assume that humans have an unconscious mind where feelings that are too painful to face are often held. A number of psychological processes known as defences are used to keep these feelings out of everyday consciousness. Psychoanalysis and psychodynamic psychotherapy aim to bring unconscious mental material and processes into full consciousness so that the individual can gain more control over his or her life. These approaches were originally regarded as unsuitable for the treatment of the psychoses (Freud, 1964). However, a number of psychoanalysts have treated people with schizophrenia and other psychoses using more or less modified versions of psychoanalysis (Fromm-Reichmann, 1950; Stack-Sullivan, 1974). Psychoanalytically-informed approaches to psychotherapy continue to be accessed by people with schizophrenia today, though the actual psychoanalytic technique is rarely used (Alanen, 1997). Approaches tend to be modified to favour relative openness on the part of the therapist, flexibility in terms of content and mode of sessions, holding off from making interpretations until the therapeutic alliance is solid, and building a relationship based on genuineness and warmth while maintaining optimal distance (Gabbard, 1994).

RCTs were undertaken in the 1970s and 1980s to investigate the use of psychoanalytically-orientated psychotherapy. Research into the effects of psychoanalytic approaches in the treatment of schizophrenia has been repeated more recently, with mixed results (Fenton & McGlashan, 1995; Jones et al., 1998; Mari & Streiner, 2000), leading to the publication of a Cochrane Review on the subject (Malmberg et al., 2001).

#### ***Definition***

Psychodynamic interventions were defined as having:

- regular therapy sessions based on a psychodynamic or psychoanalytic model; and
- sessions that could rely on a variety of strategies (including explorative insight- orientated, supportive or directive activity), applied flexibly.

To be considered as well-defined psychodynamic psychotherapy, the intervention needed to include working with transference and unconscious processes.

Psychoanalytic interventions were defined as having:

- regular individual sessions planned to continue for at least 1 year; and

- analysts required to adhere to a strict definition of psychoanalytic technique.

To be considered as well-defined psychoanalysis, the intervention needed to involve working with the unconscious and early child/adult relationships.

## 9.8.2 Clinical review protocol

The review protocol, including information about the databases searched and the eligibility criteria used for this section of the guideline, can be found in Table 81. The primary clinical questions can be found in Box 1. A new systematic search for relevant RCTs, published since the 2002 guideline, was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).

## 9.8.3 Studies considered for review

In the 2002 guideline, three RCTs (N = 492) of psychodynamic and psychoanalytic therapies were included. The search for the 2009 guideline identified one new trial. In total, four RCTs (N = 558) met the inclusion criteria for the 2009 guideline. All of the trials were published in peer-reviewed journals between 1972 and 2003. In addition, one study identified in the search for the 2009 guideline was excluded from the analysis because of an inadequate method of randomisation (further information about both included and excluded studies can be found in Appendix 22c).

**Table 81: Clinical review protocol for the review of psychodynamic and psychoanalytic therapies**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Studydesign</i>	RCT (≥10 participants per arm)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Psychodynamic and psychoanalytic therapies
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Leaving the study early for any reason Adverse events

### **9.8.4 Psychodynamic and psychoanalytic therapies versus control**

For the 2009 guideline review, two RCTs of psychodynamic and psychoanalytic therapies versus any type of control were included in the meta-analysis.

Additionally, two trials included in the 2002 guideline directly compared the format of the intervention; one trial compared insight-orientated with reality-adaptive therapy and another trial compared individual with group therapy<sup>29</sup> (see Table 82 for a summary of the study characteristics). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### **9.8.5 Clinical evidence summary**

Only one new RCT was identified for the 2009 guideline review (DURHAM2003), which used a psychodynamic-based intervention as a comparator for CBT. The new study did not provide any evidence for the effectiveness of psychodynamic approaches in terms of symptoms, functioning or quality of life.

### **9.8.6 Linking evidence to recommendations**

In the 2002 guideline, the GDG found no clear evidence to support the use of psychodynamic and psychoanalytic therapies as discrete interventions. The limited evidence found for the 2009 guideline does not justify changing this conclusion. However the GDG did acknowledge the use of psychoanalytic and psychodynamic principles to help healthcare professionals understand the experience of people with schizophrenia and their interpersonal relationships, including the therapeutic relationship. Furthermore, the GDG noted that the majority of trials included in the review assessed the efficacy of classic forms of psychodynamic and psychoanalytic therapy. However, these approaches have evolved in recent years, partly in response to a lack of demonstrable efficacy when compared with other interventions in research trials. At present, the GDG are not aware of any well-conducted RCTs assessing the efficacy of newer forms of psychodynamic and psychoanalytic therapy. It is therefore the view of the GDG that further well-conducted research is warranted.

---

<sup>29</sup>Existing subgroups comparing psychodynamic and psychoanalytic therapies with standard care and other active treatments and psychodynamic therapy with group psychodynamic therapy were also updated. However, there was insufficient data to draw any conclusions based on these subgroups. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted



**Table 82: Summary of study characteristics for psychodynamic and psychoanalytic therapies**

	Psycho dynamic and psychoanalytic therapies versus any control	Insight-orientated therapy versus reality adaptive therapy	Individual therapy versus group therapy
<i>K (total N)</i>	2 (294)	1 (164)	1 (100)
<i>Study ID</i>	DURHAM2003 May1976	Gunderson1984	O'Brien1972
<i>Diagnosis</i>	100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM II or III)	100% schizophrenia Or other related diagnoses (DSMII or III)
<i>Baseline severity</i>	BPRS: Mean (SD) ~96 (17) DURHAM2003	Not reported	Not reported
<i>Length of treatment</i>	Range: 36–104weeks	Up to 2 years	20 months
<i>Length of follow-up</i>	Up to 3 months: DURHAM2003  Up to 5 years: May1976		
<i>Setting</i>	Inpatient: May1976  Inpatient and outpatient: DURHAM2003	Inpatient: Gunderson1984 <sup>a</sup>	Outpatient: O'Brien1972 <sup>b</sup>
<i>Note.</i> <sup>a</sup> Treatment was initiated in the inpatient setting and continued in a community setting up on discharge. <sup>b</sup> All participants were newly discharge			

## **9.8.7 Recommendations**

**9.8.7.1** Healthcare professionals may consider using psychoanalytic and psychodynamic principles to help them understand the experiences of people with psychosis or schizophrenia and their interpersonal relationships. [2009]

## **9.8.8 Research recommendations**

**9.8.8.1** A pilot RCT should be conducted to assess the efficacy of contemporary forms of psychodynamic therapy when compared with standard care and other active psychological and psychosocial interventions. [2009]

# **9.9 PSYCHOEDUCATION**

## **9.9.1 Introduction**

Psychoeducation, in its literal definition, implies provision of information and education to a service user with a severe and enduring mental illness, including schizophrenia, about the diagnosis, its treatment, appropriate resources, prognosis, common coping strategies and rights (Pekkala & Merinder, 2002).

In his recent review of the NHS, Darzi (2008) emphasised the importance of ‘empowering patients with better information to enable a different quality of conversation between professionals and patients’. Precisely what and how much information a person requires, and the degree to which the information provided is understood, remembered or acted upon, will vary from person to person. Frequently, information giving has to be ongoing. As a result, psychoeducation has now been developed as an aspect of treatment in schizophrenia with a variety of goals over and above the provision of accurate information. Some psychoeducation involves quite lengthy treatment and runs into management strategies, coping techniques and role-playing skills. It is commonly offered in a group format. The diversity of content and information covered, as well as the formats of delivery, vary considerably, so that psychoeducation as a discrete treatment can overlap with family intervention, especially when families and carers are involved in both. Desired outcomes in studies have included improvements in insight, treatment adherence, symptoms, relapse rates, and family knowledge and understanding (Pekkala & Merinder, 2002).

### ***Definition***

Psychoeducational interventions were defined as:

- any programme involving interaction between an information provider and service users or their carers, which has the primary aim of offering information about the condition; and
- the provision of support and management strategies to service users and carers.

To be considered as well defined, the educational strategy should be tailored to the need of individuals or carers.

## 9.9.2 Clinical review protocol

The review protocol, including information about the databases searched and the eligibility criteria used for this section of the guideline, can be found in Table 83. The primary clinical questions can be found in Box 1. A new systematic search for relevant RCTs, published since the 2002 guideline, was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).

**Table 83: Clinical review protocol for the review of psychoeducation**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT ( $\geq 10$ participants per arm and $\geq 6$ weeks' duration)
<i>Patient population</i>	Adults (18+) with schizophrenia (schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Psychoeducation
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Leaving the study early for any reason

## 9.9.3 Studies considered for review

In the 2002 guideline, ten RCTs ( $N = 1,070$ ) of psychoeducation were included. The search for the 2009 guideline identified three papers providing follow-up data to existing trials and ten new trials. In the 2002 guideline, one study (Posner1992) included in the family intervention review was reclassified as psychoeducation for the 2009 guideline. In total, 21 trials ( $N = 2,016$ ) met the inclusion criteria for the 2009 guideline review. All were published in peer-reviewed journals between 1987 and 2008 (further information about both included and excluded studies can be found in Appendix 22c).

## 9.9.4 Psychoeducation versus control

For the 2009 guideline, four of the included studies (Jones2001; SIBITZ2007; Smith1987; XIANG2007) only included a direct comparison of different types of psychoeducation and one trial (AGARA2007) did not provide any useable data, so 16 trials of psychoeducation versus any type of control were included in the meta-

analysis (see Table 84 for a summary of the study characteristics). Subgroup analyses were used to examine the impact of the type of comparator (eight trials used standard care as the comparator and eight trials used another active treatment<sup>30</sup>). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### **9.9.5 Clinical evidence summary**

There is no new robust evidence for the effectiveness of psychoeducation on any of the critical outcomes. In particular, there are no new UK-based RCTs meeting the GDG's definition of psychoeducation.

### **9.9.6 Linking evidence to recommendations**

In the 2002 guideline, the GDG found it difficult to distinguish psychoeducation from the provision of good-quality information as required in standard care, and from good-quality family engagement, where information is provided with family members also present. There is clearly an overlap between good standard care and psychoeducation, and between psychoeducation and family intervention. It is noteworthy that most of the studies reviewed did not take place in the UK, and the nature and quality of the information provision in standard care may differ from services in the UK setting. The evidence found for the 2009 guideline does not justify making a recommendation.

---

<sup>30</sup>Existing subgroup comparisons exploring the country of the trial, format of the intervention, number of treatment sessions, duration of treatment and patient characteristics were also updated. However, there was insufficient data to draw any conclusions based on these subgroups. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted.

**Table 84: Summary of study characteristics for psychoeducation**

	Psychoeducation versus any control	Psychoeducation versus standard care	Psychoeducation versus other active treatments
<i>K (total N)</i>	16 (1610)	8 (966)	8 (644)
<i>Study ID</i>	Atkinson1996 Bauml1996 BECHDOLF2004 CATHER2005 CHABANNES2008 CHAN2007A CunninghamOwens2001 Hayashi2001 Hornung1995 <sup>a</sup> Lecompte1996 Macpherson1996 Merinder1999 Posner1992 SHIN2002 VREELAND2006 XIANG2006	Atkinson1996 Bauml1996 CHABANNES2008 CunninghamOwens2001 Hayashi2001 Macpherson1996 Posner1992 VREELAND2006	BECHDOLF2004 CATHER2005 CHAN2007A Hornung1995 <sup>a</sup> Lecompte1996 Merinder1999 SHIN2002 XIANG2006
<i>Diagnosis</i>	100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)

**Table 84: (Continued)**

	Psychoeducation versus any control	Psychoeducation versus standard care	Psychoeducation versus other active treatments
Baseline severity	<i>BPRS total:</i> Mean (SD) range: ~29 (7) to ~92 (8)  <i>PANSS total:</i> Mean (SD) range: ~14 (5) to ~51 (13)	Not reported	<i>BPRS total:</i> Mean (SD) range: ~29 (7) to ~92 (8)  <i>PANSS total:</i> Mean (SD) range: ~14 (5) to ~51 (13)
Length of treatment	<i>Range:</i> 2– 52 weeks	<i>Range:</i> 4– 52 weeks	<i>Range:</i> 2–16 weeks
Length of follow-up	<i>Range:</i> 3–60months	<i>Range:</i> 3–24months	<i>Range:</i> 12–60months
Setting	<i>Inpatient:</i> BECHDOLF2004 CHAN2007A CunninghamOwens2001 <sup>b</sup> Hayashi2001 VREELAND2006	<i>Inpatient:</i> CunninghamOwens2001 <sup>b</sup> Hayashi2001 VREELAND2006	<i>Inpatient:</i> BECHDOLF2004 CHAN2007A
	<i>Outpatient:</i> Atkinson1996 Bauml1996 CATHER2005 Hornung1995 <sup>a</sup> Macpherson1996 Merinder1999 Posner1992 SHIN2002 XIANG2006  <i>Inpatient and outpatient:</i> CHABANNES2008	<i>Outpatient:</i> Atkinson1996 Bauml1996 Macpherson1996 Posner1992  <i>Inpatient and outpatient:</i> CHABANNES2008	<i>Outpatient:</i> CATHER2005 Hornung1995 <sup>a</sup> Merinder1999 SHIN2002 XIANG2006
<i>Note.</i> <sup>a</sup> Multi-modal intervention. <sup>b</sup> Participants were recruited as inpatients prior to discharge.			

## 9.10 SOCIAL SKILLS TRAINING

### 9.10.1 Introduction

An early psychological approach to the treatment of schizophrenia involved the application of behavioural theory and methods with the aim of normalising behaviour (Ayllon & Azrin, 1965), improving communication or modifying speech (Lindsley, 1963). Given the complex and often debilitating behavioural and social effects of schizophrenia, social skills training was developed as a more sophisticated treatment strategy derived from behavioural and social learning traditions (see Wallace and colleagues (1980) for a review). It was designed to help people with schizophrenia regain their social skills and confidence, improve their ability to cope in social situations, reduce social distress, improve their quality of life and, where possible, to aid symptom reduction and relapse prevention.

Social skills training programmes begin with a detailed assessment and behavioural analysis of individual social skills, followed by individual and/or group interventions using positive reinforcement, goal setting, modelling and shaping. Initially, smaller social tasks (such as responses to non-verbal social cues) are worked on, and gradually new behaviours are built up into more complex social skills, such as conducting a meaningful conversation. There is a strong emphasis on homework assignments intended to help generalise newly learned behaviour away from the treatment setting.

Although this psychosocial treatment approach became very popular in the US and has remained so (for example, (Bellack, 2004)) since the 1980s it has had much less support in the UK, at least in part as a result of doubts in the UK about the evidence of the capacity of social skills training to generalise from the treatment situation to real social settings (Hersen & Bellack, 1976; Shepherd, 1978). No new studies, therefore, have been conducted of social skills training in the UK. Instead, the evidence base is largely derived from North America and, increasingly, from China and Southeast Asia.

#### *Definition*

Social skills training was defined as:

- a structured psychosocial intervention (group or individual) that aims to:
  - enhance social performance, and
  - reduce distress and difficulty in social situations.

The intervention must:

- include behaviourally-based assessments of a range of social and interpersonal skills, and
- place importance on both verbal and non-verbal communication, the individual's ability to perceive and process relevant social cues, and respond to and provide appropriate social reinforcement.

### 9.10.2 Clinical review protocol

A new systematic search for relevant RCTs published since the 2002 guideline was conducted for the 2009 guideline. Information about the databases searched and the eligibility criteria used for this section of the guideline can be found in Table 85 (further information about the search strategy can be found in Appendix 20).

### 9.10.3 Studies considered for review

In the 2002 guideline, nine RCTs (N = 436) of social skills training were included. One RCT from the 2002 guideline (Finch1977) was removed from the 2009 guideline analysis because of inadequate numbers of participants, and one RCT (Eckmann1992) was reclassified as social skills training and included in the analysis. The search for the 2009 guideline identified 14 new trials. In total, 23 trials (N = 1,471) met the inclusion criteria for the 2009 guideline. All were published in peer-reviewed journals between 1983 and 2007 (further information about both included and excluded studies can be found in Appendix 22c).

**Table 85: Clinical review protocol for the review of social skills training**

<i>Electronic databases</i>	Databases: CINAHL, CENTRAL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	RCT ( $\geq 10$ participants per arm and $\geq 6$ weeks' duration)
<i>Patient population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60) Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse
<i>Interventions</i>	Social skills training
<i>Comparator</i>	Any alternative management strategy
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse, rehospitalisation) Mental state (total symptoms, depression) Psychosocial functioning Quality of life Leaving the study early for any reason Adverse events



### 9.10.4 Social skills training versus control

For the 2009 guideline review, one of the included studies (GLYNN2002) only included a direct comparison of different types of social skills and two trials (GUTRIDE1973, KERN2005) did not provide any useable data for any of the critical outcomes listed in the review protocol. Thus, in total 20 trials of social skills training versus any type of control were included in the meta-analysis (see Table 86 for a summary of the study characteristics). Subgroup analyses were used to examine the impact of the type of comparator<sup>31</sup> (ten trials used standard care as the comparator and ten trials used another active treatment). Forest plots and/or data tables for each outcome can be found in Appendix 23d.

### 9.10.5 Clinical evidence summary

The review found no evidence to suggest that social skills training is effective in improving the critical outcomes. None of the new RCTs were UK based, with most new studies reporting non-significant findings. There was limited evidence for the effectiveness of social skills training on negative symptoms. However this evidence is primarily drawn from non-UK studies and is largely driven by one small study (RONCONE2004) that contains multiple methodological problems.

### 9.10.6 Linking evidence to recommendations

In the 2002 guideline, the GDG found no clear evidence that social skills training was effective as a discrete intervention in improving outcomes in schizophrenia when compared with generic social and group activities, and suggested that the evidence shows little if any consistent advantage over standard care. It is noteworthy that although a review published since the 2002 guideline (Kurtz & Mueser, 2008) indicated effects for social functioning, symptom severity and relapse, this may be attributed to the inclusion of a number of studies that are beyond the scope of the current definition of social skills used in the present review. In particular, a number of papers were included that assessed vocational and supported employment-based interventions. Consequently, the evidence found for the 2009 guideline does not justify changing the conclusions drawn in the 2002 guideline.

### 9.10.7 Recommendations

**9.10.7.1** Do not routinely offer social skills training (as a specific intervention) to people with psychosis or schizophrenia. [2009]\*\*2009\*\*

---

<sup>31</sup>Existing subgroup comparisons exploring the duration of treatment and treatment setting were also updated. However, there was insufficient data to draw any conclusions based on these subgroups. Please refer to Appendix 23d for the forest plots and/or data tables for all subgroup comparisons conducted

**Table 86: Summary of study characteristics for social skills training**

	<b>Social skills training versus any control</b>	<b>Social skill straining versus standard care</b>	<b>Social skills training versus other active treatments</b>
<i>K (total N)</i>	20 (1215)	10 (541)	10 (674)
<i>Study ID</i>	Bellack1994 BROWN1983 CHIEN2003 CHOI2006 Daniels1998 Dobson1995 Eckmann1992 GRANHOLM2005 <sup>a</sup> Hayes1995 Lieberman1998 Lukoff1986 <sup>a</sup> Marder1996 NG2007 PATTERSON2003 PATTERSON2006 PINTO1999 <sup>a</sup> Peniston1988 RONCONE2004 UCOK2006 VALENCIA2007 <sup>a</sup>	Bellack1984 CHIEN2003 CHOI2006 Daniels1998 GRANHOLM2005 <sup>a</sup> PATTERSON2003 Peniston1988 RONCONE2004 UCOK2006 VALENCIA2007 <sup>a</sup>	BROWN1983 Dobson1995 Eckmann1992 Hayes1995 Lieberman1998 Lukoff1986 Marder1996 NG2007 PATTERSON2006 PINTO1999 <sup>a</sup>

**Table 86: (Continued)**

	<b>Social skills training versus any control</b>	<b>Social skills training versus standard care</b>	<b>Social skills training versus other active treatments</b>
<i>Diagnosis</i>	100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)	100% schizophrenia or other related diagnoses (DSM or ICD-10)
<i>Baseline severity</i>	<p><i>BPRS total:</i>  Mean (SD) ~47 (10)  Hayes1995  Mean (SD) ~40 (10)  NG2007  Mean (SD) ~82 (21)  PINTO1999<sup>a</sup>  Mean (SD) ~41 (7)  UCOK2006</p> <p><i>PANSS total:</i>  Mean (SD) ~54 (14)  GRANHOLM2005<sup>a</sup>  Mean (SD) ~61 (3)  PATTERSON2006</p>	<p><i>BPRS total:</i>  Mean (SD) ~ 41 (7)  UCOK2006</p> <p><i>PANSS total:</i>  Mean (SD) ~54 (14)  GRANHOLM2005<sup>a</sup>  Mean (SD) ~ 112 (27)  VALENCIA2007<sup>a</sup></p>	<p><i>BPRS total:</i>  Mean (SD) ~47 (10)  Hayes1995  Mean (SD) ~40 (10)  NG2007  Mean (SD) ~82 (21)  PINTO1999<sup>a</sup></p> <p><i>PANSS total:</i>  Mean (SD) ~61 (3)  PATTERSON2006</p>

<i>Length of treatment</i>	Range: 4–104 weeks	Range: 4–52 weeks	Range: 8–104 weeks
<i>Length of follow-up</i>	<p>Up to 12 months: Bellack1984 CHIEN2003 Hayes1995 PATTERSON2003 PATTERSON2006</p> <p>Up to 24 months: Lieberman1998 Lukoff1986</p>	<p>Up to 12 months: Bellack1984 CHIEN2003 PATTERSON2003</p>	<p>Up to 12 months: Hayes1995 PATTERSON2006</p> <p>Up to 24 months: Lieberman1998 Lukoff1986</p>
<i>Setting</i>	<p><i>Inpatient:</i> BROWN1983 CHIEN2003 Lukoff1986 NG2007 Peniston1988 RONCONE2004</p> <p><i>Outpatient:</i> CHOI2006 GRANHOLM2005<sup>a</sup> Lieberman1998</p>	<p><i>Inpatient:</i> CHIEN2003 Peniston1988 RONCONE2004</p> <p><i>Outpatient:</i> CHOI2006 GRANHOLM2005<sup>a</sup> UCOK2006</p>	<p><i>Inpatient:</i> BROWN1983 Lukoff1986 NG2007</p> <p><i>Outpatient:</i> Lieberman1998 Marder1996</p>

	Marder1996 UCOK2006 VALENCIA2007 <sup>a</sup>  <i>Inpatient and outpatient:</i> Daniels1998 Eckmann1992 Hayes1995 PINTO1999 <sup>a</sup>  <i>Other<sup>b</sup>:</i> Bellack1984 Dobson1995 PATTERSON2003	VALENCIA2007 <sup>a</sup>  <i>Inpatient and outpatient:</i> Daniels1998  <i>Other<sup>b</sup>:</i> Bellack1984 PATTERSON2003	<i>Inpatient and outpatient:</i> Eckmann1992 Hayes1995 PINTO1999 <sup>a</sup>  <i>Other<sup>b</sup>:</i> Dobson1995 PATTERSON2006
Note. <sup>a</sup> Multi-modal interventions. <sup>b</sup> Other settings include board and care facilities, and day hospitals			

## 9.11 PSYCHOLOGICAL MANAGEMENT OF TRAUMA IN PSYCHOSIS AND SCHIZOPHRENIA

### 9.11.1 Introduction

There has been a growing interest in the relationship between psychosis (including schizophrenia) and trauma over the last decade. Studies of individuals who have experienced psychosis and schizophrenia have found that between 50 and 98% report having being exposed to at least one traumatic event in their lives (Read et al., 2005).

A recent review discussing childhood adversity and mental health problems suggests that factors related to the mother (for example, high levels of stress during pregnancy, poor nutrition, and mother's ill health), as well as childhood adversity, can have a negative impact on an individual's future mental health (Read & Bentall, 2012). Investigating early adversity, Morgan et al (2007) found that loss of a parent through separation or death in young people under the age of 16 years was associated with an increased risk of psychosis. A review by Read et al (2005) demonstrated there was a strong relationship between those people who had experienced physical and sexual abuse as children and the presence of symptoms of schizophrenia. In a Dutch prospective study, Janssen et al (2004) controlled for a number of potential variables including substance misuse and a family history of psychosis, and found that those who had been subjected to any form of childhood abuse were over seven times more likely to experience psychosis. A number of studies have found a 'dose response', with more severe or enduring abuse increasing the risk of developing psychosis. This was clearly illustrated in a study by Shevlin et al (2008) that found that the likelihood of developing psychosis increased as the number of traumatic experiences to which an individual had been exposed also increased. Those who had experienced five or more types of trauma were 198 times more likely to have a diagnosis of psychosis than those who had not experienced any adversity.

Varese et al (2012) examined the relationship between psychosis and childhood adversity (physical, sexual and emotional abuse, neglect, bullying and parental death or separation) by conducting a meta-analysis that included 36 studies ( $n = 79,397$ ). A significant association was found between the two, with an odds ratio of 2.78. Based on their findings the authors stated that if these particular forms of childhood adversity were eliminated, cases of psychosis would be reduced by a third. The authors also investigated the severity of the trauma and its relationship with psychosis. Nine out of ten of the studies that had researched a so-called 'dose effect' had found this, revealing that the likelihood of psychosis increases the more severe or prolonged the exposure to adversity. Trauma within this population is not restricted to childhood: incidence of assaults in adulthood are also elevated: up to 59% of individuals report sexual assault and up to 87% report physical assault (Grubaugh et al., 2011).

Not all adversity, however intolerable the subjective experience, fulfils diagnostic criteria to be classed as a 'trauma'. The objective definition of what does and does not constitute a trauma evidently impacts on what symptoms can be classified as part of a genuine post-traumatic stress disorder. Despite this, the prevalence of PTSD in those diagnosed with a psychotic disorder ranges from 12 to 29% (Achim et al., 2011; Buckley et al., 2009), which is a much higher rate than in the general population where prevalence is estimated to be between 0.4 and 3.5% (Alonso et al., 2004; Creamer et al., 2001; Darves-Bornoz et al., 2008). It has been suggested that there are similarities in vulnerability to PTSD and schizophrenia as a result of the cognitive processing of traumatic events, and the way in which information is processed and stored (Steel, 2011).

One issue that is commonly raised is that of the reliability of disclosures of childhood abuse among those with psychosis. Studies investigating this found corroborating evidence for reports of childhood sexual abuse by psychiatric patients in 74% (Herman & Schatzow, 1987) and 82% (Read et al., 2003). One study that focused specifically on the reports of those with a diagnosis of schizophrenia, found that the problem of false allegations of sexual assault was no different than in the general population (Darves-Bornoz et al., 1995).

### *Current practice*

Though not all of those presenting with psychosis or schizophrenia will have been exposed to early adversity, the significance of the relationship between them means there is a high likelihood that there will be a history of trauma. Currently, however, the question of what constitutes appropriate help for those with psychosis and schizophrenia with a history of trauma is unclear. NICE guidance recommends trauma-focused CBT (including prolonged exposure) and eye movement desensitisation and reprocessing (EMDR) as safe and effective interventions for those with PTSD. Unfortunately because people with psychotic disorders are often excluded from PTSD research trials, there is insufficient evidence to demonstrate whether these particular interventions are equally safe and effective in this population.

Nevertheless, service users presenting with psychosis and schizophrenia who have trauma histories have not been excluded from trials testing the efficacy of CBT for psychotic disorders. Moreover, no adverse effects or differences in outcomes have been reported for this particular group within these trials.

### *Definition and aim of intervention*

The aim of this review was to evaluate the effectiveness and safety of psychological interventions for trauma in a population of people with psychosis and schizophrenia.

Psychological interventions were included if they aimed to reduce PTSD symptoms or other related distress. PTSD symptoms could be a result of life events, a reaction

to psychosis symptoms, or trauma as a result of experiencing a first episode psychosis.

### 9.11.2 Clinical review protocol (psychological management of trauma)

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 87 (a complete list of review questions and protocols can be found in Appendix 6; further information about the search strategy can be found in Appendix 13.

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 87: Clinical review protocol for the review of psychological management of trauma**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of psychological management strategies for previous trauma compared to treatment as usual or another intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of psychological interventions for trauma for people with psychosis and schizophrenia.
<i>Population</i>	<b>Included</b> Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Psychological interventions for trauma
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>Anxiety symptoms (including PTSD)</li> <li>Depression symptoms</li> <li>Symptoms of psychosis <ul style="list-style-type: none"> <li>Total symptoms</li> <li>Positive symptoms</li> <li>Negative symptoms</li> </ul> </li> <li>Response / Relapse <ul style="list-style-type: none"> <li>Relapse (as defined in study)</li> <li>Response (improvement in symptoms)</li> </ul> </li> <li>Dropout (proxy measure for acceptability) <ul style="list-style-type: none"> <li>Withdrawal due to adverse event</li> <li>Loss to follow-up, any reason</li> </ul> </li> </ul>
<i>Electronic databases</i>	Core: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, PreMEDLINE Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	<ul style="list-style-type: none"> <li>RCT: database inception to June 2013</li> <li>SR: 1995 to June 2013</li> </ul>
<i>Review strategy</i>	<b>Time-points</b> <ul style="list-style-type: none"> <li>End of treatment</li> <li>Up to 6 months' follow-up (short-term)</li> <li>7-12 months' follow-up (medium-term)</li> </ul>



	<ul style="list-style-type: none"> <li>12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings</p> <p><b>Sub-analysis</b> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>
--	---

### 9.11.3 Studies considered<sup>32</sup>

One RCT (N = 66) met the eligibility criteria for this review: JACKSON2009 (Jackson et al., 2009). Further information about the included and excluded studies can be found in Appendix 15a.

The single included trial had sufficient data to be included in the statistical analysis. This trial involved a comparison between cognitive therapy-based recovery intervention (CRI) plus treatment as usual (case management and antipsychotic medication) compared with treatment as usual alone for the treatment of first episode psychosis-related trauma. Table 88 provides an overview of the included trial.

**Table 88: Study information table for trials comparing psychological trauma interventions with any alternative management strategy**

	Psychological management of trauma versus any alternative management strategy
<i>Total no. of trials (k); participants (N)</i>	k = 1; (N = 66)
<i>Study ID</i>	JACKSON2009
<i>Country</i>	UK
<i>Year of publication</i>	2009
<i>Mean Age of participants</i>	23.3 years
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	100%
<i>Mean gender % women</i>	25.7%
<i>Length of treatment</i>	26 weeks
<i>Length of follow-up</i>	6 months JACKSON2009
<i>Intervention type</i>	Cognitive therapy-based recovery intervention (CRI) plus TAU (k = 1)
<i>Comparisons</i>	Case management and antipsychotic medication (k = 1)

<sup>32</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

### 9.11.4 Clinical evidence for psychological management of trauma

Evidence from each important outcome and overall quality of evidence are presented in Table 89. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

**Table 89: Summary of findings table for cognitive therapy-based recovery intervention compared with treatment as usual**

Patient or population: Adults with psychosis and schizophrenia with trauma					
Intervention: Cognitive therapy + TAU					
Comparison: TAU					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TAU	Cognitive therapy + TAU			
Anxiety symptoms - end of intervention	N/A	The mean anxiety symptoms, end of intervention in the intervention groups was 0.34 standard deviations lower (0.93 lower to 0.24 higher)	N/A	46 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Anxiety symptoms - up to 6 months' follow-up	N/A	The mean anxiety symptoms, up to 6 months' follow-up in the intervention groups was 0.47 standard deviations lower (1.06 lower to 0.11 higher)	N/A	46 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Depression symptoms - end of intervention	N/A	The mean depression symptoms, end of intervention in the intervention groups was 0.29 standard deviations lower (0.87 lower to 0.3 higher)	N/A	46 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Depression symptoms - up to 6 months' follow-up	N/A	The mean depression symptoms, up to 6 months' follow-up in the intervention groups was 0.05 standard deviations lower (0.63 lower to 0.52 higher)	N/A	46 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Missing data, any reason - end of intervention	Study population		RR 1.94 (0.85 to 4.43)	66 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	200 per 1000	388 per 1000 (170 to 886)			
	200 per 1000	388 per 1000 (170 to 886)			
Missing data, any reason - up to 6 months' follow-up	Study population		RR 1.94 (0.85 to 4.43)	66 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	200 per 1000	388 per 1000 (170 to 886)			
	200 per 1000	388 per 1000 (170 to 886)			
<i>Note.</i> CI = confidence interval; RR = risk ratio; TAU = treatment as usual					
*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
<sup>1</sup> Studies included at moderate risk of bias.					
<sup>2</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).					

Low quality evidence from one study with 46 participants showed no significant difference between CRI and TAU in anxiety or depression symptoms at the end of the intervention or at 6 months' follow-up. There was no statistically significant difference between CRI and TAU in the number of participants who dropped out of the study although a trend showing fewer dropouts in the TAU arm was observed. No data were available for the critical outcomes of psychosis symptoms, or relapse and response rates.

### 9.11.5 Clinical evidence summary

Overall there is inconclusive evidence concerning the efficacy of the psychological management of trauma and a specific cognitive therapy-based recovery intervention for the treatment of trauma in people with first episode psychosis. In addition, although this review found no statistically significant difference between the active intervention and control in dropouts from the intervention, a trend favouring the control arm was observed suggesting that the intervention may not have been well tolerated. However, due to the limited evidence, and lack of trials evaluating other interventions in this population, no firm conclusions can be drawn.

### 9.11.6 Health economics evidence

No studies assessing the cost effectiveness of psychological interventions for trauma in adults with psychosis and schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

### 9.11.7 Linking evidence to recommendations

#### *Relative value placed on the outcomes considered:*

The GDG decided to focus on the following, which were considered to be critical:

For trauma-focused symptoms:

- Anxiety symptoms (including PTSD)
- Depression symptoms

To evaluate if psychological intervention for trauma was contraindicated in a population of people with psychosis and schizophrenia:

- Symptoms of psychosis (total, positive, negative)
- Response/relapse

To evaluate the acceptability of the intervention:

- Dropout (for any reason)

#### *Trade-off between clinical benefits and harms:*

In people with psychosis and schizophrenia who are experiencing trauma-related symptoms, the GDG considered that it was important to assess the potential harms of psychological interventions for trauma. The GDG judged that the evidence did not show any benefit of psychological interventions for trauma in this population but importantly did not observe any indication of harm. However, the latter was as a result of a lack of data and thus there is still come uncertainty about the effects of these interventions on symptoms of psychosis and schizophrenia.

#### *Trade-off between net health benefits and resource use:*

There were no health economic studies that attempted to assess the cost effectiveness associated with psychological interventions for trauma in a population of people

with psychosis and schizophrenia. Due to the lack of clinical data pertaining to the response and relapse rates, and effects of these interventions on symptoms of psychosis and schizophrenia, it was decided that formal economic modelling of such interventions in this area would not be useful in decision-making. The study included in clinical review point to a resource use that is more intensive than usual care (that is, intervention was provided in addition to usual care), which implies that such psychological interventions for trauma in a population of people with psychosis and schizophrenia is likely to be more costly than usual care. However, this does not exclude the possibility of such interventions being cost effective when compared to usual care since the clinical evidence is inconclusive and even small differences in effects and costs could potentially result in a cost-effective intervention.

### *Quality of the evidence*

The quality of the evidence was low. The two reasons for downgrading the evidence were: (1) potential risk of bias in the single included trial and (2) moderate imprecision in the results. The available evidence was directly applicable to the population of interest but the inclusion of only a single trial meant that the GDG could not consider issues around inconsistency. The GDG thought that there was a lack of published research in this topic area and thus could not be certain of the presence of publication bias.

### *Other considerations*

The GDG felt that it was of crucial importance that symptoms of trauma are identified and assessed in first episode psychosis in order to identify those who may be experiencing intrusions as a result of first episode psychosis and this should be reflected in recommendations. The GDG discussed the need for improved access to PTSD services for people with psychosis and schizophrenia. The GDG felt this was especially important for those experiencing first episode psychosis. The GDG thought that as there was no evidence that a psychological intervention for trauma was contraindicated in people experiencing first episode psychosis therefore recommendations in the PTSD guideline were applicable to people with psychosis and schizophrenia.

## **9.11.8 Recommendations**

- 9.11.8.1** Assess for post-traumatic stress disorder and other reactions to trauma because people with psychosis or schizophrenia are likely to have experienced previous adverse events or trauma associated with the development of the psychosis or as a result of the psychosis itself. For people who show signs of post-traumatic stress, follow the recommendations in [Post-traumatic stress disorder](#) (NICE clinical guideline 26). [new 2014]

## **9.12\*\*2009\*\*RECOMMENDATIONS (ACROSS ALL TREATMENTS)<sup>33</sup>**

### **9.12.1 Principles in the provision of psychological therapies**

**9.12.1.1** When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including service user satisfaction and, if appropriate, carer satisfaction. [2009]

**9.12.1.2** Healthcare teams working with people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review:

- access to and engagement with psychological interventions
- decisions to offer psychological interventions and equality of access across different ethnic groups. [2009]

**9.12.1.3** Healthcare professionals providing psychological interventions should:

- have an appropriate level of competence in delivering the intervention to people with psychosis or schizophrenia
- be regularly supervised during psychological therapy by a competent therapist and supervisor. [2009]

**9.12.1.4** Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological therapy interventions recommended in this guideline. [2009]\*\*2009\*\*

### **9.12.2 Research recommendation**

**9.12.2.1** What is the clinical and cost effectiveness of psychological intervention alone, compared with treatment as usual, in people with psychosis or schizophrenia who choose not to take antipsychotic medication?( See Appendix 10 for further details) [2014]

**9.12.2.2** What is the benefit of a CBT-based trauma reprocessing intervention on PTSD symptoms in people with psychosis and schizophrenia (See Appendix 10 for further details) [2014]

---

<sup>33</sup>Recommendations for specific interventions can be found at the end of each review (see the beginning of this chapter for further information).

# 10 PHARMACOLOGICAL INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA

This chapter has been partially updated. Most sections remain unchanged from the 2009 guideline; however some of the recommendations have been updated to bring them in line with the recommendations from *Psychosis and Schizophrenia in Children and Young People*. This was considered necessary to avoid discrepancies between the child and adult guidelines, particularly regarding early intervention. Consequently new sections have been added to the evidence to recommendations section. In addition some recommendations from the 2009 guideline have been amended to improve the wording and structure with no important changes to the context and meaning of the recommendation.

Sections of the guideline where the evidence has not been updated since 2002 are marked as **\*\*2002\*\*\_\*\*2002\*\*** and where the evidence has not be updated since 2009, marked by asterisks (**\*\*2009\*\*\_\*\*2009\*\***).

Please note that all references to study IDs in sections that have not been updated in this chapter can be found in Appendix 22b.

**\*\*2009\*\*** The term ‘first-generation antipsychotics’ (FGAs) is used to refer to drugs that in the 2003 guideline were called ‘conventional’ or ‘typical’ antipsychotics. Likewise, the term ‘second-generation antipsychotics’ (SGAs) is used to refer to drugs that were called ‘atypical’ antipsychotics in the 2003 guideline. This terminology is used here because it is widely used in the literature; it should not be taken to suggest that FGAs and SGAs represent distinct classes of antipsychotics (see Section 10.4.1 for further discussion of this issue).

For this chapter, there view of evidence is divided into the following areas:

- initial treatment with oral antipsychotic medication (Section 10.2)
- oral antipsychotics in the treatment of the acute episode Section 10.3
- promoting recovery in people with schizophrenia that is in remission – pharmacological relapse prevention (Section 10.4)
- promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (Section 10.5)
- combining antipsychotic medication with another antipsychotic (Section 10.5.10)
- treatment with depot/long-acting injectable antipsychotic medication (Section 10.6)

- side effects of antipsychotic medication, focusing on metabolic and neurologic adverse events – these were considered a priority by the GDG and were also highlighted as areas of concern by service users (Section 10.7)
- effectiveness of antipsychotic medication (Section 10.8)
- health economics (Section 10.9).

Because of the nature of the evidence, all recommendations can be found in Section 10.11 at the end of the chapter (rather than after each subsection), preceded by Section 10.10 (linking evidence to recommendations) that draws together the clinical and health economic evidence and provides a rationale for the recommendations.

## 10.1 INTRODUCTION

Antipsychotic drugs have been the mainstay of treatment of schizophrenia since the 1950s. Initially used for the treatment of acute psychotic states, their subsequent use to prevent relapse led to these drugs being prescribed for long-term maintenance treatment, either as oral preparations or in the form of long-acting injectable preparations ('depots').

Although a number of different classes of drugs have antipsychotic activity, the primary pharmacological action of antipsychotic drugs is their antagonistic effect on the D2 dopamine receptors. Indeed, the potency of a drug's antipsychotic effect is at least in part determined by its affinity for the D2 receptor (Agid et al., 2007; Kapur & Remington, 2001; Snyder et al., 1974), an association that informed the dopamine hypothesis of schizophrenia. It is worth noting, however, that antipsychotic drugs are also of use in the treatment of other psychotic disorders, their dopamine-blocking activity probably again being central to their pharmacological efficacy.

### *Uses of antipsychotics*

In the treatment and management of schizophrenia, antipsychotics are currently used for the treatment of acute episodes, for relapse prevention, for the emergency treatment of acute behavioural disturbance (rapid tranquillisation) and for symptom reduction. They are available as oral, intramuscular (IM) and intravenous (IV) preparations, or as medium- or long-acting depot IM preparations. In the UK, clozapine is only licensed for use in people with 'treatment-resistant' schizophrenia, defined by the manufacturers' Summary of Product Characteristics (SPC) as a 'lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration'.

Antipsychotics are usually prescribed within the recommended SPC dosage range and there is little evidence to support the use of higher dosage or combination with another antipsychotic if monotherapy proves to be ineffective (Royal College of Psychiatrists, 2006; Stahl, 2004). Antipsychotics are also used in combination with a range of other classes of drugs, such as anticonvulsants, mood stabilisers,

anticholinergics, antidepressants and benzodiazepines. Clinicians may augment antipsychotics with such drugs for several reasons:

- where there is a lack of effective response to antipsychotics alone
- for behavioural control
- for the treatment of the side effects of antipsychotics
- for the treatment of comorbid or secondary psychiatric problems, such as depression and anxiety.

Although such augmentation strategies are commonly used in clinical practice, they are outside the scope of this guideline. It is anticipated that a future guideline will address the evidence base for these interventions.

### *Antipsychotic dose*

The current British National Formulary (BNF) is the most widely used reference for the prescription of medicines and the pharmacy industry within the UK, and a complete SPC for all the drugs referred to in this guideline can be found in the Electronic Medicines Compendium (<http://emc.medicines.org.uk/>). The recommended dose ranges listed in the BNF normally echo the information contained in the manufacturers' SPC, as well as advice from an external panel of experts to ensure that the SPC recommendations on issues such as dose range reflect current good practice ('standard dosing'). 'Standard doses' are identified as doses that fall within the range likely to achieve the best balance between therapeutic gain and dose-related adverse effects. However, with up to a third of people with schizophrenia showing a poor response to antipsychotic medication, there has been a tendency for higher doses to be prescribed: surveys of prescribing practice suggest that doses of antipsychotics exceeding BNF limits, either for a single drug or through combining antipsychotics, continue to be commonly used (Harrington et al., 2002; Lehman & Steinwachs, 1998; Paton et al., 2008).

In an attempt to increase the rate or extent of response, 'loading doses' and rapid dose escalation strategies have been employed (Kane & Marder, 1993); studies have failed to show any advantage for such a strategy in terms of speed or degree of treatment response (Dixon et al., 1995). The Schizophrenia Patient Outcomes Research Team (1998) concluded that in the treatment of acute episodes of schizophrenia 'massive loading doses of antipsychotic medication, referred to as "rapid neuroleptization," should not be used'.

Evidence suggests that drug-naïve patients and those experiencing their first episode of schizophrenia respond to doses of antipsychotic drugs at the lower end of the recommended dosage range (Cookson et al., 2002; McEvoy et al., 1991; Oosthuizen et al., 2001; Remington et al., 1998; Tauscher & Kapur, 2001).

### *Relapse prevention*

For people with established schizophrenia, the chance of relapse while receiving continuous antipsychotic medication appears to be about a third of that on placebo (Marder & Wirshing, 2003). Risk factors for relapse of illness include the presence of



persistent symptoms, poor adherence to the treatment regimen, lack of insight and substance use, all of which can be reasonable targets for intervention.

Stopping antipsychotic medication in people with schizophrenia, especially abruptly, dramatically increases the risk of relapse in the short to medium term, although even with gradual cessation about half will relapse in the succeeding 6 months (Viguera et al., 1997). Low-dose prescribing and the use of intermittent dosing strategies (with medication prompted by the appearance of an individual's characteristic early signs of relapse) have also been suggested in the past as ways to minimise side effects in the long-term. However, when these were tested in controlled trials, the risks, particularly in terms of increased relapse, outweighed any benefits (Dixon et al., 1995; Hirsch & Barnes, 1995).

The Schizophrenia Patient Outcomes Research Team (1998) concluded that 'targeted, intermittent dosage maintenance strategies should not be used routinely in lieu of continuous dosage regimens because of the increased risk of symptom worsening or relapse. These strategies may be considered for patients who refuse maintenance or for whom some other contraindication to maintenance therapy exists, such as side-effect sensitivity'.

### *Clozapine*

The antipsychotic clozapine was introduced in the 1970s, only to be withdrawn soon after because of the risk of potentially fatal agranulocytosis. However, after further research revealed the drug's efficacy in treatment-resistant schizophrenia (for example, (Kane et al., 1988), clozapine was reintroduced in the 1980s with requirements for appropriate haematological monitoring. Clozapine was considered to have a novel mode of action. Its pharmacological profile includes a relatively low affinity for D2 receptors and a much higher affinity for D4 dopamine receptors, and for subtypes of serotonin receptors, although it is not clear exactly which aspects are responsible for its superior antipsychotic effect in treatment-resistant schizophrenia.

### *Side effects*

Clinical issues relating to side effects were summarised by (NICE, 2002a), as follows:

'All antipsychotic agents are associated with side effects but the profile and clinical significance of these varies among individuals and drugs. These may include EPS (such as parkinsonism, acute dystonic reactions, akathisia and tardive dyskinesia), autonomic effects (such as blurring of vision, increased intra-ocular pressure, dry mouth and eyes, constipation and urinary retention), increased prolactin levels, seizures, sedation and weight gain. Cardiac safety is also an issue because several antipsychotics have been shown to prolong ventricular repolarisation, which is associated with an increased risk of ventricular arrhythmias. Routine monitoring is a pre-requisite of clozapine use because of the risk of neutropenia and agranulocytosis. Prescribers are therefore required to ensure that effective

ongoing monitoring is maintained as alternative brands of clozapine become available.

Individuals with schizophrenia consider the most troublesome side effects to be EPS, weight gain, sexual dysfunction and sedation. EPS are easily recognised, but their occurrence cannot be predicted accurately and they are related to poor prognosis. Akathisia is also often missed or misdiagnosed as agitation. Of particular concern is tardive dyskinesia (orofacial and trunk movements), which may not be evident immediately, is resistant to treatment, may be persistent, and may worsen on treatment withdrawal. Sexual dysfunction can be a problem, sometimes linked to drug-induced hyperprolactinaemia; it is likely to be an underreported side effect of antipsychotic treatment, as discussion of this issue is often difficult to initiate.'

Blockade of D2 receptors by antipsychotic drugs is responsible for EPS, such as parkinsonism, akathisia, dystonia and dyskinesia, but the therapeutic, antipsychotic effect may occur at a lower level of D2 receptor occupancy than the level associated with the emergence of EPS (Farde et al., 1992). SGA drugs were introduced with claims for a lower risk of EPS. The individual SGAs differ in their propensity to cause EPS: for some SGAs (for example, clozapine and quetiapine), acute EPS liability does not differ from placebo across their full dose, while for some others the risk is dose dependent. These differences may reflect individual drug profiles in relation to properties such as selective dopamine D2-like receptor antagonism, potent 5-HT<sub>2A</sub> antagonism and rapid dissociation from the D2 receptor, and for aripiprazole, partial agonism at D2 and 5HT<sub>1A</sub> receptors. Interpretation of the RCT evidence for the superiority of SGAs regarding acute EPS should take into account the dosage and choice of FGA comparator, most commonly haloperidol, which is considered a high potency D2 antagonist with a relatively high liability for EPS.

Raised serum prolactin is also an important adverse effect of antipsychotic medication (Haddad & Wieck, 2004). It can lead to problems, such as menstrual abnormalities, galactorrhea and sexual dysfunction, and in the longer term to reduced bone mineral density (Haddad & Wieck, 2004; Meaney et al., 2004). While the propensity for antipsychotic drugs to affect prolactin varies between agents, the extent to which an individual service user will be affected may be difficult to determine before treatment.

Antipsychotic drugs also have strong affinity for a range of other receptors, including histaminergic, serotonergic, cholinergic and alpha-adrenergic types, which may produce a number of other effects, such as sedation, weight gain and postural hypotension. As the various antipsychotic drugs possess different relative affinities for each receptor type, each drug will have its own specific profile of side effects. For example, antipsychotic drugs vary in their liability for metabolic side effects, such as weight gain, lipid abnormalities and disturbance of glucose regulation. These are side effects that have been increasingly recognised as problems that may impact on long-

term physical health. Specifically, they increase the risk of the metabolic syndrome, a recognised cluster of features (hypertension, central obesity, glucose intolerance/insulin resistance and dyslipidaemia) (American Diabetes Association et al., 2004; Mackin et al., 2007a), which is a predictor of type-2 diabetes and coronary heart disease. Even without antipsychotic treatment, people with schizophrenia may have an increased risk of such problems, which is partly related to lifestyle factors such as smoking, poor diet, lack of exercise, and also, possibly, the illness itself. (Brown et al., 1999; Holt et al., 2005; Osborn et al., 2007a; Osborn et al., 2007b; Taylor et al., 2005; Van Nimwegen et al., 2008). While there is some uncertainty about the precise relationship between schizophrenia, metabolic problems and antipsychotic medication, there is agreement that routine physical health screening of people prescribed antipsychotic drugs in the long term is required (Barnes et al., 2007; Newcomer, 2007; Suvisaari et al., 2007) (further information about physical health screening can be found in Chapter 7).

## **10.2 INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION**

### **10.2.1 Introduction**

Evidence published before the 2002 guideline suggests that drug-naïve patients may respond to doses of antipsychotic medication at the lower end of the recommended range (Cookson et al., 2002; McEvoy et al., 1991; Oosthuizen et al., 2001; Tauscher & Kapur, 2001). This may have particular implications in the treatment of people experiencing their first episode of schizophrenia. Lehman and Steinwachs (1998) have suggested that the maximum dose for drug-naïve patients should be 500 mg chlorpromazine equivalents per day. This contrasts with a recommended optimal oral antipsychotic dose of 300 to 1000 mg chlorpromazine equivalents per day for the routine treatment of an acute episode in non-drug-naïve patients.

### **10.2.2 Clinical review protocol**

The review protocol, including the primary clinical question, information about the databases searched and the eligibility criteria can be found in Table 90. For the 2009 guideline, a new systematic search was conducted for relevant RCTs published since the 2002 guideline (further information about the search strategy can be found in Appendix 20).

### **10.2.3 Studies considered for review<sup>34</sup>**

Nine RCTs (N = 1,801) met the inclusion criteria for the 2009 guideline. Of these, two trials (Emsley1995; Jones1998) were included in the 2002 guideline, but analysed with the acute treatment trials (that is, non-initial treatment). All included studies

---

<sup>34</sup>Here and elsewhere in this chapter, each study considered for review is referred to by a study ID, with studies included in the previous guideline in lower case and new studies in upper case (primary author and date or study number for unpublished trials). References for included studies denoted by study IDs can be found in Appendix 15b

are now published in peer-reviewed journals between 1999 and 2008. Further information about both included and excluded studies can be found in Appendix 22b.

### 10.2.4 Antipsychotic drug treatment in people with first-episode or early schizophrenia

Of the nine RCTs included in the meta-analysis, two were multiple-arm trials and, therefore, there were a total of 12 evaluations: three of olanzapine versus haloperidol, one of olanzapine versus quetiapine, three of olanzapine versus risperidone, four of risperidone versus haloperidol, and one of risperidone versus quetiapine (see Table 91 for a summary of the study characteristics). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

**Table 90: Clinical review protocol for the review of initial treatment with antipsychotic medication**

<i>Primary clinical question</i>	For people with first-episode or early schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug at the initiation of treatment (when administered within the recommended dose range [BNF54])?	
<i>Electronic data bases</i>	CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO	
<i>Date searched</i>	1 January 2002 to 30 July 2008	
<i>Study design</i>	Double-blind RCT ( $\geq 10$ participants per arm and $\geq 4$ weeks' duration)	
<i>Patient population</i>	Adults (18+) with first-episode or early schizophrenia (including recent onset/ people who have never been treated with antipsychotic medication) <sup>a</sup>	
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60). Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis. People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse.	
<i>Interventions</i>	FGAs: Benperidol Chlorpromazine hydrochloride Flupentixol Fluphenazine hydrochloride Haloperidol Levomepromazine Pericyazine Perphenazine Pimozide Prochlorperazine Promazine hydrochloride Sulpiride Trifluoperazine Zuclopenthixolacetate Zuclopenthixol dihydrochloride	SGAs <sup>b</sup> : Amisulpride Aripiprazole Olanzapine Paliperidone Quetiapine Risperidone Sertindole Zotepine
<i>Comparator</i>	Any relevant antipsychotic drug	

<i>Critical outcomes</i>	Mortality (suicide) Global state (CGI) Mental state (total symptoms, depression) Social functioning Leaving the study early for any reason Adverse events	
<p><i>Note.</i> Studies (or outcomes from studies) were categorised as short term (12 weeks or fewer), medium term (12–51 weeks) and long term (52 weeks or more); studies that used drug doses outside the recommended dose range were flagged during data analysis.</p> <p><sup>a</sup>Studies that included participants under the age of 18 were not excluded from the review unless all participants were less than 18 years old.</p> <p><sup>b</sup>Clozapine and sertindole were excluded from this analysis because they are not usually used to treat people with first-episode or early schizophrenia.</p>		

**Table 91: Summary of study characteristics for RCTs of antipsychotic drugs in people with first-episode or early schizophrenia**

	<b>Olanzapine Versus haloperidol</b>	<b>Olanzapine Versus quetiapine</b>	<b>Olanzapine Versus risperidone</b>	<b>Risperidone Versus haloperidol</b>	<b>Risperidone versus quetiapine</b>
<i>k (total N)</i>	3 (331)	1 (267)	3 (446)	5 (1102)	1 (267)
<i>Study ID</i>	DEHAAN2003 Jones1998 LIEBERMAN2003A	MCEVOY2007A	Jones1998 MCEVOY2007A VANNIMWEGEN2008	Emsley1995 Jones1998 LEE2007 MOLLER2008 SCHOOLER2005	MCEVOY2007A
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV	DSM-IV	DSM-III, DSM-IV	DSM-IV
<i>Baseline severity</i>	PANSS total:~81 (SD15) (LIEBERMAN 2003A)	PANSS total: Mean ~74 (SD ~16)	PANSS total: mean~74 (SD 16) (MCEVOY2007A)	PANSS total: Range 77.3 to 94.2	PANSS total: Mean ~74 (SD 16)
<i>Selected inclusion criteria</i>	DEHAAN2003: 1-2psychotic episodes; aged 17-28 years Jones1998: first 5 years of illness; aged 18-65 years LIEBERMAN 2003A: experienced	Participants had to be in first episode of their psychotic illness, and had to be continuously ill for ≥1 month and no more than 5 months	Jones1998: first 5 years of illness MCEVOY2007A: participants had to be in first episode of their psychotic illness, and had to be continuously ill for ≥ 1 month and no more than 5 months	Emsley1995: first-episode Jones1998: first 5 years of illness; aged 18-65 years LEE2007: drug-naïve MOLLER2008: first episode; aged 18-60 years	Participants had to be in first episode of Their psychotic illness, and had to be continuously ill for ≥1 month and no more than 5 months

**Table 91: (Continued)**

	<b>Olanzapine Versus haloperidol</b>	<b>Olanzapine Versus quetiapine</b>	<b>Olanzapine Versus risperidone</b>	<b>Risperidone Versus haloperidol</b>	<b>Risperidone versus quetiapine</b>
	Psychotic symptoms for $\geq 1$ month but not more than 60 months; aged 16–40 years		VANNIMWEGEN2008: Recent onset; aged 18–30 years	SCHOOLER2005: schizophrenia, <1 year, during which there were no more than two psychiatric hospitalisations for psychosis and $\leq 12$ weeks cumulative exposure to antipsychotics; Aged 16–45 years	
<i>Age of participants</i>	DEHAAN2003: 17–26 years Jones 1998: mean ~29 years LIEBERMAN2003A: mean 23.9 (SD4.6)	16–44 years, mean 24.5 (SD5.8)	Jones 1998: mean ~29 years MCEVOY2007A: 16–44 years, mean 24.5 (SD 5.8) VANNIMWEGEN2008: mean 25 years	Emsley1995: 15–50 years, median ~23 years Jones1998: mean ~29 years LEE2007: mean 32.6 (SD1) years MOLLER2008: mean 30.1 (9.8) years SCHOOLER2005: mean ~24 years	16–44 years, mean 24.5 (SD5.8) years
<i>Setting</i>	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient
<i>Duration of treatment</i>	Short term: 6 weeks Medium term: 12 weeks Long term: 54–104 weeks	Long term: 52 weeks	Short term: 6 weeks Long term: 52–54 weeks	Short term: 6–8 weeks Medium term: 24–30 weeks Long term: 54–104 weeks	Long term: 52 weeks
<i>Medication dose (mg/day)</i>	Olanzapine: 5–20 (range) Haloperidol: 2.5–20 (range)	Olanzapine: 2.5–20 (range) Quetiapine: 100–800 (range)	Olanzapine: 2.5–20 (range) Risperidone: 0.5–10 (range)	Risperidone: 2–10 (range) Haloperidol: 1–20 (range)	Risperidone: 0.5–4 (range) Quetiapine: 100–800 (range)

### **10.2.5 Clinical evidence summary**

In nine RCTs with a total of 1,801 participants with first-episode or early schizophrenia (including people with a recent onset of schizophrenia and people who have never been treated with antipsychotic medication), the evidence suggested there were no clinically significant differences in efficacy between the antipsychotic drugs examined. Most of the trials were not designed to examine differences in adverse effects of treatment, but metabolic and neurological side effects reported were consistent with those identified in the SPC for each drug.

## **10.3 ORAL ANTIPSYCHOTICS IN THE TREATMENT OF THE ACUTE EPISODE**

### **10.3.1 Introduction**

Early clinical studies established that antipsychotic medications are effective in the treatment of acute schizophrenic episodes (Davis & Garver, 1978 ), although they proved to be more effective at alleviating positive symptoms than negative symptoms, such as alogia or affective blunting. However, no consistent difference between the FGAs was demonstrated in terms of antipsychotic efficacy or effects on individual symptoms, syndromes or schizophrenia subgroups. Accordingly, the choice of drug for an individual was largely dependent on differences in side-effect profiles (Davis & Garver, 1978 ; Hollister, 1974). The limitations of these FGAs included heterogeneity of response in acute episodes, with a proportion of individuals showing little improvement (Kane, 1987) and a range of undesirable acute and long-term side effects. The search for better-tolerated and more effective drugs eventually generated a series of second-generation drugs, characterised by a lower liability for EPS (Barnes & McPhillips, 1999; Cookson et al., 2002; Geddes et al., 2000).

### **10.3.2 Clinical review protocol**

The review protocol, including the primary clinical question, information about the databases searched and the eligibility criteria can be found in Table 92. A new systematic search for relevant RCTs, published since the 2002 guideline, was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).



**Table 92: Clinical review protocol for the review of oral antipsychotics in the treatment of the acute episode**

Primary clinical question	For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug (when administered within the recommended dose range [BNF 54])?	
Electronic databases	CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO	
Date searched	1 January 2002 to 30 July 2008	
Study design	Double-blind RCT (≥10 participants per arm and ≥4 weeks' duration)	
Patient population	Adults (18+) with an acute exacerbation or recurrence of schizophrenia	
Excluded populations	Very late onset schizophrenia (onset after age 60). Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis. People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse. People with schizophrenia who have met established criteria for treatment-resistant schizophrenia.	
Interventions	FGAs: Benperidol Chlorpromazine hydrochloride Flupentixol Fluphenazine hydrochloride Haloperidol Levomepromazine Pericyazine Perphenazine Pimozide Prochlorperazine Promazine hydrochloride Sulpiride Trifluoperazine Zuclopenthixol acetate Zuclopenthixol dihydrochloride	SGAs <sup>35</sup> : Amisulpride Aripiprazole Olanzapine Paliperidone Quetiapine Risperidone Sertindole Zotepine
Comparator	Any relevant antipsychotic drug	
Critical outcomes	Mortality (suicide) Global state (CGI) Mental state (total symptoms, depression) Social functioning Leaving the study early for any reason Adverse events	
Note. Studies (or outcomes from studies) were categorised as short term (12 weeks or fewer), medium term (12–51 weeks) and long term (52 weeks or more); studies that used drug doses outside the recommended dose range were flagged during data analysis		

<sup>35</sup>Clozapine was excluded from this analysis because it is not usually used to treat people with schizophrenia unless criteria for treatment-resistant schizophrenia are met (see Section 10.5)

### 10.3.3 Studies considered for review

In the 2002 guideline, 180 RCTs were included<sup>36</sup>. The search for the 2009 guideline identified ten papers providing follow-up or published data for existing trials and 19 new trials. Two trials (Klieser1996; Malyarov1999) were multi-arm and contributed to more than one comparison. Because of the large volume of evidence, the GDG excluded open-label studies, head-to-head comparisons of two FGAs and comparisons with placebo from the 2009 guideline review, leaving 72 RCTs (N = 16,556) that met inclusion criteria. Further information about both included and excluded studies can be found in Appendix 22b.

### 10.3.4 Treatment with antipsychotic drugs in people with an acute exacerbation or recurrence of schizophrenia

Because most included studies involved olanzapine or risperidone, comparisons involving these drugs are reported first followed by comparisons involving other drugs. Twenty-six RCTs compared olanzapine with another antipsychotic (see Table 93 for a summary of the study characteristics) and 30 compared risperidone with another antipsychotic (see Table 94). Six RCTs were included in the analysis comparing amisulpride with an FGA, two in the analysis compared aripiprazole with an FGA and one compared aripiprazole with ziprasidone (see Table 95); seven compared quetiapine with an FGA and two compared sertindole with an FGA (see Table 96), and seven compared zotepine with an FGA (see Table 97). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### 10.3.5 Clinical evidence summary

In 72 RCTs involving 16,556 participants with an acute exacerbation or recurrence of schizophrenia, there was little evidence of clinically significant differences in efficacy between the oral antipsychotic drugs examined. Metabolic and neurological side effects were consistent with those reported in the SPC for each drug.

---

<sup>36</sup>Of these, 146 trials came from the following existing sources: NICE TA43 (NICE, 2002) and the Cochrane reviews of benperidol (Leucht & Hartung, 2002), loxapine (Fenton et al., 2002), pimozide (Sultana & McMonagle, 2002), sulpiride (Soares et al., 2002) and thioridazine (Sultana et al., 2002). New systematic reviews were conducted for chlorpromazine, flupentixol, fluphenazine, oxyperline, pericyazine, perphenazine, prochlorperazine, promazine, trifluoperazine, and zuclopenthixol dihydrochloride. Data from poor quality trials, placebo comparisons and drugs not available in the UK were excluded

**Table 93: Summary of study characteristics for olanzapine versus another antipsychotic drug (acute treatment)**

	Olanzapine versus haloperidol	Olanzapine versus another FGA	Olanzapine versus amisulpride	Olanzapine versus paliperidone
<i>k</i> (total N)	9 (3,071)	4 (249)	2 (429)	3 (1,090)
<i>Study ID</i>	Beasley1996a Beasley1997 HGCJ1999 (HK) HGPU1998 (Taiwan) Malyarov1999 Reams1998 Tollefson1997 KONGSAKON2006 ROSENHECK2003	HGBL1997 Loza1999 Jakovljevic1999 Naukkarinen 1999/ HGBJ (Finland)	MARTIN2002 WAGNER2005	DAVIDSON2007 KANE2007A MARDER2007
<i>Diagnostic criteria</i>	DSM-III-R, DSM-IV,	DSM-IV	DSM-IV	DSM-IV
<i>Setting</i>	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient
<i>Duration of treatment</i>	Short term: 6 weeks Medium term: 14–26 weeks Long term: 52 weeks	Short term: 4–6 weeks Medium term: 26 weeks	Short term: 8 weeks Medium term: 24 weeks	Short term: 6 weeks
<i>Medication dose (mg/day)</i>	Olanzapine: 5–20 (range) Haloperidol: 5–20 (range)	Olanzapine: 5–20 (range) Chlorpromazine hydrochloride: 200–800 (range) Flupentixol: 5–20 (range) Fluphenazine: 6–21 (range) Perphenazine: 8–32 (range)	Olanzapine: 5–20 (range) Amisulpride: 200–800 (range)	Olanzapine: 10 (range) Paliperidone: 6 or 9 <sup>kk</sup>

<sup>kk</sup>For the purpose of the review, data from the 6 mg group (MARDER2007) and the 9 mg group (DAVIDSON2007) were used in the meta-analysis

**Table 93: Summary of study characteristics for olanzapine versus another antipsychotic drug (acute treatment) (*Continued*)**

	Olanzapine versus quetiapine	Olanzapine versus risperidone	Olanzapine versus ziprasidone
<i>k</i> (total <i>N</i> )	1 (52)	5 (928)	2 (817)
<i>Study ID</i>	RIEDEL2007B	Conley2001 Gureje1998 Malyarov1999 Tran1997 STUDY-S036	StudyR-0548 (SIMPSON2004) BREIER2005
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV or ICD-10	DSM-IV
<i>Setting</i>	Inpatient	Inpatient and outpatient	Inpatient and outpatient
<i>Duration of treatment</i>	Short term: 8 weeks	Short term: 6–8 weeks Medium term: 26–30 weeks	Short term: 6 weeks Medium term: 28 weeks
<i>Medication dose (mg/day)</i>	Olanzapine: 15.82 (mean); 10–20 (range) Quetiapine: 586.86 (mean); 400–800 (range)	Olanzapine: 5–20 (range) Risperidone: 2–12 (range)	Olanzapine: 11.3–15.27 (range of means) Ziprasidone: 115.96–129.9 (range of means)

**Table 94: Summary of study characteristics for risperidone versus another antipsychotic drug (acute treatment)**

	<b>Risperidone versus haloperidol</b>	<b>Risperidone versus another FGA</b>	<b>Risperidone versus amisulpride</b>	<b>Risperidone versus aripiprazole</b>
<i>k (total N)</i>	14 (2,437)	2 (205)	3 (585)	2 (487)
<i>Study ID</i>	Blin1996 Ceskova1993 Cetin1999 Chouinard1993 Claus1991 Janicak1999 Liu2000 Malyarov1999 Marder1994 Mesotten1991 Min1993 Muller-Siecheneder1998 Peuskens1995 ZHANG2001	Hoyberg1993 Huttunen1995	Fleurot1997 Lecrubier2000 HWANG2003	CHAN2007B POTKIN2003A
<i>Diagnostic criteria</i>	DSM-III-R, DSM-IV, ICD-9, ICD-10	DSM-III-R	DSM-IV	DSM-IV
<i>Setting</i>	Inpatient	Not reported	Inpatient	Inpatient
<i>Duration of treatment</i>	Short term: 4–8 weeks Medium term: 12–26 weeks	Short term: 8 weeks	Short term: 6–8 weeks Medium term: 26 weeks	Short term: 4 weeks
<i>Medication dose (mg/day)</i>	Risperidone: 5.5–12 (range of means); 1–20 (range) Haloperidol: 9.2–20 (range of means); 2–20 (range)	Risperidone: 8–8.5 (range of means); 15–20 (max) Perphenazine: 28 (mean); 48 (max) Zuclopenthixol: 38 (mean); 100 (max)	Risperidone: 4–10 (range) Amisulpride: 400–1000 (range)	Risperidone: 6 (fixed) Aripiprazole: 15, 20, 30 (fixed)

**Table 94: Summary of study characteristics for risperidone versus another antipsychotic drug (acute treatment) (Continued)**

	Risperidone versus quetiapine	Risperidone versus sertindole	Risperidone versus ziprasidone	Risperidone versus zotepine
<i>k</i> (total <i>N</i> )	1 (673)	1 (187)	1 (296)	1 (59)
<i>Study ID</i>	ZHONG2006	AZORIN2006	Study128-302 (ADDINGTON2004)	Klieser1996
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV	DSM-III-R	ICD-9
<i>Setting</i>	Inpatient and outpatient	Inpatient and outpatient	Not reported	Not reported
<i>Duration of treatment</i>	Short term: 8 weeks	Medium term: 12 weeks	Short term: 8 weeks	Short term: 4 weeks
<i>Medication dose (mg/day)</i>	Risperidone: 6.0 (mean); 2–8 (range) Quetiapine: 525 (mean); 200–800 (range)	Risperidone: 6.6 (mean); 4–10 (range) Sertindole: 16.2 (mean); 12–24 (range)	Risperidone: 7.4 (mean); 3–10 (range) Ziprasidone: 114 (mean);	Risperidone: 4 or 8 (fixed) Zotepine: 225 (fixed)

**Table 95: Summary of study characteristics for amisulpride or aripiprazole versus another antipsychotic drug (acute treatment)**

	Amisulpride versus haloperidol	Amisulpride versus another FGA	Aripiprazole versus haloperidol	Aripiprazole versus ziprasidone
<i>k (total N)</i>	5 (921)	1 (132)	2 (1,708)	1 (256)
<i>Study ID</i>	Carriere2000 Delcker1990 Moller1997 Puech1998 Ziegler1989	Hillert1994	KANE2002 KASPER2003	ZIMBROFF2007
<i>Diagnostic criteria</i>	DSM-III-R, DSM-IV, ICD-9	DSM-III-R	DSM-IV	DSM-IV
<i>Setting</i>	Inpatient and outpatient	Inpatient	Inpatient and outpatient	Inpatient and outpatient
<i>Duration of treatment</i>	Short term: 4–6 weeks Medium term: 16 weeks	Short term: 6 weeks	Short term: 4 weeks Long term: 52 weeks	Short term: 4 weeks
<i>Medication dose (mg/day)</i>	Amisulpride: 400–2,400 (range) Haloperidol: 10–40 (range)	Amisulpride: 956 (mean); 1000 (maximum) Flupentixol: 22.6 (mean); 25 (maximum)	Aripiprazole: 15 or 30 (fixed) Haloperidol: 10 (fixed)	Aripiprazole: 20.9 (mean modal) Ziprasidone: 149 (mean modal)

**Table 96: Summary of study characteristics for quetiapine or sertindole versus an FGA (acute treatment)**

	Quetiapine versus haloperidol	Quetiapine versus another FGA	Sertindole versus haloperidol
k (total N)	4 (818)	1 (201)	1 (617)
Study ID	Arvanitis1997 Fleischhacker1996 Purdon2000 ATMACA2002	Link1994	Hale2000
Diagnostic criteria	DSM-III-R, DSM-IV, ICD-10	DSM-III-R	DSM-III-R
Setting	Inpatient and outpatient	Not reported	Inpatient
Duration of treatment	Short term: 6 weeks Medium term: 26 weeks	Short term: 6 weeks	Short term: 8 weeks
Medication dose (mg/day)	Quetiapine: 50–800 (range) Haloperidol: 1–16 (range)	Quetiapine: 407 (mean) Chlorpromazine hydrochloride: 384 (mean)	Sertindole: 8, 16 or 20, 24 (fixed) Haloperidol: 10 (fixed)

**Table 97: Summary of study characteristics for zotepine versus an FGA (acute treatment)**

	Zotepine versus haloperidol	Zotepine versus another FGA
k (total N)	5 (386)	2 (146)
Study ID	Barnas1987 Fleischhacker1989 Klieser1996 Petit1996 KnollCTR (StudyZT4002)	Cooper1999a Dieterle1999
Diagnostic criteria	DSM-III, DSM-III-R, ICD-9	DSM-III-R, ICD-9
Setting	Inpatient	Mostly inpatient
Duration of treatment	Short term: 4–8 weeks Medium term: 26 weeks	Short term: 4–8 weeks
Medication dose (mg/day)	Zotepine: 94–309 (range of means); 150–300 (range) Haloperidol: 4–15 (range of means); 10–20 (range)	Zotepine: 241 (mean); 300 (max) Chlorpromazine hydrochloride: 600 (max) Perphenazine: 348 (mean)



## **10.4 PROMOTING RECOVERY IN PEOPLE WITH SCHIZOPHRENIA THAT ARE IN REMISSION - PHARMACOLOGICAL RELAPSE PREVENTION**

### **10.4.1 Introduction**

Following their introduction into clinical practice in the early 1950s, chlorpromazine and related drugs rapidly became widely used for both acute treatment of people experiencing symptoms of psychosis and for prevention of relapse. By the 1980s, haloperidol (synthesised in 1959) became the most widely used drug for these purposes in the US (Davis et al., 1993; Gilbert et al., 1995; Healy, 2002; Hirsch & Barnes, 1995). A meta-analysis (Davis et al., 1993) of 35 double-blind studies compared maintenance treatment using FGAs with placebo in over 3,500 service users. Relapse was reported in 55% of those who were randomised to receive placebo, but in only 21% of those receiving active drugs. Gilbert et al. (1995) reviewed 66 antipsychotic withdrawal studies, published between 1958 and 1993, and involving over 4,000 service users. The mean cumulative rate of relapse in the medication withdrawal groups was 53% (follow-up period 6 to 10 months) compared with 16% (follow-up of 8 months) in the antipsychotic maintenance groups. Over a period of several years, continuing treatment with conventional antipsychotics appears to reduce the risk of relapse by about two-thirds (Kissling, 1991).

When the effects of stopping antipsychotic drugs after an acute psychotic episode or after long-term maintenance treatment were examined, the subsequent rate of relapse seemed to be similar in both situations. Individuals who are well stabilised on maintenance medication show high rates of relapse when their antipsychotic therapy is discontinued (Kane, 1990) or switched to placebo (Hogarty et al., 1976). A recent Cochrane review (Almerie et al., 2007) including ten trials of chlorpromazine cessation in stable participants (total N = 1,042) showed that those stopping chlorpromazine had a relative risk of relapse in the short term (up to 8 weeks) of 6.76 (95% CI, 3.37 to 13.54) and in the medium term (9 weeks to 6 months) of 4.04 (95% CI, 2.81 to 5.8). Relative risk of relapse after 6 months was 1.70 (95% CI, 1.44 to 2.01). Another meta-analysis of data from several large collaborative studies (Davis et al., 1993) suggested that the number of people who survive without relapse after discontinuing drug treatment declines exponentially by around 10% a month. Whether maintenance drug treatment is required for all people with schizophrenia is uncertain. Around 20% of individuals will only experience a single episode (Möller & van Zerssen, 1995). A recent pragmatic observational study analysing over 4,000 participants who achieved remission in the Schizophrenia Outpatient Health Outcomes study, showed that 25% relapsed over a 3-year follow-up period with a constant rate of relapse over this time (Haro et al., 2007). It therefore appears that a proportion of people will experience a relapse despite continued antipsychotic drug treatment. It is unclear whether such people benefit from an increase in antipsychotic dosage during episodes of psychotic exacerbation (Steingard et al., 1994).

Given that there are no consistent reliable predictors of prognosis or drug response, the 2009 guideline, as well as other consensus statements and guidelines, generally recommend that pharmacological relapse prevention is considered for every patient diagnosed with schizophrenia (for example (Lehman et al., 1998) and (Dixon et al., 1995). Possible exceptions are people with very brief psychotic episodes without negative psychosocial consequences, and the uncommon patient for whom all available antipsychotics pose a significant health risk (Fleischhacker & Hummer, 1997).

It is clear from the placebo-controlled RCTs and discontinuation studies cited above that the efficacy of antipsychotics in relapse prevention is established. However, it is also clear from recent pragmatic trials that switching of medication over time is common in clinical practice (Jones et al., 2006; Lieberman et al., 2005). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al., 2005), 74% of participants discontinued their randomised treatment over 18 months (further information about this trial can be found in Section 10.8 on the effectiveness of antipsychotic medication). This may well reflect the need in clinical practice to search collaboratively for the drug that offers the best balance of efficacy and tolerability for the individual patient. The role of depot preparations in contributing to concordance and continuation on medication is discussed in Section 10.6.

All the antipsychotics identified for review have established supremacy over placebo in the prevention of relapse, although the evidence that any individual antipsychotic drug, or group of antipsychotics (FGAs and SGAs), has greater efficacy or better tolerability than another is still very uncertain. One of the main aims of antipsychotic drug development in recent decades has been to produce compounds with equivalent antipsychotic efficacy, but without troubling EPS. The doses of haloperidol that came to be used in routine clinical practice by the 1980s and early 1990s were higher than those required for its antipsychotic effect, and EPS were common. The trials conducted in the 1990s comparing SGAs and haloperidol often tested the latter at relatively high doses, arguably above the optimum for at least a proportion of the subjects treated, and highlighted the propensity of haloperidol to cause such side effects in comparison with SGAs. The widespread introduction of SGAs to clinical practice from the mid 1990s onwards thus appeared to offer a genuine therapeutic advance. However, more recent effectiveness (pragmatic) trials have suggested that the claimed advantages of these drugs may have been overstated, especially if their propensity to cause metabolic abnormalities and other side effects is taken into account, and if they are compared with FGAs (other than higher dose haloperidol) (Geddes et al., 2000; Jones et al., 2006; Lieberman et al., 2005; NICE, 2002a). SGAs are not a homogeneous class and may not deserve a group title. They differ widely in their pharmacology and side effect profile. There are unanswered questions regarding their relative efficacy and tolerability and their use over the long-term compared with FGAs. Their risks of long-term metabolic disturbance are not yet fully quantified and neither is the risk of movement disorders, such as tardive dyskinesia compared with FGAs, so any small advantage

that may be offered by reduced EPS may be offset by these other adverse consequences not shown by the earlier drugs.

While evaluating each drug against each other would appear superficially the best way of approaching the question posed for this review, in reality the number of possible comparisons and the limited number of studies available would render this a meaningless task. Therefore, the GDG considered that comparing the individual SGAs against all FGA comparators, primarily in terms of relapse, provided the most meaningful analysis of the available data.

### ***Definitions***

The definitions of relapse used in this review were those adopted by the individual studies. This definition varied between studies (see Sections 10.4.4 and 10.4.5), and therefore, caution should be exercised in the interpretation of the results.

### **10.4.2 Clinical review protocol**

The review protocol, including the primary clinical question, information about the databases searched and the eligibility criteria used for this section of the guideline can be found in Table 98. A new systematic search for relevant RCTs, published since the 2002 guideline, was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20 and information about the search for health economic evidence can be found in Section 10.9.1).

### 10.4.3 Studies considered for review

In the 2002 guideline, nine RCTs comparing an SGA with an FGA were included (based on a then unpublished review by Leucht and colleagues). Leucht and colleagues published their review in 2003; it included one additional trial and six trials comparing an SGA with placebo that were not included in the 2002 guideline. For the 2009 guideline, the review was limited to double-blind RCTs of antipsychotics used for relapse prevention; therefore, four studies (Daniel1998; Essock1996; Rosenheck1999; Tamminga1994) included in the 2002 guideline were excluded from the 2009 guideline review. In addition, one trial of an SGA versus another SGA, included in the 2002 review of acute treatment, met the criteria for inclusion in this review (Tran1997). The search for the 2009 guideline identified four additional RCTs (one comparing an SGA with an FGA, one comparing an SGA with an SGA, and one comparing an SGA with placebo). For the purposes of the health economic model (see Section 10.9.2), trials of ziprasidone versus placebo were included because this drug has been compared with a licensed SGA.

In total, 17 RCTs (N = 3,535) met the inclusion criteria for the 2009 guideline review. Of these, one was unpublished (STUDY-S029) and the remainder were published in peer-reviewed journals between 1994 and 2007. Further information about both included and excluded studies can be found in Appendix 22b.

**Table 98: Clinical review protocol for the review of relapse prevention**

<i>Primary clinical question</i>	For people with schizophrenia that is in remission, what are the benefits and down sides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?
<i>Electronic databases</i>	CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	Double-blind RCT (≥10 participants per arm and ≥ 6 months' duration)
<i>Patient population</i>	Adults (age 18+) with schizophrenia that is in remission (for the purposes of the guideline, remission includes people who have responded fully or partially to treatment)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60). Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis. People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse.

<i>Interventions</i>	FGAs: Benperidol Chlorpromazine hydrochloride Flupentixol Fluphenazine hydrochloride Haloperidol Levomepromazine Pericyazine Perphenazine Pimozide Prochlorperazine Promazine hydrochloride Sulpiride Trifluoperazine Zuclopenthixol acetate Zuclopenthixol dihydrochloride	SGAs: Amisulpride Aripiprazole Olanzapine Paliperidone Quetiapine Risperidone Zotepine
<i>Comparator</i>	Any relevant antipsychotic drug or placebo	
<i>Critical outcomes</i>	Global state (relapse). Overall treatment failure (relapse or leaving the study early for any reason). Leaving the study early because of adverse events.	
<i>Note.</i> Studies (or outcomes from studies) were categorised as short term (12 weeks or fewer), medium term (12–51 weeks) and long term (52 weeks or more); studies that used drug doses outside the recommended dose range were flagged during data analysis		

#### 10.4.4 Second-generation antipsychotics versus placebo in people with schizophrenia that is in remission (relapse prevention)

Eight RCTs were included in the meta-analysis comparing an SGA (amisulpride, aripiprazole, olanzapine, paliperidone, ziprasidone, zotepine) with placebo (see Table 99). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

**Table 99: Summary of study characteristics for of an SGA versus placebo (relapse prevention)**

	<b>Amisulpride versus placebo</b>	<b>Aripiprazole versus placebo</b>	<b>Olanzapine versus placebo</b>
k (total N)	1 (141)	1 (310)	3 (446)
StudyID	LOO1997	PIGOTT2003	BEASLEY2000 DELLVA1997(study1) DELLVA1997(study2)
Selected inclusion criteria	Residual or disorganised schizophrenia; predominant negative symptoms	Chronic schizophrenia with diagnosis made at least 2 years prior to entry and continued antipsychotic treatment during this period	BEASLEY2000 <sup>a</sup> DELLVA1997(studies 1and 2) <sup>b</sup>
Diagnostic criteria	DSM-III-R	DSM-IV	DSM-III-R
Definition of relapse	Withdrawal because of inefficacy of treatment and PANSS > 50	Impending decompensation based on one or more of the following: a CGI-I $\geq$ 5; a PANSS $\geq$ 5 on subscore items of hostility or uncooperativeness on 2 successive days; or a $\geq$ 20% increase in PANSS total score	BEASLEY2000: Hospitalisation for positive symptoms or $\geq$ 4 increase on BPRS positive score or increase of single BPRS item to 4 and increase from baseline $\geq$ 2  DELLVA1997: Hospitalisation for psychopathology
Duration of treatment	26 weeks	26 weeks	42– 46 weeks
Setting	Outpatient	Inpatient and outpatient	Outpatient
Medication dose (mg/ day)	Amisulpride: 100 (fixed)	Aripiprazole: 15 (fixed)	BEASLEY2000, olanzapine: 10–20 (range) DELLVA1997, olanzapine: ~12 (semi-fixed)

	Paliperidone versus placebo	Ziprasidone versus placebo	Zotepine versus placebo
<i>k</i> (total <i>N</i> )	1 (207)	1 (277)	1 (119)
<i>Study ID</i>	KRAMER2007	ARATO2002	COOPER2000
<i>Selected inclusion criteria</i>	Achieved stabilisation after 8-week hospitalisation for an acute episode, then further 6-week stabilisation	Lack of acute relapse, lack of treatment resistance, and living under medical supervision for at least 2 months	Rating of at least mildly ill according to CGI; relapse in the 18 months before inclusion
<i>Diagnostic criteria</i>	DSM-IV	DSM-III-R	DSM-III-R
<i>Definition of relapse</i>	Recurrent episode of schizophrenia	Hospitalisation for psychopathology	Hospitalisation for psychopathology
<i>Duration of treatment</i>	46 weeks	52 weeks	26 weeks
<i>Setting</i>	Inpatient initially, then outpatient	Inpatient	Inpatient/outpatient
<i>Medication dose (mg/day)</i>	Paliperidone: 10.8 (mean); 3–15 (range)	Ziprasidone: 40, 80 or 160 (fixed)	Zotepine: 150 or 300 (fixed)
<i>Note.</i> <sup>a</sup> Minimally symptomatic; negative symptoms; at least 6 weeks of stability; continued stability while taking olanzapine during an 8-week period. <sup>b</sup> Responder from 6-week acute treatment phase (responders defined as $\geq 40\%$ reduction in BPRS score or BPRS score $\leq 18$ ).			

### **10.4.5 Second-generation antipsychotics versus another antipsychotic drug in people with schizophrenia that is in remission (relapse prevention)**

Nine RCTs were included in the meta-analysis comparing an SGA (amisulpride, olanzapine, risperidone) with an FGA (haloperidol) (see Table 100), and two were included in the analysis comparing an SGA (olanzapine) with another SGA (risperidone, ziprasidone) (see Table 101). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### **10.4.6 Clinical evidence summary**

In 17 RCTs including 3,535 participants with schizophrenia, the evidence suggested that, when compared with placebo, all of the antipsychotics examined reduced the risk of relapse or overall treatment failure. Although some SGAs show a modest benefit over haloperidol, there is insufficient evidence to choose between antipsychotics in terms of relapse prevention.

## **10.5 PROMOTING RECOVERY IN PEOPLE WITH SCHIZOPHRENIA WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO TREATMENT**

### **10.5.1 Introduction**

The phrase ‘treatment-resistant’ is commonly used to describe people with schizophrenia whose illness has not responded adequately to treatment. The essence of treatment resistance in schizophrenia is the presence of poor psychosocial and community functioning that persists despite trials of medication that have been adequate in terms of dose, duration and adherence. While treatment resistance is sometimes conceptualised in terms of enduring positive psychotic symptoms, other features of schizophrenia can contribute to poor psychosocial and community functioning, including negative symptoms, affective symptoms, medication side effects, cognitive deficits and disturbed behaviour. Treatment resistance in schizophrenia is relatively common, in that between a fifth and a third of service users show a disappointing response to adequate trials of antipsychotic medication (Brenner et al., 1990; Conley & Buchanan, 1997; Lieberman et al., 1992). In a small proportion of people experiencing their first episode of schizophrenia, the illness will be resistant to antipsychotic medication, showing only a limited response (for example, precluding early discharge from hospital) (Lambert et al., 2008; Lieberman et al., 1989; Lieberman et al., 1992; MacMillan et al., 1986; May, 1968), but more commonly the illness becomes progressively more unresponsive to medication over time (Lieberman et al., 1993; Wiersma et al., 1998).



**Table 100: Summary of study characteristics for RCTs of an SGA versus another antipsychotic drug (relapse prevention)**

	<b>Amisulpride versus haloperidol</b>	<b>Olanzapine versus haloperidol</b>	<b>Risperidone versus haloperidol</b>
<i>K (total N)</i>	1 (60)	4 (1082)	2 (428)
<i>StudyID</i>	Speller1997	Tran1998a Tran1998b Tran1998c STUDY-S029	Csernansky2000 MARDER2003 <sup>a</sup>
<i>Selected inclusion criteria</i>	Chronic, long-term hospitalised inpatient; moderate to severe negative symptoms	Tran1998(a,b,c): Responder from a 6-week acute treatment (at least 40% reduction of BPRS score or BPRS score ≤18) STUDY-S029: Received a stable dose of the same conventional antipsychotic drug ≥8weeks before visit 1; had a PANSS score ≥49 at visit 2; considered as possible patient in the patients with schizophrenia study (that is, patient global outcome improvement or benefit, such as optimisation of long-term therapy) who should benefit from a switch of current therapy based on investigator's judgment as a result of efficacy (PANSS score ≥ 49) or tolerability concerns.	Csernansky2000: Stability according to clinical judgment; receipt of the same medication for 30days; same residence for 30 days MARDER2003: Atleast two acute episodes in last 2 years or 2 years of continuing symptoms; receipt of treatment as an outpatient for at least 1 month
<i>Diagnostic criteria</i>		DSM-III-R, DSM-IV	DSM-IV

**Table 100: (Continued)**

	<b>Amisulpride versus haloperidol</b>	<b>Olanzapine versus haloperidol</b>	<b>Risperidone versus haloperidol</b>
<i>Definition of relapse</i>	Increase of three or more BPRS positive symptom items that did not respond to a dose increase	Tran1998(a,b,c): Hospitalisation for psychopathology STUDY-S029: Psychiatric hospitalisation or 25% increase in the PANSS total score in relation to baseline or major deterioration in clinical condition defined by a CGI-I score of 6 or 7, or suicide attempt that required medical treatment and/or jeopardised vital prognosis	Csernansky2000: (1) Hospitalisation; (2) increase of level of care and 20% increase in PANSS score; (3) self-injury, suicidal or homicidal ideation, Violent behaviour; (4) CGI rating >6  MARDER2003: Increase >3 in the BPRS scores for the thought disorder and hostile-suspiciousness clusters, or an increase > 2 in the score for either of these clusters and as core >3 on at least one item of these clusters
<i>Duration of treatment</i>	52 weeks	22–84 weeks	52 weeks
<i>Setting</i>	Inpatient	Inpatient/outpatient	Outpatient
<i>Medication dose (mg/day)</i>	Amisulpride: 100–800; Haloperidol: 3–20 <sup>b</sup>	Tran1998 a and b Olanzapine: ~12 (semi-fixed) Haloperidol: ~14 (semi-fixed)  Tran1998c Olanzapine: 14 (mean); 5–20 (range) Haloperidol: 13 (mean); 5–20 (range)	Risperidone: ~5 (mean); 2–16 (range) Haloperidol: <5–12 (range of means); 2–20 (range)
<i>Note.</i> <sup>a</sup> Duration was 2 years, but 1-year data was used for the review to enhance comparability <sup>b</sup> A minimum effective dose strategy was followed.			

**Table 101: Summary of study characteristics for RCTs of an SGA versus another SGA (relapse prevention)**

	Olanzapine versus risperidone	Olanzapine versus ziprasidone
<i>K (total N)</i>	1 (339)	1 (126)
<i>Study ID</i>	Tran1997	SIMPSON2005
<i>Selected inclusion criteria</i>	Minimum BPRS of 42 and excluded for failure to show minimal clinical response with antipsychotics in three chemical classes dosed at $\geq 800$ chlorpromazine hydrochloride equivalents/day or clozapin edosed at $\geq 400$ mg/day for at least 6weeks	Responders to 6-week acute treatment trial of olanzapine or risperidone (response defined as a CGI-I of $\leq 2$ or a $\geq 20\%$ reduction in PANSS at acute-study end point, and outpatient status)
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV
<i>Definition of relapse</i>	20% or greater worsening in the PANSS total score along with a CGI-S score $\geq 3$ after 8 weeks of therapy	$\geq 20\%$ worsening of PANSS total score and a CGI severity score $\geq 3$
<i>Duration of treatments</i>	28 weeks	28 weeks
<i>Setting</i>	Inpatient or outpatient	Outpatient
<i>Medication dose (mg/day)</i>	Olanzapine: 17.2 (mean modal); 10–20 (range) Risperidone: 7.2 (mean modal); 4–12 (range)	Olanzapine: 12.6 (mean); 5–15 (range) Ziprasidone: 135.2 (mean); 78–162 (range)

The definition of the term ‘treatment-resistant schizophrenia’ varies considerably in the studies covered in this review. Kane et al. (1988) introduced rigorous criteria involving aspects of the clinical history, cross-sectional measures and prospective assessments. One trend has been a move towards broader definitions of treatment resistance that allow a larger number of individuals to be viewed as clinically eligible for treatment with clozapine. For example, Bondolfi et al. (1998) included in their trial people with chronic schizophrenia who ‘had previously failed to respond to or were intolerant of at least two different classes of antipsychotic drugs given in appropriate doses for at least 4 weeks each’. Others have adopted an even wider clinical notion of ‘incomplete recovery’ (Pantelis & Lambert, 2003), which acknowledges the presence of lasting disability in functional and psychosocial aspects despite psychological/psychosocial and pharmacological interventions, while also recognising the potential for improvement.

### 10.5.2 Treatment-resistant schizophrenia and antipsychotic medication

High-dosage antipsychotic medication is commonly used for treatment-resistant schizophrenia, although there is little evidence to suggest any significant benefit with such a strategy (Royal College of Psychiatrists, 2006). Clinicians may also try switching to another antipsychotic, although similarly the research evidence on the possible value of such a strategy is not consistent or promising (Kinon et al., 1993; Lindenmayer et al., 2002; Shalev et al., 1993). An alternative strategy has been to try

to potentiate antipsychotics by combining them either with each other (see Section 10.5.3) or with other classes of drugs. Possible adjuncts to antipsychotic treatment include mood stabilisers and anticonvulsants, such as lithium, carbamazepine, sodium valproate, lamotrigine, antidepressants and benzodiazepines (Barnes et al., 2003; Chong & Remington, 2000; Durson & Deakin, 2001). However, the use of such adjunctive treatments to augment the action of antipsychotics is beyond the scope of this guideline.

Kane and colleagues (1988; 2001) established the efficacy of clozapine over FGAs in strictly-defined treatment-resistant schizophrenia, and subsequent meta-analyses have confirmed the superiority of clozapine in terms of reducing symptoms and the risk of relapse (Chakos et al., 2001; Wahlbeck et al., 1999). However, Chakos et al. (2001) concluded from their meta-analysis that the evidence for clozapine when compared with the SGAs tested was inconclusive. Even with optimum clozapine treatment, the evidence suggests that only 30 to 60% of treatment-resistant schizophrenia will show a satisfactory response (Iqbal et al., 2003). As clozapine is associated with severe and potentially life-threatening side effects, particularly the risk of agranulocytosis, the SPC states that drug should only be considered where there has been a lack of satisfactory clinical improvement despite adequate trials, in dosage and duration, of at least two different antipsychotic agents including an SGA.

Monitoring plasma clozapine concentration may be helpful in establishing the optimum dose of clozapine in terms of risk-benefit ratio, and also in assessing adherence (Gaertner et al., 2001; Llorca et al., 2002; Rostami-Hodjegan et al., 2004) particularly for service users showing a poor therapeutic response or experiencing significant side effects despite appropriate dosage. An adequate trial will involve titrating the dosage to achieve a target plasma level, usually considered to be above 350mg/l, although response may be seen at lower levels (Dettling et al., 2000; Rostami-Hodjegan et al., 2004). If the response to clozapine monotherapy is poor, augmentation strategies may be considered (see Section 10.5.3 for a review of the evidence).

A number of patient-related factors have been reported to increase the variability of plasma clozapine concentrations, with gender, age and smoking behaviour being the most important (Rostami-Hodjegan et al., 2004). Smoking is thought to increase the metabolism of clozapine by inducing the cytochrome P450 1A2 (CYP1A2) and other hepatic enzymes (Flanagan, 2006; Ozdemir et al., 2002). The metabolism of clozapine is mainly dependent on CYP1A2. This has several clinical implications. First, there is some evidence that smokers are prescribed higher doses by clinicians to compensate for higher clozapine clearance (Tang et al., 2007). Secondly, plasma concentrations of clozapine and its active metabolite, norclozapine, vary considerably at a given dosage, and this variation may be greater in heavy smokers receiving lower doses of clozapine, increasing the risk of subtherapeutic concentrations (Diaz et al., 2005). Thirdly, prompt adjustment of clozapine dosage in patients who stop smoking during treatment is important, to avoid the substantially elevated clozapine

concentrations and increased risk of toxicity that would otherwise be expected (Flanagan, 2006; McCarthy, 1994; Zullino et al., 2002).

### 10.5.3 Combining antipsychotic drugs

In clinical practice, the prescription of combined antipsychotics is relatively common. A multi-centre audit of the prescription of antipsychotic drugs for inpatients in 47 mental health services in the UK, involving over 3,000 inpatients, found that nearly half were receiving more than one antipsychotic drug (Harrington et al., 2002). Similarly, prescription surveys in the UK by Taylor and colleagues (2000; 2002) and the Prescribing Observatory for Mental Health (Paton et al., 2008) have confirmed a relatively high prevalence of combined antipsychotics for people with schizophrenia, including co-prescription of FGAs and SGAs.

The reasons for such prescriptions include as required ('p.r.n.') medication, a gradual switch from one antipsychotic drug to another and adding an oral antipsychotic to depot treatment to stabilise illness. A common rationale for combining antipsychotics is to achieve a greater therapeutic response when there has been an unsatisfactory response to a single antipsychotic. In this respect, there is little supportive evidence for superior efficacy (Chan & Sweeting, 2007; Chong & Remington, 2000), and Kreyenbuhl and colleagues (2007) reported that psychiatrists perceive antipsychotic polypharmacy to be generally ineffective for persistent positive psychotic symptoms. The concerns with combined antipsychotics include prescribing higher than necessary total dosage and an increased risk of side effects. If there is clinical benefit, one problem is the attribution of this to the combination rather than one or other of the individual antipsychotics, and thus uncertainty about the implications for optimal pharmacological treatment longer term.

For treatment-resistant schizophrenia that has proved to be unresponsive to clozapine alone, adding a second antipsychotic would seem to be a relatively common strategy. The prevalence of this augmentation strategy in people with schizophrenia on clozapine ranges from 18 to 44% depending on the clinical setting and country (Buckley et al., 2001; Potter et al., 1989; Taylor et al., 2000).

The mechanisms that might underlie any increase in therapeutic effect with combined antipsychotics have not been systematically studied (McCarthy & Terkelsen, 1995). However, in relation to the strategy of adding an antipsychotic to clozapine, it has been hypothesised that any pharmacodynamic synergy might be related to an increased level of D2 dopamine receptor occupancy, above a threshold level (Chong & Remington, 2000; Kontaxakis et al., 2005). However, such an increase might also be expected to be associated with an increased risk of EPS. An alteration of the interaction between serotonin (5-hydroxytryptamine) and D2 activity has also been suggested as a relevant mechanism (Shiloh et al., 1997). Further, pharmacokinetic interactions might play a part, although there is no consistent evidence that adding an antipsychotic leads to increased clozapine plasma levels (Honer et al., 2006; Josiassen et al., 2005; Yagcioglu et al., 2005).

RCTs and open studies have reported clozapine augmentation with a second antipsychotic to be relatively well tolerated. The main treatment-emergent side effects have been predictable from the pharmacology of the augmenting drug, with EPS and prolactin elevation among the most common problems. However, with risperidone as the augmenting antipsychotic there are isolated reports of problems such as agranulocytosis, a trial ectopics and possible neuroleptic malignant syndrome (Chong et al., 1996; Godleski & Sernyak, 1996; Kontaxakis et al., 2002); with aripiprazole as the second antipsychotic, there are reports of nausea, vomiting, insomnia, headache and agitation in the first 2 weeks (Ziegenbein et al., 2006) and also modest weight loss (Karunakaran et al., 2006; Ziegenbein et al., 2006).

### 10.5.4 Clinical review protocol

The clinical review protocol, including the primary clinical questions, information about the databases searched and the eligibility criteria, can be found in Table 102. A new systematic search for relevant RCTs, published since the 2002 guideline, was conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).

**Table 102: Clinical review protocol for the review of interventions for people with schizophrenia whose illness has not responded adequately to treatment**

<i>Primary clinical questions</i>	For people with schizophrenia whose illness has not responded adequately to treatment, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?  For people with schizophrenia with persistent negative symptoms, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another antipsychotic drug (when administered within the recommended dose range [BNF54])?  For people with schizophrenia whose illness has not responded adequately to clozapine treatment, is augmentation of clozapine with another antipsychotic associated with an enhanced therapeutic response?
<i>Electronic databases</i>	CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO
<i>Date searched</i>	1 January 2002 to 30 July 2008
<i>Study design</i>	Double-blind RCT ( $\geq 10$ participants per arm and $\geq 4$ weeks' duration)
<i>Patient population</i>	Adults (18+) with schizophrenia whose illness has not responded adequately to treatment (including those with persistent negative symptoms)
<i>Excluded populations</i>	Very late onset schizophrenia (onset after age 60). Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis. People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse.

<i>Interventions</i>	FGAs: Benperidol Chlorpromazine hydrochloride Flupentixol Fluphenazine hydrochloride Haloperidol Levomepromazine Pericyazine Perphenazine Pimozide Prochlorperazine Promazine hydrochloride Sulpiride Trifluoperazine Zuclopenthixol acetate Zuclopenthixol dihydrochloride	SGAs: Amisulpride Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone Sertindole Zotepine
<i>Comparator</i>	Any relevant antipsychotic drug	
<i>Critical outcomes</i>	Mortality (suicide) Global state (relapse) Mental state (total symptoms, negative symptoms, depression) Social functioning Cognitive functioning Leaving the study early for any reason Adverse events	
<i>Note.</i> Studies (or outcomes from studies) were categorised as short term (12 weeks or fewer), medium term (12–51 weeks) and long term (52 weeks or more); studies that used drug doses outside the recommended dose range were flagged during data analysis. <sup>a</sup> Studies that only included participants with persistent negative symptoms were analysed separately.		

### 10.5.5 Studies considered for review

In the 2002 guideline, 19 RCTs were included in the review of antipsychotic medication for people with schizophrenia whose illness has not responded adequately to treatment. The search for the 2009 guideline identified five papers providing follow-up data or published versions of existing trials, and eight new trials (one trial [LIBERMAN2002] provided no useable outcome data and was excluded from the analysis). In addition, six trials (Altamura1999; Breier2000; Conley1998a; Emsley1999; Heck2000; Kern1998) analysed in the 2002 guideline as acute phase studies were now included in the 2009 review, and three (Essock1996a; Gelenberg1979b; Wahlbeck2000) previously included in the 2002 guideline were excluded in the 2009 guideline. In total, 26 trials (N = 3,932) met the inclusion criteria for the 2009 guideline review. Further information about both included and excluded studies can be found in Appendix 22b.

A new analysis, not conducted for the 2002 guideline, examined RCTs of antipsychotic medication in people with persistent negative symptoms of

schizophrenia. Three trials (Boyer1990; Lecrubier1999; Murasaki1999) included in the 2002 review of acute treatment are now included here, but excluded from the review of acute treatment in the 2009 guideline. One trial (OLIE2006<sup>1</sup>) excluded from the 2002 guideline is now included. One trial (Speller1997) included in the relapse prevention review also met the inclusion criteria for this review. The search for the 2009 guideline also identified five new RCTs that are included in this review, and one trial (HERTLING2003) that reported no appropriate data and so was excluded from the analysis. In total, ten RCTs (N =1,200) met the inclusion criteria for the 2009 guideline review. Further information about both included and excluded studies can be found in Appendix 22b.

For the review of clozapine augmentation, an existing systematic review and meta-analysis (Paton et al., 2007), published since the 2002 guideline, was used as the basis for an updated meta-analysis in the 2009 guideline. This published review focused on the augmentation of clozapine with another SGA and included four RCTs. The search for the 2009 guideline identified two further RCTs. In total, six trials (N = 252) met the inclusion criteria for the update. In addition, two small studies (Assion et al., 2008; Mossaheb et al., 2006) with fewer than ten participants in either arm were excluded, and one trial of clozapine plus amisulpride versus clozapine plus quetiapine (Genc et al., 2007) was excluded. Further information about both included and excluded studies can be found in Appendix 22b.

#### **10.5.6 Clozapine versus another antipsychotic drug in people with schizophrenia whose illness has not responded adequately to treatment**

Seven RCTs were included in the analysis comparing clozapine with an FGA in people with schizophrenia whose illness has not responded adequately to treatment (see Table 103), and ten RCTs were included in the analysis of clozapine versus another SGA (see Table 104). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

---

<sup>1</sup> In the previous guideline this trial this was labelled as 'Study 128-305'.



**Table 103: Summary of study characteristics for RCTs of clozapine versus an FGA in people with schizophrenia whose illness has not responded adequately to treatment**

	Clozapine versus haloperidol	Clozapine versus anon-haloperidol FGA
<i>K (total N)</i>	4 (607)	3 (459)
<i>Study ID</i>	Buchanan1998 Klieser1989 Rosenheck1997 VOLAVKA2002	Claghorn1987 Hong1997 Kane1988
<i>Diagnostic criteria</i>	DSM-III-R, DSM-IV	DSM-II, DSM-III, DSM-IV
<i>Selected inclusion criteria</i>	Buchanan1998: Non-complete response to at least two trials of therapeutic doses of antipsychotics for at least 6 weeks Klieser1989: Chronic treatment-resistant (no diagnostic criteria) Rosenheck1997: Treatment-resistant, high level use of inpatient services VOLAVKA2002: Suboptimal response to previous treatment, defined by history of persistent positive symptoms after at least 6 contiguous weeks of treatment with one or more typical antipsychotics at $\geq 600\text{mg/d}$ in chlorpromazine hydrochloride equivalents, and a poor level of functioning over past 2 years	Claghorn1987: In tolerant to at least two prior antipsychotics Hong1997: Treatment-refractory (severe psychotic symptoms according to BPRS item scores for $> 6$ months despite treatment with antipsychotics from at least two different classes at dosages of at least 1000 mg chlorpromazine hydrochloride equivalents) Kane1988: $\geq 3$ periods of antipsychotic treatment, 1000mg/day of chlorpromazine hydrochloride equivalents without significant symptomatic relief and BPRS total score of at least 45
<i>Setting</i>	Inpatient/outpatient	Inpatient
<i>Duration of treatment</i>	Short term: 6–10 weeks Medium term: 14 weeks Long term: 52weeks	Short term: 4–8weeks Medium term: 12weeks
<i>Medication dose (mg/day)</i>	Clozapine: 400–552mg/day (range of means); 100–900mg/day (range) Haloperidol: 20–28mg/day (range of means); 5–30mg/day (range)	Clozapine: 417–543mg/d (range of means); 150–900mg/d (range) Chlorpromazine hydrochloride: 798–1163mg/day (range of means); 300–1800mg/day (range)
<i>Note.</i> <sup>a</sup> All three trials used chlorpromazine as the comparator.		

**Table 104: Summary of study characteristics for RCTs of clozapine versus another SGA in people with schizophrenia whose illness has not responded adequately to treatment**

	Clozapine versus olanzapine	Clozapine versus risperidone	Clozapine versus zotepine
K (total N)	5 (485)	5 (529)	1 (50)
Study ID	Beuzen1998 Bitter1999 (BITTER2004) MELTZER2008 Oliemeulen2000 VOLAVKA2002	Anand1998 Bondolfi1998 Breier1999 Chowdhury1999 VOLAVKA2002	Meyer-Lindberg 1996
Diagnostic criteria	DSM-IV	DSM-III-R, DSM-IV, ICD-10	DSM-III-R
Selected inclusion criteria	Beuzen1998: Treatment resistant, >3 on at least two items of PANSS positive subscale Bitter1999: Treatment-resistant or intolerant individuals must have not responded adequately to standard acceptable antipsychotic medication, either because of ineffectiveness or because of intolerable side effects caused by the medication MELTZER2008: Documented history of treatment-resistant schizophrenia based on Kane and colleagues' (1988) criteria Oliemeulen2000: Therapy-resistant; schizophrenia or other psychotic disorders	Anand1998: Treatment resistant: severe, chronic disease and poor response to previous antipsychotics (no period of good functioning for at least 24 months despite the use of two antipsychotics, current episode without significant improvement for at least 6 months despite the use of an antipsychotic equivalent to haloperidol 20mg for at least 6 weeks, total BPRS at least 45, and CGI at least 4 Bondolfi1998: Treatment resistant: failed to respond/intolerant to >2 different classes of antipsychotics in appropriate doses for >4 weeks Breier1999: Partial response to antipsychotics, defined as a history of	Unresponsive to >3 weeks of two FGAs ineffective doses, BPRS>39

	VOLAVKA2002: Suboptimal response to previous treatment, defined by history of persistent positive symptoms after at least 6 contiguous weeks of treatment with one or more typical antipsychotics at $\geq 600$ mg/day in chlorpromazine hydrochloride equivalents, and a poor level of functioning over past 2 years	residual positive and/or negative symptoms after at least a 6-week trial of a therapeutic dose of an antipsychotic and at least a minimum level of symptoms Chowdhury1999: Duration of illness >6 months and received at least one full course of FGA without adequate response, or cases intolerant to FGAs because of intractable neurological and non-neurological side effects, necessitating withdrawal of drug or inadequate dosing VOLAVKA2002: see left	
Setting	Inpatient/outpatient	Inpatient (not stated in three trials)	Not stated
Duration of treatment	Short term: 8 weeks Medium term: 14–26 weeks	Short term: 6–8 weeks Medium term: 12–16 weeks	Short term: 6 weeks
Medication dose (mg/day)	Clozapine: 564 mg/day (mean); 200–900 mg/day (range) Olanzapine: 33.6 mg/day (mean); 10–45 mg/day (range)	Clozapine: 291–597.5 mg/d (range of means); 150–900 mg/d (range) Risperidone: 5.8–8.3 mg/day (range of means); 2–16 mg/day (range)	Clozapine: 150–450 mg/day (range) Zotepine: 150–450 mg/d (range)

### **10.5.7 Second-generation antipsychotic drugs (other than clozapine) versus first-generation antipsychotic drugs in people with schizophrenia whose illness has not responded adequately to treatment**

Ten RCTs were included in the analysis comparing clozapine with another antipsychotic in people with schizophrenia whose illness has not responded adequately to treatment (see Table 105). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### **10.5.8 Second-generation antipsychotic drugs (other than clozapine) versus second-generation antipsychotic drugs in people with schizophrenia whose illness has not responded adequately to treatment**

Three RCTs were included in the analysis comparing an SGA (olanzapine and risperidone) with another SGA in people with schizophrenia whose illness has not responded adequately to treatment (see Table 106). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### **10.5.9 Second-generation antipsychotic drugs (other than clozapine) versus another antipsychotic in people who have persistent negative symptoms**

Five RCTs were included in the analysis comparing an SGA (amisulpride, olanzapine, quetiapine, risperidone) with another SGA in people who have persistent negative symptoms (see Table 107). Five RCTs were included in the analysis comparing an SGA (amisulpride, olanzapine, quetiapine, risperidone) with another SGA in people who have persistent negative symptoms (see Table 108). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### **10.5.10 Combining antipsychotics (augmentation of clozapine with another second-generation antipsychotic drug)**

One trial was included in the analysis comparing clozapine plus aripiprazole with clozapine plus placebo, four trials compared clozapine plus risperidone with clozapine plus placebo, and one trial compared clozapine plus sulpiride with clozapine plus placebo (see Table 109). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

**Table 105: Summary of study characteristics for RCTs of SGAs versus FGAs in people with schizophrenia whose illness has not responded adequately to treatment**

	Aripiprazole versus a non-haloperidol FGA	Olanzapine versus haloperidol	Olanzapine versus a non-haloperidol FGA
<i>K (total N)</i>	1 (300)	3 (617)	1 (84)
<i>Study ID</i>	KANE2007B	Altamura1999 (ALTAMURA2002) Breier2000 BUCHANAN2005	Conley1998a
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV	DSM-III-R
<i>Selected inclusion criteria</i>	Treatment resistant (defined as failure to experience satisfactory symptom relief despite at least two periods of treatment, each lasting ≥6 weeks with adequate doses of antipsychotics)	Altamura1999: Partial or non- responders to treatment according to preset criteria Breier2000: Sub-population from Tollefson1997 with treatment- resistant schizophrenia, defined as failure to respond to at least one neuroleptic over a period of at least 8 weeks during the previous 2 years BUCHANAN2005: Partial response to fluphenazine during 4-week open-label phase	Treatment resistant: Non-responders during haloperidol phase.
<i>Setting</i>	Inpatient/outpatient	Inpatient/outpatient	Inpatient
<i>Duration of treatment</i>	Short term: 6weeks	Short term: 6weeks Medium term: 14–16weeks	Short term: 8weeks
<i>Medication dose (mg/day)</i>	Aripiprazole: 15–30mg/ day (range) Perphenazine: 8–64mg/ day (range)	Olanzapine: 11.1–12.4mg/ day (range of means); 5–30mg/ day (range) Haloperidol: 10–12.3mg/ day (range of means); 5–30mg/ day (range)	Olanzapine: 25mg/ day (fixed) Chlorpromazine hydrochloride: 1200mg/ day (fixed)

**Table 105: Summary of study characteristics for RCTs of SGAs versus FGAs in people with schizophrenia whose illness has not responded adequately to treatment (*Continued*)**

	Quetiapine versus haloperidol	Quetiapine versus a non-haloperidol FGA	Risperidone versus haloperidol	Risperidone versus a non-haloperidol FGA
K (total N)	1 (288)	1 (25)	3 (161)	1 (26)
Study ID	Emsley1999	CONLEY2005	Heck2000 Kern1998 SEE1999	CONLEY2005
Diagnostic criteria	DSM-IV	DSM-IV	DSM-III-R, DSM-IV	DSM-IV
Selected inclusion criteria	Persistent positive symptoms while previously taking antipsychotics	Treatment resistant <sup>a</sup>	Heck2000: Disturbing EPS during their previous neuroleptic treatment Kern1998: Treatment resistant according to the Kane criteria SEE1999: A history of partial responsiveness to FGAs and residual symptoms	Treatment resistant
Setting	Not reported	Inpatient	Not reported	Inpatient
Duration of treatment	Short term: 8weeks	Medium term: 12weeks	Short term: 5–8 weeks	Medium term: 12 weeks
Medication dose (mg/ day)	Quetiapine: 600mg/day (fixed) Haloperidol: 20mg/day (fixed)	Quetiapine: 400mg/day (fixed) Fluphenazine hydrochloride: 12.5mg/day (fixed)	Risperidone: 7mg/day (mean) (Kern1998); 16mg/day (max) (Heck2000) Haloperidol: 19mg/day (mean) (Kern1998); 24mg/day (max) (Heck2000)	Risperidone: 4mg/day (fixed) Fluphenazine hydrochloride: 12.5mg/day (fixed)
<i>Note.</i> <sup>a</sup> Defined by: (1) Persistent positive symptoms ( $\geq 4$ points on 2 of 4 BPRS psychosis items); (2) Persistent global illness severity (BPRS total $\geq 45$ and CGI $\geq 4$ ); (3) At least two prior failed treatment trials with two different antipsychotics at doses of $\geq 600$ mg/day chlorpromazine hydrochloride equivalent each of at least 6 weeks' duration; (4) No stable period of good social/occupational functioning in past 5 years.				

**Table 106: Summary of study characteristics for RCTs of SGAs versus SGAs in people with schizophrenia whose illness has not responded adequately to treatment**

	Olanzapine versus risperidone	Olanzapine versus ziprasidone	Risperidone versus quetiapine
<i>k</i> (total N)	1 (80)	1 (394)	1 (25)
<i>Study ID</i>	VOLAVKA2002	KINON2006A	CONLEY2005
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV	DSM-IV
<i>Selected inclusion criteria</i>	Suboptimal response to previous treatment <sup>a</sup>	Prominent depressive symptoms	Treatment resistant <sup>c</sup>
<i>Setting</i>	Inpatient	Outpatient	Inpatient
<i>Duration of treatment</i>	Medium term: 14 weeks	Medium term: 24 weeks	Medium term: 12 weeks
<i>Medication dose (mg/day)</i>	Olanzapine: 10–40mg/day (range) Risperidone: 4–16mg/day (range)	Olanzapine: 10, 15 or 20mg/day (fixed) Ziprasidone: 80, 120 or 160mg/day (fixed)	Risperidone: 4mg/day (fixed) Quetiapine: 400mg/day (fixed)
<p>Note. <sup>a</sup> Defined by history of persistent positive symptoms after at least 6 contiguous weeks of treatment with one or more typical antipsychotics at <math>\geq 600</math>mg/day chlorpromazine hydrochloride equivalent, and a poor level of functioning over past 2 years.</p> <p><sup>b</sup> Defined by a MADRS score <math>\geq 16</math> (mild depression) and a score <math>\geq 4</math> (pervasive feelings of sadness or gloominess) on item 2 (reported sadness) of the MADRS.</p> <p><sup>c</sup> Defined by: (1) Persistent positive symptoms (<math>\geq 4</math> points on 2 of 4 BPRS psychosis items); (2) Persistent global illness severity (BPRS total <math>\geq 45</math> and CG I <math>\geq 4</math>); (3) At least two prior failed treatment trials with two different antipsychotics at doses of <math>\geq 600</math> mg/day chlorpromazine hydrochloride equivalent each of at least 6 weeks' duration; (4) No stable period of good social/occupational functioning in past 5 years.</p>			

**Table 107: Summary of study characteristics for RCTs of SGAs versus a FGA in people who have persistent negative symptoms**

	Amisulpride versus haloperidol	Amisulpride versus A non-haloperidol FGA	Olanzapine versus haloperidol	Quetiapine versus Haloperidol	Risperidone versus a non-haloperidol FGA
<i>K (total N)</i>	1 (60)	1 (62)	1 (35)	1 (197)	1 (153)
<i>Study ID</i>	Speller1997	Boyer1990	LINDENMAYER2007	Murasaki1999	RUHRMANN2007
<i>Diagnostic criteria</i>	Not reported	DSM-III	DSM-IV	DSM-IV or ICD-10	ICD-10
<i>Selected inclusion criteria</i>	Chronic, long-term hospitalised inpatients with moderate to severe negative symptoms	All met Andreasen criteria for negative symptoms and absence of marked positive symptoms.	Fulfilled criteria for the Schedule for the Deficit Syndrome (SDS) which included negative symptoms that are stable rather than unstable-state manifestations	Predominantly negative symptoms	Negative symptoms ( $\geq 3$ on PANSS negative subscale)
<i>Setting</i>	Not reported	Not reported	Inpatient/outpatient	Inpatient/outpatient	Inpatient/outpatient
<i>Duration of treatment</i>	Long term: 52 weeks	Short term: 6 weeks	Medium term: 12 weeks	Short term: 8 weeks	Medium term: 25 weeks
<i>Medication dose (mg/day)</i>	Amisulpride: 100–800mg/day Haloperidol: 3–20mg/day	Amisulpride: 225mg/day (mean); 50–300mg/day (range) Fluphenazine hydrochloride: 10mg/day (mean); 2–12mg/day (range)	Olanzapine: 15–20mg/day (range) Haloperidol: 15–20mg/day (range)	Quetiapine: 226mg/day (mean); 600mg/day (max) Haloperidol: 6.7mg/day (mean); 18mg/day (max)	Risperidone: 2–6mg/day (range) Flupentixol: 4–12mg/day (range)



**Table 108: Summary of study characteristics for RCTs of SGAs versus another SGA in people who have persistent negative symptoms**

	<b>Amisulpride versus ziprasidone</b>	<b>Olanzapine versus amisulpride</b>	<b>Olanzapine versus quetiapine</b>	<b>Risperidone versus quetiapine</b>
<i>K (total N)</i>	1 (123)	1 (140)	2 (386)	1 (44)
<i>Study ID</i>	OLIE2006	Lecrubier1999 (LECRUBIER2006)	KINON2006B SIROTA2006	RIEDEL2005
<i>Diagnostic criteria</i>	DSM-III-R	DSM-IV	DSM-IV	DSM-IV or ICD-10
<i>Selected inclusion criteria</i>	Negative symptoms (baseline scores on the PANSS negative subscale had to exceed the PANSS positive subscale by $\geq 6$ )	Primarily negative symptoms according to PANSS and SANS	Prominent negative symptoms according to PANSS and GAF/SANS.	Predominantly primary negative symptoms according to PANSS.
<i>Setting</i>	Outpatient	Inpatient/outpatient	Inpatient/outpatient	Inpatient/outpatient
<i>Duration of treatment</i>	Medium term: 12weeks	Medium term: 26weeks	Medium term: 12–26 weeks	Medium term: 12 weeks
<i>Medication dose (mg/day)</i>	Amisulpride: 144.7mg/day (mean); 100–200mg/day (range) Ziprasidone: 118mg/day (mean); 80–160mg/day (range)	Olanzapine: 5 or 20mg/day (fixed) Amisulpride: 150mg/day (fixed)	Olanzapine: 5–20mg/day (range) Quetiapine: 200–800mg/day (range)	Risperidone: 4.9mg/day (mean); 2–6mg/day (range) Quetiapine: 589.7mg/day (mean); 50–600mg/day (range)

**Table 109: Summary of study characteristics for trials of clozapine augmentation**

	Clozapine+aripiprazole versus clozapine+placebo	Clozapine+risperidone versus clozapine+placebo	Clozapine+sulpiride versus clozapine+placebo
<i>K (total N)</i>	1 (62)	4 (162)	1 (28)
<i>Study ID</i>	CHANG2008	FREUDENREICH2007 HONER2006 JOSIASSEN2005 YAGCIOGLU2005	SHILOH1997
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV	DSM-IV
<i>Inclusion criteria</i>	(1) Failure to respond to at least two previous antipsychotic drugs; (2) Clozapine treatment for more than 1 year with at least 8 weeks at a stable daily dose of 400 mg or more, unless compromised by adverse effects; (3) No change in clozapine daily dose or other concomitant medication for more than 3 months, indicating a plateau of clinical response to clozapine; (4) Either a baseline BPRS total score of at least 35 or more than two SANS global rating item scores of at least 3	FREUDENREICH2007: (1) Failure to respond to at least two previous antipsychotics; (2) currently treated with clozapine monotherapy for at least 6 months, at a stable dose for at least 8 weeks and with clozapine plasma levels of at least 200ng/mL, unless the clozapine dose necessary to achieve that level was not tolerated  HONER2006: (1) DSM diagnosis of schizophrenia; (2) 80 or more on PANSS and 4 or more on CGI; 3) 40 or less on Social and Occupational Functioning Assessment Scale; 4) Failure to respond ( $\geq 20\%$ reduction in BPRS) after one placebo augmentation for 1 week	(1) DSM diagnosis of schizophrenia; (2) Clozapine prescribed after failure to respond to three typical antipsychotics at adequate doses for at least 6 weeks each; (3) 25 or more on BPRS; (4) BPRS scores stable for 5 weeks; (5) Inability to function as an outpatient

		<p>JOSIASSEN2005: 1) DSM diagnosis of schizophrenia; 2) Continued significant psychotic symptoms; 3) Failure to respond to at least two previous antipsychotic drugs; 4) 45 or more on BPRS or 4 or more (moderately ill) on at least two BPRS positive symptoms subscale items (hallucinatory behaviour, conceptual disorganisation, unusual thought content, suspiciousness)</p> <p>YAGCIOGLU2005: 1) DSM diagnosis of schizophrenia; 2) Failure to respond to at least two previous antipsychotic drugs; 3) 72 or more on PANSS or 4 or more on CGI (moderate level of psychopathology); 4) Prescribed clozapine because of failure to respond to other antipsychotic treatments</p>	
<i>Setting</i>	Inpatient/outpatient	Inpatient/outpatient	Inpatient
<i>Baseline severity</i>	BPRS total 47.6 (clozapine + aripiprazole)/48.5 (clozapine + placebo)	Range of means: PANSS total 72.4–102.5 (clozapine + risperidone)/73.5–97.8 (clozapine + placebo)	BPRS total 41.9 (clozapine + sulpiride)/43.5 (clozapine + placebo)
<i>Duration of treatment</i>	8 weeks	<p>FREUDENREICH2007: 6 weeks</p> <p>HONER2006: 8 weeks</p> <p>JOSIASSEN2005: 12 weeks</p> <p>YAGCIOGLU2005: 6 weeks</p>	10 weeks

### **10.5.11 Clinical evidence summary**

In 18 RCTs including 2,554 participants whose illness had not responded adequately to treatment, clozapine had the most consistent evidence for efficacy over the FGAs included in the trials. Further evidence is required to establish equivalence between clozapine and any other SGA, and to establish whether there are differences between any of the other antipsychotic drugs. Side effects were consistent with those reported in the SPC for each drug.

In 10 RCTs including 1,200 participants with persistent negative symptoms, there was no evidence of clinically significant differences in efficacy between any of the antipsychotic drugs examined. Careful clinical assessment to determine whether such persistent features are primary or secondary is warranted, and may identify relevant treatment targets, such as drug-induced parkinsonism, depressive features or certain positive symptoms.

In six RCTs including 252 participants with schizophrenia whose illness had not responded adequately to clozapine treatment, there was some evidence that clozapine augmentation with a second antipsychotic might improve both total and negative symptoms if administered for an adequate duration.

## **10.6 TREATMENT WITH DEPOT/ LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATION**

### **10.6.1 Introduction**

The introduction of long-acting injectable formulations ('depot') of antipsychotic medication in the 1960s was heralded as a major advance in the treatment of established schizophrenia outside hospital. At the time it was hoped that depot preparations would lead to improved outcomes from antipsychotic pharmacotherapy. Consistent drug delivery and avoidance of the bioavailability problems that occur with oral preparations (such as gut wall and hepatic first-pass metabolism) were felt to be important factors. Other benefits include eliminating the risk of deliberate or inadvertent overdose. In the subsequent decades, the main practical clinical advantage to emerge has been the avoidance of covert non-adherence (both intentional and unintentional)<sup>1</sup> to antipsychotic drug treatment, where there is close nursing supervision and documentation of clinic attendance (Barnes & Curson, 1994; Patel & David, 2005). Service users who are receiving depot treatment and who decline their injection or fail to receive it (through forgetfulness or any other reason) can be immediately identified; allowing appropriate

---

<sup>1</sup>Further information about medicines concordance and adherence to treatment can be found in the NICE guideline on this topic (see <http://www.nice.org.uk>).

intervention, bearing in mind that poor adherence to the medication can be both a cause and consequence of worsening illness. In practice, the use of depot drugs does not guarantee good treatment adherence, with a significant number who are prescribed maintenance treatment with depot preparations after discharge from hospital failing to become established on the injections (Crammer & Eccleston, 1989; Young et al., 1999; Young et al., 1986). But for those who continue with long-acting injections, there may be some adherence advantage over oral antipsychotics, indicated by a longer time to medication discontinuation (Zhu et al., 2008). There is also some evidence to suggest a better global outcome with depot as compared with oral antipsychotics (Adams et al., 2001) with a reduced risk of rehospitalisation (Schooler, 2003; Tiihonen et al., 2006). In 2002, a long-acting formulation of an SGA, risperidone, became available, offering the same advantages of convenience and the avoidance of covert non-adherence (Hosalli & Davis, 2003.).

Information on the use of long-acting antipsychotic injections has been limited (Adams et al., 2001), but relevant surveys and audits of antipsychotic prescription in the UK suggest that between a quarter and a third of psychiatric patients prescribed an antipsychotic may be receiving a long-acting injection, depending on the clinical setting (Barnes et al., 2009; Foster et al., 1996; Paton et al., 2003).

### **10.6.2 Use of long-acting antipsychotic injections**

Long-acting injectable antipsychotic formulations generally consist of an ester of the drug in an oily solution. Another way of formulating such a preparation is to use microspheres of the drug suspended in aqueous solution. These drugs are administered by deep intramuscular injection and are then slowly released from the injection site, giving relatively stable plasma drug levels over long periods, allowing the injections to be given every few weeks. However, this also represents a potential disadvantage because there is a lack of flexibility of administration, with adjustment to the optimal dosage being a protracted and uncertain process. The controlled studies of low-dose maintenance treatment with depot preparations suggest that any increased risk of relapse consequent upon a dose reduction may take months or years to manifest. Another disadvantage is that, for some people, receiving the depot injection is an ignominious and passive experience. Further, there have been reports of pain, oedema, pruritus and sometimes a palpable mass at the injection site. In some people, these concerns may lead service users to take active steps to avoid these injections and even disengage with services altogether rather than receive medication via this route. Nevertheless, a substantial proportion of people receiving regular, long-acting antipsychotic injections prefer them to oral therapy, largely because they consider them to be more convenient (Patel & David, 2005; Walburn et al., 2001).

### **10.6.3 Clinical review protocol**

The review protocol, including the primary clinical questions, information about the databases searched and the eligibility criteria, can be found in Table 110. A new systematic search for relevant RCTs, published since the 2002 guideline, was

conducted for the 2009 guideline (further information about the search strategy can be found in Appendix 20).

**Table 110: Clinical review protocol for the review of depot/long-acting injectable antipsychotics**

<b>Primary clinical questions</b>	For people with schizophrenia that is in remission, is any depot or long-acting antipsychotic medication associated with improved relapse prevention overtime? For people with schizophrenia whose illness has not responded adequately to treatment and who have had long-term antipsychotic drug treatment, is there any evidence that patients have a preference for either depot/long-acting or oral preparations?
<b>Electronic databases</b>	CENTRAL, CINAHL, EMBASE, MEDLINE, PsycINFO
<b>Date searched</b>	1 January 2002 to 30 July 2008
<b>Study design</b>	Double-blind RCT ( $\geq 10$ participants per arm and $\geq 4$ weeks' duration)
<b>Patient population</b>	Adults (18+) with schizophrenia
<b>Excluded populations</b>	Very late onset schizophrenia (onset after age 60). Other psychotic disorders, such as bipolar disorder, mania or depressive psychosis. People with coexisting learning difficulties, significant physical or sensory difficulties, or substance misuse.
<b>Interventions</b>	FGAs: Flupentixol decanoate Fluphenazine decanoate Haloperidol (as decanoate) Pipotiazine palmitate Zuclopenthixol decanoate  SGAs: Risperidone (long-acting injection)
<b>Comparator</b>	Any relevant antipsychotic drug or placebo
<b>Critical outcomes</b>	Mortality (suicide) Global state (CGI, relapse) Mental state (total symptoms, negative symptoms, depression) Social functioning Leaving the study early for any reason Adverse events
<i>Note.</i> Studies (or outcomes from studies) were categorised as short term (12 weeks or fewer), medium term (12–51 weeks) and long term (52 weeks or more).	

#### 10.6.4 Studies considered for review

In the 2002 guideline, the review of depot antipsychotic medication was based on a meta-review of five Cochrane reviews (David & Adams, 2001), which included 13

RCTs of flupentixol decanoate, 48 of fluphenazine decanoate, 11 of haloperidol decanoate, ten of pipothiazine palmitate and three of zuclopenthixol decanoate. Since publication of the 2002 guideline, the review of fluphenazine decanoate (David & Adams, 2001) was updated and now includes 70 trials. The review of pipothiazine palmitate (Dinesh et al., 2004) was also updated and now includes 18 trials. In addition, one SGA (long-acting injectable risperidone) has been licensed for use as a depot. A Cochrane review of this medication for people with schizophrenia was published in 2003 (Hosalli & Davis, 2003.). The search for the 2009 guideline identified no additional trials that met the eligibility criteria. Because of the volume of evidence for FGA depots, the GDG checked the updated Cochrane reviews were consistent with the 2002 guideline and then focused on the evidence for long-acting risperidone, which had not previously been reviewed. In total, two trials (N = 1,042) met inclusion criteria (one trial of long-acting risperidone versus placebo, and one trial of long-acting risperidone versus oral risperidone). Both trials were published in peer-reviewed journals between 2003 and 2005. Further information about the included studies can be found in Appendix 22b.

### **10.6.5 Long-acting risperidone injection versus placebo or oral risperidone**

One RCT was included in the analysis comparing long-acting risperidone injection with placebo injection, and one RCT was included in the analysis comparing long-acting risperidone with oral risperidone plus placebo injection (see Table 111). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

### **10.6.6 Clinical evidence summary**

The search for the 2009 guideline did not identify any new evidence for the efficacy and safety of depot FGAs beyond that included in the updated Cochrane reviews (utilised in the 2002 guideline). These reviews did not indicate robust new evidence that would warrant changing the existing recommendations for depot antipsychotic medication.

Since publication of the 2002 guideline, the first depot SGA (risperidone) was licensed for use in the UK. However, there is currently only limited evidence from two double-blind RCTs regarding the efficacy and safety of long-acting injectable risperidone compared with placebo or oral antipsychotic medication (risperidone). The placebo controlled trial suggests that 25–75 mg of long-acting risperidone may improve the chance of response and produce a clinically significant reduction in the symptoms of schizophrenia, but larger doses carry an increased risk of neurological side effects. There is no evidence to suggest that long-acting risperidone has either greater efficacy or greater risk of adverse effects when compared with oral risperidone. However, as suggested by the trial authors, the trial was only designed to investigate the short-term switching of participants from oral medication to long-acting risperidone; further studies are needed to understand the effect of continuous delivery of this medication.

**Table 111: Summary of study characteristics for RCTs of long-acting risperidone versus placebo or oral risperidone**

	<b>Intramuscular injection of long-acting risperidone versus placebo injection</b>	<b>Intramuscular injection of long-acting risperidone versus oral risperidone+ placebo injection</b>
<i>K (total N)</i>	1 (400)	1 (642)
<i>Study ID</i>	KANE2003	CHUE2005
<i>Diagnostic criteria</i>	Schizophrenia (DSM-IV)	Schizophrenia (DSM-IV)
<i>Baseline severity</i>	25mg long-acting risperidone: PANSS total: Mean 81.7 (SD 12.5), n = 99 50mg long-acting risperidone: PANSS total: Mean 82.3 (SD 13.9), n = 103 75mg long-acting risperidone: PANSS total: Mean 80.1 (SD 14.0), n = 100 Placebo: PANSS total: mean 82.0 (SD 14.4), n = 98	Long-acting risperidone: PANSS total: mean 68.4 (SD 1.0), n = 319 Oral risperidone: PANSS total: Mean 69.3 (SD 0.9), n = 321  All participants were required to be symptomatically stable during the last 4 weeks of the run-in period
<i>Run-in</i>	1-week oral risperidone run-in period	8 weeks open-label period during which participants were stabilised on oral risperidone
<i>Setting</i>	Inpatient/outpatient	Inpatient/outpatient
<i>Duration of treatment</i>	12 weeks	12 weeks
<i>Medication dose (mg/day)</i>	Fixed dose of 25, 50 or 75 mg every 2 weeks	Long-acting risperidone: 88 participants received 25mg every 2 weeks, 126 received 50mg and 105 received 75mg  Oral risperidone: 86 participants received 2mg/day, 126 received 4mg/day and 109 received 6mg/day



## **10.7 SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION**

### **10.7.1 Introduction**

Given that for some antipsychotics there was a paucity of side-effect data, the GDG decided to pool data, where appropriate, from the studies included in the other meta-analyses reported in this chapter and from any other relevant clinical trial. The review focused on metabolic and neurological side effects as these were considered a priority by the GDG and were also highlighted as areas of concern by service users.

### **10.7.2 Studies considered for review**

All RCTs included in the efficacy reviews (except studies of depot/long-acting antipsychotics) were included in the overall side effects meta-analysis. In addition, four trials (ATMACA2003; LIEBERMAN2003B; MCQUADE2004; MELTZER2003) did not meet the inclusion criteria for any of the efficacy reviews, but reported relevant side effect data and so were included here.

### **10.7.3 Second-generation antipsychotic drugs versus another antipsychotic drug (overall analysis of side effects)**

As shown in Table 112, 14 separate RCTs were included in the analysis of amisulpride against haloperidol ( $k = 6$ ), a non-haloperidol FGA ( $k = 2$ ), or an SGA ( $k = 6$ ). Seven separate trials were included in the analysis of aripiprazole against haloperidol ( $k = 2$ ), a non-haloperidol FGA ( $k = 1$ ), or an SGA ( $k = 4$ ). Sixteen separate trials were included in the analysis of clozapine against haloperidol ( $k = 4$ ), a non-haloperidol FGA ( $k = 4$ ), or an SGA ( $k = 9$ ). Forty-one separate trials were included in the analysis of olanzapine against haloperidol ( $k = 18$ ), a non-haloperidol FGA ( $k = 5$ ), or an SGA ( $k = 19$ ). Three trials were included in the analysis of paliperidone against an SGA ( $k = 3$ ). Thirteen separate trials were included in the analysis of quetiapine against haloperidol ( $k = 5$ ), a non-haloperidol FGA ( $k = 2$ ), or an SGA ( $k = 7$ ). Forty separate trials were included in the analysis of risperidone against haloperidol ( $k = 20$ ), a non-haloperidol FGA ( $k = 4$ ), or an SGA ( $k = 18$ ). Three separate trials were included in the analysis of sertindole against haloperidol ( $k = 2$ ), or an SGA ( $k = 1$ ). Seven separate trials were included in the analysis of zotepine against haloperidol ( $k = 5$ ), a non-haloperidol FGA ( $k = 1$ ), or an SGA ( $k = 1$ ). Forest plots and/or data tables for each outcome can be found in Appendix 23c.

**Table 112: Summary of studies included in the overall analysis of side effects**

Treatment	Comparator		
	Versus haloperidol (FGA)	Versus non-haloperidol FGA	Versus SGA
<b>Amisulpride</b>	Carriere2000 [16 weeks] Delcker1990 [6 weeks] Moller1997 [6 weeks] Puech1998 [4 weeks] Speller1997 [52 weeks] Ziegler1989 [4 weeks]	Boyer1990 (fluphenazine) [6 weeks] Hillert1994 (flupentixol) [6 weeks]	Fleurot1997 (risperidone) [8 weeks] HWANG2003 (risperidone) [6 weeks] Lecrubier1999 (olanzapine) [26 weeks] Lecrubier2000 (risperidone) [26 weeks] MARTIN2002 (olanzapine) [24 weeks] WAGNER2005 (olanzapine) [8 weeks]
	$k = 6$	$k = 2$	$k = 6$
<b>Aripiprazole</b>	KANE2002 [4 weeks] KASPER2003 [52 weeks]	KANE2007B (perphenazine) [6 weeks]	CHAN2007B (risperidone) [4 weeks] MCQUADE2004 (olanzapine) [26 weeks]* POTKIN2003A (risperidone) [4 weeks] ZIMBROFF2007 (ziprasidone) [4 weeks]
	$k = 2$	$k = 1$	$k = 4$
<b>Clozapine</b>	Buchanan1998 [10 weeks] Rosenheck1997 [52 weeks] Tamminga1994 [52 weeks] VOLAVKA2002 [14 weeks]	Claghorn1987 (chlorpromazine) [4–8 weeks] Hong1997 (chlorpromazine) [12 weeks] Kane1988 (chlorpromazine) [6 weeks] LIEBERMAN2003B [52 weeks]*	Anand1998 (risperidone) [12 weeks] ATMACA2003 (olanzapine/ quetiapine/risperidone) [6 weeks]* Beuzen1998 (olanzapine) [18 weeks] Bitter1999 (olanzapine) [18 weeks] Bondolfi1998 (risperidone) [8 weeks] Breier1999 (risperidone) [18 weeks] Chowdhury1999 (risperidone) [16 weeks] MELTZER2003A (olanzapine) [104 weeks]* VOLAVKA2002 (olanzapine/risperidone) [14 weeks]
	$k = 4$	$k = 4$	$k = 9$

<b>Olanzapine</b>	Altamura1999 [14 weeks] Beasley1996a [6weeks] Beasley1997 [6 weeks] Breier2000 [6 weeks] BUCHANAN2005 [16 weeks] HGCJ1999 (HK) [14 weeks] HGPU1998 (Taiwan) [14 weeks] Jones1998 [54 weeks] KONGSAKON2006 [24 weeks] LIEBERMAN2003A [24 weeks] LINDENMAYER2007 [12 weeks] ROSENHECK2003] [52 weeks] STUDY-S029 [52 weeks] Tollefson1997 [6 weeks] Tran1998a [52 weeks] Tran1998b [52 weeks] Tran1998c [22-84 weeks] VOLAVKA2002 [14 weeks]	Conley1998a (chlorpromazine) [8weeks] HGBL1997 (flupentixol) [4 weeks] Jakovljevic1999 (fluphenazine) [6 weeks] Loza1999 (chlorpromazine) [6 weeks] Naukkarinen1999/HGBJ (perphenazine) [26 weeks]	ATMACA2003 (quetiapine/ risperidone) [6weeks]* Conley2001 (risperidone) [8 weeks] DAVIDSON2007 (paliperidone) [6 weeks] Gureje1998 (risperidone) [30 weeks] Jones1998 (risperidone) [54 weeks] KANE2007A (paliperidone) [6 weeks] KINON2006B (quetiapine) [26 weeks] Lecrubier1999 (amisulpride) [26 weeks] MARDER2007 (paliperidone) [6 weeks] MARTIN2002 (amisulpride) [24 weeks] MCEVOY2007A (quetiapine/ risperidone) [52 weeks] MCQUADE2004 (aripiprazole) [26 weeks]* RIEDEL2007B (quetiapine) [8 weeks] SIROTA2006 (quetiapine) [26 weeks] StudyS036 (risperidone) [6 weeks] Tran1997 (risperidone) [28 weeks] VANNIMWEGEN2008 (risperidone)[6 weeks] VOLAVKA2002 (risperidone) [14 weeks] WAGNER2005 (amisulpride)[8 weeks]
	$k = 18$	$k = 5$	$k = 19$
<b>Paliperidone</b>	-	-	DAVIDSON2007 (paliperidone)[6 weeks] KANE2007A (paliperidone) [6 weeks] MARDER2007 (paliperidone) [6 weeks]
			$k = 3$

<b>Quetiapine</b>	Arvanitis1997 [6 weeks] Emsley1999 [8 weeks] Fleischhacker1996 [6 weeks] Murasaki1999 [8 weeks] Purdon2000 [26 weeks]	CONLEY2005 (fluphenazine) [12 weeks] Link1994 (chlorpromazine) [6 weeks]	ATMACA2003 (clozapine/ olanzapine/risperidone) [6 weeks]* CONLEY2005 (risperidone) [12 weeks] KINON2006B (olanzapine) [26 weeks] RIEDEL2005 (risperidone) [12 weeks] RIEDEL2007B (olanzapine) [8 weeks] SIROTA2006 (olanzapine) [26 weeks] ZHONG2006 (risperidone) [8 weeks]
	$k = 5$	$k = 2$	$k = 7$
<b>Risperidone</b>	Blin1996 [4 weeks] Ceskova1993 [8 weeks] Chouinard1993 [8 weeks] Claus1991 [12 weeks] Csernansky1999/2000 [52 weeks] Emsley1995 [6 weeks] Heck2000 [6 weeks] Janicak1999 [6 weeks] Jones1998 [54 weeks] Kern1998 [8 weeks] LEE2007 [24 weeks]	CONLEY2005 (fluphenazine) [12 weeks] Hoyberg1993 (perphenazine) [8 weeks] Huttunen1995 (zuclopenthixol) [8 weeks] RUHRMANN2007 (flupentixol) [25 weeks]	ATMACA2003 (olanzapine/quetiapine) [6 weeks]* AZORIN2006 (sertindole) [12 weeks] CHAN2007A (aripiprazole) [4 weeks] Conley2001 (olanzapine) [8 weeks] CONLEY2005 (quetiapine) [12 weeks] Fleurot1997 (amisulpride) [8 weeks] Gureje1998 (olanzapine) [30 weeks] HWANG2003 (amisulpride) [6 weeks] Jones1998 (olanzapine) [54 weeks] Klieser1996 (zotepine) [4 weeks] Lecrubier2000 (amisulpride) [26 weeks]

	Marder1994 [8 weeks] Mesotten1991 [8 weeks] Min1993 [8 weeks] MOLLER2008 [8weeks] Peuskens1995 [8weeks] SCHOOLER2005 [104 weeks] SEE1999 [5 weeks] ZHANG2001 [12 weeks] VOLAVKA2002 [14 weeks]		MCEVOY2007A (olanzapine/quetiapine) [52 weeks] POTKIN2003A (aripiprazole) [4 weeks] RIEDEL2005 (quetiapine) [12 weeks] StudyS036 (olanzapine) [6 weeks] Tran1997 (olanzapine) [28 weeks] VANNIMWEGEN2008 (olanzapine) [6 weeks] VOLAVKA2002 (clozapine/olanzapine) [14 weeks] ZHONG2006 (quetiapine) [8 weeks]
	$k = 20$	$k = 4$	$k = 19$
<b>Sertindole</b>	Hale2000 [8 weeks] Daniel1998 [52 weeks]*	-	AZORIN2006 (risperidone) [12 weeks]
	$k = 2$		$k = 1$
<b>Zotepine</b>	Barnas1987 [7 weeks] Fleischhacker1989 [6 weeks] Klieser1996 [4 weeks] KnollCTR (StudyZT4002) [26 weeks] Petit1996 [8 weeks]	Cooper1999a (chlorpromazine) [8 weeks]	Klieser1996 (risperidone) [4 weeks]
	$k = 5$	$k = 1$	$k = 1$
Note.*Study did not meet the inclusion criteria for any other review reported in this chapter.			

### **10.7.4 Clinical evidence summary**

Pooling data from 138 evaluations of one antipsychotic versus another antipsychotic did not reveal metabolic and neurological side effects that were inconsistent with those reported in the SPC for each drug. Because most trials were of relatively short duration and not designed to prospectively examine side effects, these trials provide little insight into the longer-term adverse effects of treatment or whether there are clinically significant differences between antipsychotic drugs.

## **10.8 EFFECTIVENESS OF ANTIPSYCHOTIC MEDICATION**

### **10.8.1 Introduction**

The RCT is widely recognised as the ‘gold standard’ for evaluating treatment efficacy, but some methodological issues may compromise the generalisability of the findings of research to the ordinary treatment setting. Nevertheless, it is still recognised that the RCT is an indispensable first step in the evaluation of interventions in mental health and provides the most valid method for determining the impact of two contrasting treatment conditions (treatment efficacy), while controlling for a wide range of participant factors including the effects of spontaneous remission.

Once an approach has been demonstrated as efficacious under the stringent conditions of an RCT, a next step is to examine its effectiveness in ordinary treatment conditions, including large-scale effectiveness (pragmatic) trials (very few of which were available when the 2002 guideline was developed).

In addition, the use of RCTs and other studies in the evaluation of interventions in the treatment of schizophrenia is limited in many cases by the absence of important outcome measures. For example, few trials report evidence on quality of life or satisfaction with services, despite the fact that service users and carers view these measures as very important. Effectiveness studies address this issue by focusing on patient-important outcomes.

### **10.8.2 Effectiveness (pragmatic) trials**

Given the large scope of the guideline update, the GDG decided to focus on effectiveness trials that included a comparison between an SGA and an FGA. To ensure that the evidence was from high-quality research and reduce the risk of bias, studies were included only if they used a randomised design with an intention-to-treat analysis and at least independent rater-blinding (that is, the clinicians doing the assessment of outcome were independent and blind to treatment allocation). All studies identified during the searches for other sections of this chapter were considered for inclusion.

Two studies published since the 2002 guideline met the inclusion criteria for this review. These were the CATIE study (Lieberman et al., 2005; Stroup et al., 2003),

funded by the National Institute of Mental Health, and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) (Jones et al., 2006; Lewis et al., 2006b), funded by the NHS Research and Development Health Technology Assessment Programme.

In the initial phase of CATIE (phase 1), which was conducted at 57 clinical sites in the US, 1,493 participants with chronic schizophrenia were randomised (double-blind) to one of four SGAs or an FGA (perphenazine) (see Table 113). Participants with current tardive dyskinesia could enrol, but were not able to be randomised to perphenazine. For the purposes of the 2009 guideline, the GDG focused on the primary outcome (discontinuation of treatment for any reason), tolerability, and both metabolic and neurological side effects. An evidence summary table for these outcomes can be found in Appendix 23c (the section on effectiveness of antipsychotic drugs).

In the initial phase of CUtLASS (Band 1), 227 participants with schizophrenia (or a related disorder) were randomised to an FGA or SGA (the choice of individual drug was made by the psychiatrist responsible for the care of the patient). The study was conducted in 14 NHS trusts in England and was specifically designed to test effectiveness in routine NHS practice. For the purposes of the 2009 guideline, the GDG focused on the primary outcome (the Quality of Life Scale;(Heinrichs et al., 1984)), tolerability, and neurological side effects. An evidence summary table for these outcomes can be found in Appendix 23c (the section on effectiveness of antipsychotic drugs).

Further analysis of cost effectiveness, including Band 2 of the CUtLASS trial can be found in Section 10.9.

**Table 113: Summary of study characteristics for the initial phases of CATIE and CUtLASS**

	CATIE (Phase1)	CUtLASS (Band1)
<i>Total N</i>	1,493	227
<i>Diagnostic criteria</i>	DSM-IV	DSM-IV
<i>Intervention</i>	Number randomised (number that did not take drug): Olanzapine: 336 (6) Quetiapine: 337 (8) Risperidone: 341 (8) Perphenazine: 261 (4)	Number randomised (most common at 52 weeks): FGA: 118 (26% were taking sulpiride) SGA: 109 (34% were taking olanzapine)
<i>Baseline severity–Mean PANSS (SD)</i>	Olanzapine: 76.1 (18.2) Quetiapine: 75.7 (16.9) Risperidone: 76.4 (16.6) Perphenazine: 74.3 (18.1)	FGA: 72.9 (17.2) SGA: 71.3 (16.5)

<i>Selected inclusion criteria</i>	Diagnosis of schizophrenia, no history of serious adverse reactions to study medications, not experiencing their first episode, not treatment-resistant.	Diagnosis of schizophrenia (or schizoaffective disorder or delusional disorder), requiring change of current FGA or SGA treatment because of inadequate clinical response or intolerance, at least 1 month since the first onset of positive psychotic symptoms.
<i>Setting</i>	Inpatient/outpatient	Inpatient/outpatient
<i>Duration of treatment</i>	Up to 18 months	Up to 12 months
<i>Medication dose (mg/day)</i>	Mean modal dose: Olanzapine: 20.1 (n = 312) Quetiapine: 534.4 (n = 309) Risperidone: 3.9 (n = 305) Perphenazine: 20.8 (n = 245)	Varied depending on drug taken
<p><i>Note.</i> In the CATIE trial, after ~40% of participants were enrolled, ziprasidone was added as treatment option and 185 participants were randomised to this arm. However, this drug is not licensed in the UK and is therefore not included in this review.</p> <p><sup>a</sup> Thirty-three participants from one site were excluded from the analysis because of concerns regarding the integrity of the data.</p>		

### 10.8.3 Clinical evidence summary

Two trials involving 1,720 participants failed to establish clinically significant differences in effectiveness between the oral (non-clozapine) antipsychotic drugs examined. Although both trials have limitations (for further information see (Carpenter & Buchanan, 2008; Kasper & Winkler, 2006; Lieberman, 2006; Möller, 2008), it is clear that more effective medication is needed. Furthermore, neither study included participants experiencing their first episode of schizophrenia or examined depot/long-acting antipsychotic medication.

With regard to adverse effects of treatment, the diverse side effect profiles seen in the efficacy trials reported elsewhere in this chapter were supported by CATIE and CUTLASS and primarily confirmed differential metabolic effects. However, there were no consistent clinically significant differences between antipsychotics in terms of treatment-emergent EPS. It should be noted that the various FGAs tested (such as perphenazine and sulpiride) were generally not high-potency antipsychotics and were prescribed in standard doses. Further analyses of baseline data from CATIE also confirm other reports that people with schizophrenia are undertreated for metabolic disorders (Nasrallah et al., 2006).

## 10.9 HEALTH ECONOMICS

### 10.9.1 Systematic literature review

The systematic search of the economic literature, undertaken for the 2009 guideline, identified 33 eligible studies on pharmacological treatments for people with schizophrenia. Of these, one study assessed oral antipsychotic medications for initial treatment of schizophrenia (Davies & Lewis, 2000); 15 studies examined oral drug



treatments for acute psychotic episodes (Alexeyeva et al., 2001; Almond & O'Donnell, 2000; Bagnall et al., 2003; Beard et al., 2006; Bounthavong & Okamoto, 2007; Cummins et al., 1998; Edgell et al., 2000; Geitona et al., 2008; Hamilton et al., 1999; Jerrell, 2002; Lecomte et al., 2000; Nicholls et al., 2003; Palmer et al., 2002; Palmer et al., 1998; Rosenheck et al., 2003); eight studies assessed oral antipsychotic medications aimed at promoting recovery (Davies et al., 1998; Ganguly et al., 2003; Knapp et al., 2008; Launois et al., 1998; Oh et al., 2001; Rosenheck et al., 2006; Tunis et al., 2006; Vera-Llonch et al., 2004); four studies examined pharmacological treatments aiming at promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (Davies et al., 2008; Lewis et al., 2006a; Lewis et al., 2006b; Rosenheck et al., 1997; Tilden et al., 2002); and six studies evaluated depot antipsychotic treatments (Chue et al., 2005; De Graeve et al., 2005; Edwards et al., 2005; Heeg et al., 2008; Laux et al., 2005; Oh et al., 2001). Details on the methods used for the systematic review of the economic literature in the 2009 guideline are described in Appendix 11; references to included and excluded studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 25.

### *Initial treatment with antipsychotic medication*

One study that assessed oral antipsychotics for the treatment of people with a first episode of schizophrenia was included in the systematic economic literature review (Davies & Lewis, 2000). The study, which was conducted in the UK, was a cost-utility analysis based on a decision-analytic model in the form of a decision tree. The antipsychotic treatments assessed were olanzapine, risperidone, chlorpromazine, haloperidol and clozapine. All drugs, with the exception of clozapine, were assessed as first, second, third or fourth lines of treatment, whereas clozapine was assessed as a third or fourth line of treatment only. According to the model structure, people switched to the next line of treatment when an antipsychotic was not acceptable to them; treatment unacceptability was defined as treatment intolerance (development of non-treatable or unacceptable side effects), inadequate response or non-compliance. People who found treatment acceptable were transferred to maintenance therapy. If they experienced a relapse during acceptable treatment over the time frame of the analysis, they were treated with the same antipsychotic. Acceptable side effects were treated without change in antipsychotic therapy. The adverse events considered in the analysis were EPS (except tardive dyskinesia, which was considered separately), tardive dyskinesia, neuroleptic malignant syndrome, hepatic dysfunction and agranulocytosis. Clinical efficacy data were derived from a systematic literature review and meta-analysis. The perspective of the analysis was that of health and social care services including expenses of people with schizophrenia. Resource use was based on published literature, other national sources and further assumptions. Prices were taken from national sources. The time horizon of the analysis was 3 years.

Results were reported separately for different scenarios regarding sequence of antipsychotic treatments. Olanzapine and haloperidol were dominated by chlorpromazine when used as any line of treatment. Risperidone was more effective

than chlorpromazine, but always at an additional cost, which reached £34,241 per QALY when first-line treatment was assessed. Clozapine dominated olanzapine and risperidone when used as third- or fourth-line treatment. It was shown to yield the highest number of QALYs out of all antipsychotics included in the analysis. Its incremental cost-effectiveness ratio (ICER) versus chlorpromazine was £35,689 and £47,980 per QALY, when they were compared as third- and fourth-line treatments, respectively.

The results of the analysis were statistically significant and indicated that olanzapine and haloperidol were not cost-effective options compared with the other antipsychotic drugs assessed for the treatment of people with a first episode of schizophrenia. The authors concluded that clozapine (as third- or fourth-line treatment) and risperidone might be more effective than chlorpromazine, but at a higher cost. However, they recognised that because multiple comparisons of costs and QALYs had been made, some statistically important differences might have occurred by chance rather than reflected real differences. Moreover, they recognised the limited availability of clinical data used in the model.

An additional limitation of the analysis was that efficacy data for each antipsychotic medication were apparently derived from 'naïve' addition of data across relevant treatment arms of all RCTs included in the systematic literature review. This method treats the data as if they came from a single trial and practically breaks the randomisation: data from treatment arms not directly relevant to the analysis are not taken into account and between-trial variance is completely ignored (Glenny et al., 2005). Glenny and colleagues argue that such a method of combining trial data is liable to bias, highly unpredictable and also produces over-precise answers. They conclude that results of such analysis are completely untrustworthy and, therefore, naïve comparisons should never be made.

Furthermore, utility data used in the base-case analysis by Davies and Lewis (2000) were based on published utility values of seven people with schizophrenia in Canada (Glennie, 1997), which appeared to be favouring FGAs and clozapine. Overall, the conclusions of this analysis should be interpreted with caution.

### *Oral antipsychotics in the treatment of the acute episode*

The systematic review of the economic literature considered 15 studies evaluating oral antipsychotic medications for the management of acute psychotic episodes (Alexeyeva et al., 2001; Almond & O'Donnell, 2000; Bagnall et al., 2003; Beard et al., 2006; Bounthavong & Okamoto, 2007; Cummins et al., 1998; Edgell et al., 2000; Geitona et al., 2008; Hamilton et al., 1999; Jerrell, 2002; Lecomte et al., 2000; Nicholls et al., 2003; Palmer et al., 2002; Palmer et al., 1998; Rosenheck et al., 2003). Of these, four were conducted in the UK (Almond & O'Donnell, 2000; Bagnall et al., 2003; Cummins et al., 1998; Nicholls et al., 2003) (and are described in more detail. Of the remaining 11 studies, seven were conducted in the US (Alexeyeva et al., 2001; Bounthavong & Okamoto, 2007; Edgell et al., 2000; Hamilton et al., 1999; Jerrell, 2002; Palmer et al., 1998; Rosenheck et al., 2003), one in Germany (Beard et al., 2006),

one in Belgium (Lecomte et al., 2000), one in Mexico (Palmer et al., 2002) and one in Greece (Geitona et al., 2008). Bagnall et al. (2003), using the same economic model structure as Davies and Lewis (2000), evaluated the cost effectiveness of SGAs for the treatment of acute episodes in people with schizophrenia in the UK. Ten antipsychotic medications were included in a cost-utility analysis: olanzapine, risperidone, quetiapine, amisulpride, zotepine, sertindole, ziprasidone, clozapine, chlorpromazine and haloperidol. Clinical data were based on a systematic literature review and meta-analysis, and other published literature. The study adopted the perspective of health and social care services. Resource use was based on published literature and further assumptions. National unit costs were used. Outcomes were expressed in QALYs. Utility values in the base-case analysis were also taken from Glennie (1997). The time horizon of the analysis was 1 year.

Results were reported separately for first, second, third and fourth lines of treatment. The authors performed comparisons between each SGA and the other medications. Ziprasidone and amisulpride were associated with the highest costs and QALYs. According to the authors, amisulpride was the most cost-effective SGA drug if ziprasidone remained unlicensed. Amisulpride and ziprasidone were the most effective and costliest drugs, followed by risperidone, which was both the third most effective and costliest drug of those examined. Olanzapine was the least costly and least effective antipsychotic. The authors suggested that sertindole, zotepine and quetiapine were not superior to other SGAs in terms of cost effectiveness. However, the cost and the effectiveness results were characterised by high uncertainty. In addition, clinical data for haloperidol and chlorpromazine were taken from the control arms of SGA trials because no systematic review of the literature was undertaken for FGAs; this methodology may have introduced bias to the analysis. A further limitation of the study was that analysis of efficacy data utilised the 'naïve' method for data pooling, as described earlier, and therefore the analysis is subject to bias. For all of these reasons, no clear conclusions on the relative cost effectiveness of SGAs can be drawn from this analysis, and this was also the authors' conclusion.

Cummins et al. (1998) used the results of an RCT comparing olanzapine with haloperidol for acute treatment of people with schizophrenia (TOLLEF-SON1997) to inform a decision tree that was constructed to assess the relative cost effectiveness of the two antipsychotic drugs in the UK. According to the model structure, people in an acute episode were started on one of the two evaluated drugs and followed up for 1 year. Those who did not respond to treatment, withdrew or relapsed following any response had their medication switched to haloperidol (if they had been started on olanzapine) or fluphenazine (if they had been started on haloperidol). The perspective of the analysis was that of the NHS. Resource use was based on published literature and further assumptions. Prices were taken from national sources. Outcomes were expressed in QALYs. Utility values were estimated using the index of health-related quality of life (IHRQoL), a generic measure designed to capture social, psychological and physical functioning.

Olanzapine was found to dominate haloperidol because it produced more QALYs (0.833 versus 0.806) and resulted in lower costs (£26,200 versus £31,627). The results were robust in a number of sensitivity analyses carried out. Limitations of the analysis, as stated by the authors, were the weak evidence on longer-term effects of antipsychotics, which led to a number of assumptions in the model, and the simplicity of the model structure, which did not capture all events related to treatment of acute episodes with antipsychotics.

Almond and O'Donnell (2000) conducted an economic analysis to compare the costs and benefits associated with olanzapine, risperidone, and haloperidol in the treatment of acute psychotic episodes in the UK. Analysis was based on decision-analytic modelling. The economic model considered cycles of acute episodes, remission and relapse over a period of 5 years. Efficacy data were taken from two clinical trials (TOLLEFSON1997 and TRAN1997). The outcomes of the analysis were the percentage of people with a Brief Psychiatric Rating Scale (BPRS) score below 18 and the percentage of people without relapse over the time frame of the analysis. The study adopted the NHS perspective. Resource use estimates were based on published literature and further assumptions. UK national prices were used.

Olanzapine was reported to be less costly than both risperidone and haloperidol (costs of olanzapine, risperidone and haloperidol were £35,701, £36,590 and £36,653 respectively). In addition, olanzapine was found to be more effective (percentages of people with a BPRS score below 18 over 5 years for olanzapine, risperidone and haloperidol were 63.6%, 63.0%, and 52.2%, respectively; percentages of people without relapse over 5 years were 31.2%, 29.3% and 18.2%, respectively). These figures show that olanzapine and risperidone dominated haloperidol (olanzapine was more effective at a lower cost; risperidone was more effective at a similar cost). Olanzapine also dominated risperidone (it was slightly more effective at a lower cost). Cost results were sensitive to daily dosages, relapse rates and dropout rates. The authors reported as limitations of their analysis the assumptions needed to estimate resource utilisation and the omission of some categories of cost, such as the costs of monitoring drug therapy, owing to lack of relevant data.

Nicholls et al. (2003) performed a cost-minimisation analysis alongside an international, multicentre clinical trial that compared amisulpride with risperidone over a 6-month treatment period (LECRUBIER2000). The trial had demonstrated that amisulpride and risperidone had similar effectiveness, as measured using the Positive and Negative Syndrome Scale (PANSS), BPRS and Clinical Global Impression (CGI) scale scores. The economic analysis, which adopted the perspective of the NHS, utilised resource use estimates from the trial and UK unit costs.

Amisulpride was found to be overall less costly than risperidone by £2,145, but the result was not statistically significant (95% CI: -£5,379 to £1,089). The findings of the study are not directly applicable to the UK setting, as resource use was based on settings other than the UK, where clinical practice is likely to be different. For

example, part-time hospitalisations were recorded in some settings; the authors stated that this type of care was not universally recognised in the NHS, and for this reason respective UK unit costs were not available and needed to be based on assumptions.

Of the further 11 studies included in the systematic review of the cost effectiveness of oral antipsychotics in the management of acute psychotic episodes, nine involved comparisons between olanzapine, risperidone and haloperidol. Relative cost effectiveness between olanzapine and risperidone cannot be established with certainty from the results of these studies: Beard et al. (2006) suggested that olanzapine was dominant over risperidone because it was shown to be more effective at a lower cost. The analysis, which was conducted from the perspective of the German healthcare system, was based on decision-analytic modelling. Other models of similar structure replicated this result in other countries: olanzapine dominated risperidone in the US (Palmer et al., 1998) and in Mexico (Palmer et al., 2002). On the other hand, the modelling studies by Bounthavong and Okamoto (2007) in the US and (Lecomte et al., 2000) in Belgium indicated that risperidone might be marginally dominant over olanzapine because it was associated with better or similar outcomes at similar or slightly lower costs. Two economic analyses conducted along-side clinical trials in the US (Edgell et al., 2000; Jerrell, 2002) were also unable to draw certain conclusions: in both trials, olanzapine appeared to be less costly than risperidone, but cost results were not statistically significant. In one of the trials, olanzapine was associated with longer maintenance of response and lower EPS rates (Edgell et al., 2000) but the other trial (Jerrell, 2002) failed to demonstrate a superiority of olanzapine over risperidone in terms of clinical effectiveness.

With respect to the comparative cost effectiveness of olanzapine and haloperidol, there was less variety in the study results: two modelling studies (Bounthavong & Okamoto, 2007; Palmer et al., 1998) and one economic analysis undertaken alongside a clinical trial (Hamilton et al., 1999) demonstrated that olanzapine dominated haloperidol in the US because it was more effective at a lower cost. Another multi-centre RCT conducted in the US (Rosenheck et al., 2003) showed that olanzapine had similar effectiveness to haloperidol (measured by BPRS scores) and lower akathisia rates. It was more expensive than haloperidol, but cost results were not statistically significant. Finally, two modelling studies suggested that olanzapine was more effective than haloperidol at an additional cost approximating £3 per day with minimum symptoms and toxicity in Belgium (Lecomte et al., 2000) and £11,350 per relapse avoided in Mexico (Palmer et al., 2002). Overall, these results suggest that olanzapine may be more cost effective than haloperidol in the treatment of acute episodes.

Two of the comparisons of risperidone versus haloperidol showed that risperidone was the dominant option in the US (Bounthavong & Okamoto, 2007) and in Belgium (Lecomte et al., 2000), while one economic model used to assess the relative cost effectiveness of the two antipsychotics in two different countries found risperidone to be more effective than haloperidol at an additional cost that reached

\$2,100/QALY in the US (Palmer et al., 1998) and about £13,900 per relapse avoided in Mexico (Palmer et al., 2002). These findings suggest that risperidone may be more cost effective than haloperidol.

Finally, of the remaining two studies included in the systematic economic literature review of acute treatment for people with schizophrenia, the study conducted by Alexeyeva and colleagues (2001) compared the cost effectiveness of olanzapine and ziprasidone in the US; the study, which was based on decision-analytic modelling, utilised published and unpublished clinical data and concluded that olanzapine dominated ziprasidone because it was more effective at a similar total cost. The other study (Geitona et al., 2008) assessed the cost effectiveness of paliperidone relative to risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone from the perspective of the Greek healthcare system. The study, which was also based on decision-analytic modelling, utilised efficacy data from selected placebo-controlled trials and other published sources. Resource utilisation estimates were based on expert opinion.

According to the authors' conclusions, paliperidone was the most cost-effective drug as it dominated all other treatment options assessed. This finding was reported to be robust in sensitivity analysis. However, dominance of paliperidone over olanzapine was only marginal (paliperidone resulted in 0.3 additional days free of symptoms per year and an annual extra saving of €4 compared with olanzapine).

It must be noted that the results of most modelling studies were sensitive to changes in response and dropout rates, drug acquisition costs, and hospitalisation rates for an acute episode. Most of these studies did not maintain randomisation effects because they used (and in some cases combined) efficacy data from arms of different trials for each antipsychotic drug evaluated, using a 'naïve' method of pooling. The impact of side effects on health related quality of life (HRQoL) was not explored in the majority of them.

### ***Promoting recovery in people with schizophrenia that is in remission-pharmacological relapse prevention***

Eight studies that were included in the systematic economic literature review assessed oral antipsychotic medications for relapse prevention (Davies et al., 1998; Ganguly et al., 2003; Knapp et al., 2008; Launois et al., 1998; Oh et al., 2001; Rosenheck et al., 2006; Tunis et al., 2006; Vera-Llonch et al., 2004). None of the studies was undertaken in the UK.

The most relevant study to the UK context was that by Knapp and colleagues (2008); it evaluated the cost effectiveness of olanzapine versus a number of other antipsychotic medications (including risperidone, quetiapine, amisulpride and clozapine, as well as oral and depot FGAs) using clinical and resource use data from a multicentre prospective observational study conducted in outpatient settings in ten European countries. The analysis adopted the health service payer's perspective; costs were estimated by applying UK national unit cost data to recorded healthcare

resource use. Outcomes were expressed in QALYs, estimated by recording and analysing participants' EQ-5D scores and linking them to respective UK population tariffs to determine utility values. The time horizon of the analysis was 12 months.

The study made separate comparisons of olanzapine with each of the other antipsychotic medications considered; no direct comparisons were made between the other antipsychotic medications. According to the performed comparisons, olanzapine dominated quetiapine and amisulpride; it was more effective than risperidone and clozapine at an additional cost reaching £5,156 and £775 per QALY, respectively. Compared with oral and depot FGAs, olanzapine was more effective and more costly, with an ICER of £15,696 and £23,331 per QALY respectively (2004 prices). However, FGAs were analysed together as a class, and no results from comparisons between olanzapine and specific FGAs were reported. Probabilistic sensitivity analysis conducted using bootstrap techniques revealed that the probability of olanzapine being more cost effective than quetiapine was 100% at a willingness-to-pay lower than £5,000/QALY; the probability of olanzapine being cost effective when compared with risperidone and amisulpride was 100% at a willingness-to-pay around £18,000/QALY; at a willingness-to-pay equalling £30,000 per QALY, the probability of olanzapine being more cost effective than clozapine, oral FGAs and depot FGAs was 81%, 98% and 79% respectively.

The results of the analysis indicated that olanzapine had a high probability of being cost effective relative to each of the other options assessed. However, no formal incremental analysis across all comparators was performed, as all comparisons involved olanzapine versus each of the other antipsychotics included in the analysis. The study conclusions may have limited applicability in the UK because reported healthcare resource use reflected average routine clinical practice in European countries and only unit costs were directly relevant to the UK health service.

The rest of the economic studies on pharmacological relapse prevention mainly included comparisons between olanzapine, risperidone and haloperidol. Two modelling studies, one in Australia (Davies et al., 1998) and one in Canada (Oh et al., 2001) concluded that risperidone was more cost effective than haloperidol because it was more effective at a lower cost. One US modelling study reported that risperidone was more effective and also more expensive than haloperidol (Ganguly et al., 2003). The measure of outcome was the number of employable persons in each arm of the analysis; employability was determined by a PANSS score reduction of at least 20% from baseline and a WCST-Cat score of  $\geq 3.5$ . The ICER of risperidone versus haloperidol was estimated at \$19,609 per employable person.

An economic analysis undertaken alongside an open-label trial in the US (Tunis et al., 2006) showed that olanzapine was associated with better outcomes and lower costs than risperidone in people with chronic schizophrenia, but results were statistically insignificant. Another study based on mainly unpublished data and employing Markov modelling techniques (Vera-Llonch et al., 2004) came to different conclusions: according to this study, risperidone led to lower discontinuation rates,

had over- all lower side effect rates and was less costly than olanzapine. A modelling study carried out in France (Launois et al., 1998) reported that sertindole dominated olanzapine and haloperidol; between olanzapine and haloperidol, the former was the cost effective option. Overall, results of modelling studies were sensitive to changes in response rates, compliance rates and hospital discharge rates.

Finally, Rosenheck and colleagues (2006) performed an economic analysis alongside a large effectiveness trial in the US (CATIE, Lieberman et al., 2005). The study compared olanzapine, quetiapine, risperidone, ziprasidone and perphenazine in people with chronic schizophrenia. It was demonstrated that perphenazine dominated all other antipsychotic medications, being significantly less costly than the other antipsychotics but with similar effectiveness expressed in QALYs (perphenazine was significantly more effective than risperidone at the 0.005 level in intention-to-treat analysis). Differences in total healthcare costs were mainly caused by differences in drug acquisition costs between perphenazine and the other antipsychotic drugs considered.

***Promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (treatment resistance)***

Four studies examining pharmacological treatments aiming at promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment were included in the systematic review (Davies et al., 2008; Lewis et al., 2006a; Lewis et al., 2006b; Rosenheck et al., 1997; Tilden et al., 2002).

Tilden and colleagues (2002) constructed a Markov model to assess the cost effectiveness of quetiapine versus haloperidol in people with schizophrenia only partially responsive to FGAs, from the perspective of the UK NHS. The model was populated with clinical data taken from various sources: rates of response to treatment were taken from a multicentre RCT, which compared two antipsychotics in people with schizophrenia partially responsive to FGAs (EMSLEY1999). In this study, response to treatment was defined as an improvement in PANSS total score of at least 20% between the beginning and the end of the trial. Compliance rates in the economic model were estimated by linking non-compliance with the presence of EPS. Relapse rates were estimated by linking relapse with non-response to treatment. Other clinical data were derived from published literature. Resource use estimates were based on published studies and further assumptions; national unit costs were used. The measure of outcome for the economic analysis was the average number of relapses and the expected duration of time in response per person with schizophrenia, over the time horizon of the analysis, which was 5 years. Quetiapine was found to be more effective than haloperidol, at a slightly lower cost. Sensitivity analysis revealed that cost results were sensitive to differences in response rates between the two antipsychotic drugs, to the risk of relapse in non-responding and non-compliant individuals, and to the proportion of people requiring hospitalisation following relapse.



Rosenheck and colleagues (1997) assessed the cost effectiveness of clozapine relative to haloperidol in people with schizophrenia refractory to treatment and a history of high level use of inpatient services in the US, using a societal perspective. The analysis was based on clinical and resource use evidence from a multicentre RCT carried out in 15 Veterans Affairs medical centres. Clinical outcomes included PANSS scores, Quality of Life Scale (QLS) scores, side effect rates and compliance rates. Clozapine resulted in significantly lower mean PANSS scores, better compliance rates and lower rates of EPS compared with haloperidol. The total medical cost associated with clozapine was lower than the respective cost of haloperidol, but the difference in costs was not statistically significant.

In addition to the above two studies, Lewis and colleagues (2006a) described two effectiveness trials conducted in the UK that aimed at determining the clinical and cost effectiveness of SGAs versus FGAs and clozapine versus SGAs in people with schizophrenia responding inadequately to, or having unacceptable side effects from, their current medication (CUtLASS, Bands 1 and 2). The studies would normally have been excluded from the systematic review of the economic literature because they treated SGAs and FGAs as classes of antipsychotic medications; no data relating to specific antipsychotic drugs were reported. However, these studies were directly relevant to the UK context and their findings could lead to useful conclusions supporting formulation of guideline recommendations. Therefore, their methods and economic findings are discussed in this section.

Both trials were conducted in adult mental health settings in 14 NHS trusts in Greater Manchester, Nottingham and London. Participants in Band 1 (N = 227) were randomised to either an SGA (olanzapine, risperidone, quetiapine or amisulpride) or an FGA in oral or depot form. Participants in Band 2 (N = 136) were randomised to either clozapine or one of the four SGAs named above. The primary clinical outcome of the analyses was the QLS, with secondary outcomes PANSS scores, side effects from medication and participant satisfaction. The measure of outcome in economic analyses was the number of QALYs gained. QALYs were estimated by recording and analysing participants' EQ-5D scores and subsequently linking them to respective UK population tariffs to determine utility values. Costs were estimated from the perspective of health and social care services, and included medication, hospital inpatient and outpatient services, primary and community care services and social services. The time horizon of the analyses was 12 months.

According to the results for Band 1, FGAs dominated SGAs as they resulted in better outcomes at a lower total cost, but the results were not statistically significant. Bootstrap analysis of costs and QALYs, including imputed values for missing observations and censored cases, demonstrated that FGAs resulted in 0.08 more QALYs and net savings of £1,274 per person compared with SGAs (2001/02 prices). In univariate sensitivity analyses, FGAs dominated SGAs or had an ICER lower than £5,000 per QALY. Probabilistic sensitivity analysis (employing bootstrap techniques) showed that at a zero willingness-to-pay, FGAs had a 65% probability of being cost effective; this probability rose up to 91% at a willingness-to-pay equalling £50,000 per QALY. At a willingness-to-pay of £20,000 per QALY, the probability of FGAs

being more cost effective than SGAs was roughly 80%. The results of the economic analysis indicate that FGAs are likely to be more cost effective than SGAs at the NICE cost-effectiveness threshold of £20,000–£30,000 per QALY (NICE, 2008b).

According to the results for Band 2, clozapine resulted in a statistically significant improvement in symptoms, but not in quality of life. Total costs associated with clozapine were also significantly higher than respective costs of SGAs. Updated bootstrap analysis of costs and QALYs showed that clozapine yielded 0.07 more QALYs per person relative to SGAs, at an additional cost of £4,904 per person (Davies et al., 2007). The ICER of clozapine versus SGAs was estimated at £33,240 per QALY (2005/06 prices). This value ranged from approximately £23,000 to £70,000 per QALY in univariate sensitivity analyses. Probabilistic sensitivity analysis showed that at a zero willingness-to-pay, clozapine had a 35% probability of being cost effective compared with SGAs; this probability reached 50% at a willingness-to-pay ranging between £30,000 and £35,000 per QALY. Results indicate that clozapine is unlikely to be cost effective at the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY (NICE, 2008b).

Analysis of costs in both trials revealed that the vast majority of costs (approximately 90% of total costs) were incurred by psychiatric hospital attendances; only 2 to 4% of total costs constituted drug acquisition costs. Overall, there was great variance in the use of health services and associated costs among study participants. The significant difference in cost between clozapine and SGAs was caused by great difference in psychiatric hospital costs between the two arms, possibly reflecting the licensing requirement for inpatient admission for initiation of therapy with clozapine at the time of the study. Currently, such requirements are no longer in place; therefore, at present, the cost effectiveness of clozapine versus SGAs is likely to be higher than demonstrated in the analysis.

### *Treatment with depot/long-acting injectable antipsychotic medication*

The systematic review of the economic literature identified six studies assessing the cost effectiveness of depot antipsychotic medications for people with schizophrenia (Chue et al., 2005; De Graeve et al., 2005; Edwards et al., 2005; Heeg et al., 2008; Laux et al., 2005; Oh et al., 2001). All studies were conducted outside the UK and employed modelling techniques.

According to the results of these studies, long-acting risperidone was dominant over haloperidol depot in Belgium (De Graeve et al., 2005), Germany (Laux et al., 2005), Portugal (Heeg et al., 2008), Canada (Chue et al., 2005) and the US (Edwards et al., 2005). Risperidone was dominant over olanzapine in Belgium (De Graeve et al., 2005), Germany (Laux et al., 2005) and the US (Edwards et al., 2005). Risperidone was dominant over oral risperidone in Portugal (Heeg et al., 2008), Canada (Chue et al., 2005) and the US (Edwards et al., 2005). Finally, risperidone was also shown to dominate quetiapine, ziprasidone and aripiprazole in the US (Edwards et al., 2005). In all of the studies, the cost effectiveness of long-acting risperidone was largely determined by its estimated higher compliance compared with oral antipsychotics.

However, in most studies, the methodology used to estimate compliance as well as other clinical input parameters was not clearly described; a number of economic models were populated with estimates based to a great extent on expert opinion. Oh and colleagues (2001), using data from published meta-analyses and expert opinion, reported that both haloperidol depot and fluphenazine depot were dominated by oral risperidone in Canada. Although the methodology adopted was clearly reported, the main limitation of this study was that randomisation effects from clinical trials were not maintained because clinical input parameters were estimated by pooling data from different clinical trials for each drug ('naïve' method of synthesis).

Overall, the quality of evidence on depot antipsychotic medications was rather poor and of limited applicability to the UK context, given that no study was conducted in the UK.

### ***The impact of compliance with antipsychotic treatment on healthcare costs incurred by people with schizophrenia***

The systematic search of economic literature identified a number of studies that assessed the impact of non-adherence to antipsychotic medication on healthcare costs incurred by people with schizophrenia. Although these studies did not evaluate the cost effectiveness of specific pharmacological treatments and therefore do not form part of the systematic review of economic evidence, they are described in this section because they provide useful data on the association between compliance, risk of relapse and subsequent healthcare costs. This information was considered by the GDG at formulation of the guideline recommendations.

Knapp and colleagues (2004) analysed data from a national survey of psychiatric morbidity among adults living in institutions in the UK, conducted in 1994. Approximately 67% of the population surveyed had a diagnosis of schizophrenia. According to the data analysis, non-adherence was one of the most significant factors that increased health and social care costs. Non-adherence predicted an excess annual cost reaching £2,500 per person for inpatient services and another £2,500 for other health and social care services, such as outpatient and day care, contacts with community psychiatric nurses, occupational therapists and social workers, and sheltered employment (2001 prices).

A modelling exercise that simulated the treated course of schizophrenia assessed the impact of compliance on health benefits and healthcare costs in people with schizophrenia in the UK over a period of 5 years (Heeg et al., 2005). The study considered people experiencing a second or third episode of schizophrenia and took into account factors such as gender, disease severity, potential risk of harm to self and society, and social and environmental factors. Other factors, such as number of psychiatric consultations, presence of psychotic episodes, symptoms and side effects, were also incorporated into the model structure. People with a first episode of schizophrenia were excluded from the analysis. The analysis demonstrated that a 20% increase in compliance with antipsychotic treatment resulted in cost savings of

£16,000 and in prevention of 0.55 psychotic episodes per person with schizophrenia over 5 years. Cost savings were almost exclusively attributed to the great reduction in hospitalisation costs following improved compliance. Higher levels of compliance were also associated with increased time between relapses, decreased symptom severity and improved ability of people to take care of themselves.

With regard to people experiencing a first episode of schizophrenia, Robinson and colleagues (1999) assessed the rates of relapse following response to antipsychotic treatment in 104 people with a first episode of schizophrenia or schizoaffective disorder. The authors reported that, after initial recovery, the cumulative first-relapse rate was 82% over 5 years. Discontinuation of pharmacological treatment increased the risk of relapse by almost five times. The authors concluded that the risk of relapse within 5 years of recovery from a first episode of schizophrenia or schizoaffective disorder was high, but could be diminished with maintenance antipsychotic drug therapy. Although the study did not assess the costs associated with non-compliance, its results indicate that compliance with treatment can reduce healthcare costs considerably by reducing rates of relapse (relapse can lead to high hospitalisation costs).

Finally, two published reviews examined the impact of compliance with antipsychotic therapy on healthcare costs incurred by people with schizophrenia (Sun et al., 2007; Thieda et al., 2003). The reviews analysed data from 21 studies in total and concluded that antipsychotic non-adherence led to an increase in relapse and, subsequently, hospitalisation rates and hospitalisation costs.

### *Summary of findings and conclusions from systematic economic literature review*

The economic literature review included 31 economic evaluations of specific antipsychotic treatments for the management of people with schizophrenia, plus two effectiveness trials conducted in the UK, which assessed antipsychotic medications grouped in classes. Twenty-two studies were based on decision-analytic modelling and were characterised by varying quality with respect to sources of clinical and utility data and methods of evidence synthesis. Clinical data were derived from a variety of sources, ranging from published meta-analyses and RCTs to unpublished trials and expert opinion. Even when data were taken from meta-analyses of trial data, the effects of randomisation were not retained, because data were simply pooled (by using weighted mean values) from the respective trials evaluating the drug under assessment. This 'naïve' method is likely to have introduced strong bias in the analyses, and therefore is inappropriate for evidence synthesis of trial data (Glenny et al., 2005). The impact of side effects on the HRQoL was explored in few studies, and even in these cases it was the decrement in HRQoL owing to the presence of EPS that was mostly considered. The impact of other side effects on HRQoL was not explored. The majority of the studies were funded by industry, which may have resulted in additional bias.

The included studies reported a variety of findings. The results of modelling exercises were sensitive, as expected, to a number of parameters, such as response and dropout rates, as well as rates and/or length of hospitalisation. Most of the cost results derived from clinical studies were statistically insignificant. With the exception of a few studies, the majority of economic evaluations included a very limited number of antipsychotic medications for the treatment of people in schizophrenia, mainly olanzapine, risperidone and haloperidol; however, a wider variety of antipsychotic medications has been shown to be clinically effective and is available in the market. Results of comparisons between the three most examined drugs were in some cases contradictory. Nevertheless, overall findings of the systematic review seem to suggest that olanzapine and risperidone may be more cost effective than haloperidol. Similarly, there is evidence that long-acting risperidone may lead to substantial cost savings and higher clinical benefits compared with oral forms of antipsychotic medication because of higher levels of adherence characterising long-acting injectable forms. However, evidence on long-acting injectable forms comes from non-UK modelling studies that are characterised by unclear methods in estimating a number of crucial input parameters (such as levels of adherence).

The results of non-UK studies are not directly applicable to the UK context and therefore, although they may be indicative of trends in relative cost effectiveness of different antipsychotic drugs worldwide, they should not be used exclusively to inform decisions in the UK context. On the other hand, the results of UK studies were characterised by high uncertainty and several important limitations.

The results of the economic analyses alongside effectiveness trials in the UK (Davies et al., 2008; Lewis et al., 2006b) suggest that hospitalisation costs are the drivers of total costs associated with treatment of people with schizophrenia. Drug acquisition costs are only a small part of total costs, and are unlikely to affect significantly the cost effectiveness of antipsychotic medications. It could be hypothesised that in the short term and for people with schizophrenia treated as inpatients (for example, during an acute episode), there are no big differences in total costs between antipsychotic medications, unless there are differences in the length of hospital stays. It might be reasonable to argue that antipsychotic drugs that reduce the rate and length of hospital admissions (for example drugs that reduce the rate of future relapses and/or the length of acute episodes) are cost-saving options in the long term, despite potentially high acquisition costs. A related factor affecting the magnitude of healthcare costs and subsequently the cost effectiveness of antipsychotic medications is the level of adherence: according to published evidence, high levels of adherence to antipsychotic treatment can greatly reduce the risk of relapse and subsequent hospitalisation costs.

Details of the methods and the results of all economic evaluations described in this section are provided in Appendix 25.

### 10.9.2 Economic modelling

A decision-analytic model was developed to assess the relative cost effectiveness of antipsychotic medications aimed at promoting recovery (preventing relapse) in people with schizophrenia in remission. The rationale for economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in Chapter 11. This section provides a summary of the methods employed and the results of the economic analysis.

#### *Overview of methods*

A Markov model was constructed to evaluate the relative cost effectiveness of a number of oral antipsychotic medications over two different time horizons, that is, 10 years and over a lifetime. The antipsychotic drugs assessed were olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol. The choice of drugs was based on the availability of relapse prevention data identified in clinical evidence review (see Section 10.4). The study population consisted of people with schizophrenia in remission. The model structure considered events such as relapse, discontinuation of treatment because of intolerable side effects and switching to another antipsychotic drug, discontinuation of treatment because of other reasons and moving to no treatment, development of side effects such as acute EPS, weight gain, diabetes and glucose intolerance, complications related to diabetes and death. Clinical data were derived from studies included in the guideline systematic review of clinical evidence and other published literature. Where appropriate, clinical data were analysed using mixed treatment comparison or standard meta-analytic techniques. The measure of outcome in the economic analysis was the number of QALYs gained. The perspective of the analysis was that of health and personal social care services. Resource use was based on published literature, national statistics and, where evidence was lacking, the GDG expert opinion. National UK unit costs were used. The cost year was 2007. Two methods were employed for the analysis of input parameter data and presentation of the results. First, a deterministic analysis was undertaken, where data were analysed as point estimates and results were presented in the form of ICERs following the principles of incremental analysis. A probabilistic analysis was subsequently performed in which most of the model input parameters were assigned probability distributions. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Results of probabilistic analysis were summarised in the form of cost effectiveness acceptability curves, which express the probability of each intervention being cost effective at various levels of willingness-to-pay per QALY gained (that is, at various cost-effectiveness thresholds).

#### *Overview of results*

Results of deterministic analysis demonstrated that zotepine dominated all other treatment options, as it was less costly and resulted in a higher number of QALYs, both at 10 years and over a lifetime of antipsychotic medication use. After zotepine, olanzapine and paliperidone appeared to be the second and third most cost-effective

drugs respectively, in both time horizons of 10 years and over a lifetime. Paliperidone and olanzapine dominated all other drugs (except zotepine) at 10 years; the ICER of paliperidone versus olanzapine was approximately £150,000/QALY. Over a lifetime, olanzapine was shown to be the least effective and least costly intervention among those examined, but according to incremental analysis it was still ranked as the second most cost-effective option following zotepine, using a cost-effectiveness threshold of £20,000/QALY (note that adopting a threshold of £30,000/QALY would result in paliperidone being ranked the second most cost-effective option and olanzapine third, as the ICER of paliperidone versus olanzapine was just above the £20,000/QALY threshold, at £20,872/QALY). According to sensitivity analysis, results were highly sensitive to the probability of relapse attached to each antipsychotic drug, but were not driven by the estimated probabilities of developing each of the side effects considered in the analysis.

Probabilistic analysis revealed that zotepine had the highest probability of being the most cost-effective option among those assessed, but this probability was rather low, roughly 27 to 30%, reflecting the uncertainty characterising the results of the analysis. This probability was practically independent of the cost-effectiveness threshold and the time horizon examined. The other antipsychotic medications had probabilities of being cost effective that ranged from approximately 5% (haloperidol) to 16% (paliperidone). Again, these probabilities were rather unaffected by different levels of willingness-to-pay and consideration of different time horizons.

The results of the economic analysis are characterised by substantial levels of uncertainty as illustrated in probabilistic analysis, indicating that no antipsychotic medication can be considered clearly cost effective compared with the other options included in the assessment. Moreover, it needs to be emphasised that the evidence base for the economic analysis was in some cases limited because clinical data in the area of relapse prevention for three medications (zotepine, paliperidone and aripiprazole) came from three single placebo-controlled trials.

## **10.10 LINKING EVIDENCE TO RECOMMENDATIONS**

In the 2002 guideline (which incorporated the recommendations from the NICE technology appraisal of SGAs [NICE, 2002]), SGAs were recommended in some situations as first-line treatment, primarily because they were thought to carry a lower potential risk of EPS. However, evidence from the updated systematic reviews of clinical evidence presented in this chapter, particularly with regard to other adverse effects such as metabolic disturbance, and together with new evidence from effectiveness (pragmatic) trials, suggest that choosing the most appropriate drug and formulation for an individual may be more important than the drug group.

Moreover, design problems in the individual trials continue to make interpretation of the clinical evidence difficult. Such problems include: (a) high attrition from one or both treatment arms in many studies; (b) differences between treatment arms in terms of medication dose; (c) small numbers of studies reporting the same outcomes for some drugs.

For people with schizophrenia whose illness has not responded adequately to antipsychotic medication, clozapine continues to have the most robust evidence for efficacy. In addition, evidence from the effectiveness studies (CATIE, Phase 2; CUtLASS, Band 2) suggests that in people who have shown a poor response to non-clozapine SGAs, there is an advantage in switching to clozapine rather than another SGA. Nevertheless, even with optimum clozapine treatment it seems that only 30 to 60% of treatment-resistant illnesses will respond satisfactorily (Chakos et al., 2001; Iqbal et al., 2003).

The systematic review of the economic literature identified a number of studies of varying quality and relevance to the UK setting. Results were characterised, in most cases, by high uncertainty. The majority of studies assessed the relative cost effectiveness between olanzapine, risperidone and haloperidol. Although study findings are not consistent, they seem to indicate that, overall, olanzapine and risperidone might be more cost effective than haloperidol.

In the area of antipsychotic treatment for first episode or early schizophrenia, the economic evidence is limited and characterised by important limitations, and therefore no safe conclusions on the relative cost effectiveness of antipsychotic medications can be drawn.

The amount of economic evidence is substantially higher in the area of pharmacological treatment for people with an acute exacerbation or recurrence of schizophrenia. However, the number of evaluated drugs is very limited and does not cover the whole range of drugs licensed for treatment of people with schizophrenia in the UK. In addition, existing studies are characterised by a number of limitations and, in many cases, by contradictory results. Available evidence indicates that olanzapine and risperidone may be more cost-effective options than haloperidol for acute exacerbation or recurrence of schizophrenia.

The economic literature in the area of relapse prevention is characterised by similar methodological limitations and also by the limited number of drugs assessed. Olanzapine and risperidone have been suggested to be more cost effective than haloperidol in preventing relapse, but these conclusions are based on results from analyses conducted outside the UK. On the other hand, evidence from CATIE suggests that perphenazine may be more cost effective than a number of SGAs (that is, olanzapine, quetiapine, risperidone and ziprasidone) in the US.

For people with schizophrenia whose illness has not responded adequately to treatment, sparse data on the cost effectiveness of specific antipsychotic medications are available. Evidence from CUtLASS, although not providing data on the cost effectiveness of individual drugs, provides useful insight into the factors that affect total costs incurred by people with schizophrenia. According to economic findings from CUtLASS, psychiatric inpatient care costs are the drivers of total healthcare



costs incurred by people with schizophrenia, with drug acquisition costs being only a small fraction of total costs.

CUtlASS Band 2 found that clozapine was more effective than SGAs in the treatment of people with inadequate response to, or unacceptable side effects from, current medication, but at a higher cost that reached £33,000/QALY (ranging from £23,000 to £70,000/QALY in univariate sensitivity analysis). It was suggested that the significant difference in cost between clozapine and SGAs might have been caused by a great difference in psychiatric hospital costs between clozapine and SGAs, possibly reflecting the licensing requirement for inpatient admission for initiation of therapy with clozapine at the time of the study. Currently, clozapine can be initiated in an outpatient setting; therefore, the current cost effectiveness of clozapine versus SGAs for people with inadequate response to treatment or unacceptable side effects is likely to be higher than was estimated when CUtlASS Band 2 was conducted.

Regarding depot/long-acting injectable antipsychotic medication, there is evidence that long-acting risperidone may lead to substantial cost savings and greater clinical benefits compared with oral forms of antipsychotic medication because of higher levels of adherence characterising long-acting injectable forms. However, this evidence comes from non-UK modelling studies that are characterised by unclear methods in estimating a number of crucial input parameters.

The economic analysis undertaken for this guideline estimated the cost effectiveness of oral antipsychotic medications for relapse prevention in people with schizophrenia. The results of the analysis suggest that zotepine is potentially the most cost-effective oral antipsychotic drug included in the model. However, results were characterised by high uncertainty and probabilistic analysis showed that no antipsychotic medication could be considered to be clearly cost effective compared with the other treatment options assessed: according to results of probabilistic analysis, the probability of each drug being cost effective ranged from roughly 5% (haloperidol) to about 27 to 30% (zotepine), and was independent of the cost effectiveness threshold used and the time horizon of the analysis (that is, 10 years or a lifetime). The probability of 27 to 30% assigned to zotepine, although indicative, is rather low and inadequate to be able to come to a safe conclusion regarding zotepine's superiority over the other antipsychotics assessed in terms of cost effectiveness. Moreover, clinical data for zotepine in the area of relapse prevention were exclusively derived from one small placebo-controlled RCT. Similarly, clinical data for paliperidone and aripiprazole were taken from two placebo-controlled trials. It must be noted that the economic analysis did not examine the cost effectiveness of quetiapine and any FGAs apart from haloperidol, owing to lack of respective clinical data in the area of relapse prevention.

An interesting finding of the economic analysis was that drug acquisition costs did not affect the cost effectiveness of antipsychotic medications: in fact haloperidol, which has the lowest price in the UK among those assessed, appeared to have the

lowest probability (about 5%) of being cost effective at any level of willingness-to-pay. On the other hand, zotepine, which had the lowest average relapse rate across all evaluated treatments, dominated all other options in deterministic analysis and demonstrated the highest probability of being cost effective in probabilistic analysis; this finding together with results of sensitivity analysis indicate that the effectiveness of an antipsychotic drug in preventing relapse is the key determinant of its relative cost effectiveness, apparently because relapse prevention, besides clinical improvement, leads to a substantial reduction in hospitalisation rates and respective costs.

Hospitalisation costs have been shown to drive healthcare costs incurred by people with schizophrenia, both in published evidence and in the economic analysis carried out for this guideline. It might be reasonable to argue that antipsychotic drugs that reduce the rate and length of hospital admissions (for example, drugs that reduce the rate of future relapses and/or the length of acute episodes) are cost-saving options in the long term, despite potentially high acquisition costs. This hypothesis is supported by published evidence, which shows that increased adherence to antipsychotic treatment is associated with a significant decrease in healthcare costs incurred by people with schizophrenia through a reduction in the risk of relapse and subsequent need for hospitalisation.

The GDG considered all clinical and economic evidence summarised in this section to formulate recommendations. In therapeutic areas where clinical and/or economic evidence on specific antipsychotic medications was lacking, as in the case of quetiapine and FGAs other than haloperidol in the area of relapse prevention, the GDG made judgements on the clinical and cost effectiveness of antipsychotic medication by extrapolating existing evidence and conclusions from other therapeutic areas.

Taking into account the findings from the systematic reviews of both the clinical and health economic literature, and the uncertainty characterising the results of economic modelling undertaken for this guideline, the evidence does not allow for any general recommendation for one antipsychotic to be preferred over another, but the evidence does support a specific recommendation for clozapine for people whose illness does not respond adequately to other antipsychotic medication.

Finally, the GDG noted that the following are the key points to be considered before initiating an antipsychotic medication in an acute episode of schizophrenia. First, there may be some lack of insight into the presence of a mental illness and the relevance of drug treatment. Careful explanation is needed regarding the rationale for antipsychotic medications and their modes of action. People with schizophrenia will usually accept that they have been stressed, experiencing insomnia and not eating well, so the acceptance of a tranquillising medication to help reduce stress and improve sleep and appetite might be acceptable. It can also be explained, if the patient is insightful enough, that the medication is antipsychotic and can help reduce the severity of distressing hallucinations, delusions and thought disorder.

Second, medication should always be started at a low dose if possible, after a full discussion of the possible side effects. Starting at a low dose allows monitoring for the early emergence of side effects, such as EPS, weight gain or insomnia. The dose can then be titrated upwards within the BNF treatment range. Although polypharmacy with antipsychotic medications is not recommended, it is equally important not to under treat the acute psychotic episode.

Third, people with schizophrenia should be consulted on their preference for a more or less sedative medication option. Medication is ideally started following a period of antipsychotic-free assessment within an acute ward setting or under the supervision of a crisis home treatment team, early intervention in psychosis team or assertive outreach team. \*\*2009\*\*

Following the publication of *Psychosis and Schizophrenia in Children and Young People*, the GDG for the 2014 guideline took the view that the recommendations should be consistent where appropriate, including changing the population from 'people with schizophrenia' to 'people with psychosis and schizophrenia'. The GDG also wished to make it explicit that the options for first episode psychosis and for an acute exacerbation or recurrence of psychosis or schizophrenia should be oral antipsychotic medication combined with psychological interventions (individual CBT and family intervention). This does not constitute a change to the meaning or content of the original recommendations about antipsychotics, and it continues to reflect the evidence. Rather, it clarifies what was implicit in the 2009 guideline, that all people with psychosis and schizophrenia should be offered antipsychotic medication together with a psychological intervention for both a first episode and for subsequent exacerbations.

The GDG also considered the physical health of the service user and the effects of antipsychotic medication on mortality and morbidity. The GDG suggested that when antipsychotic medication is initiated for the first time as well as thought-out treatment with antipsychotic medication, it is important that the physical health of the service user is assessed and monitored. The GDG thought that was well as collecting data of baseline measurements of weight and waist circumference, and possible cardiovascular risks (using blood and pulse pressure), indicators of possibility future weight gain, for example, levels of physical activity, eating habits, and any current or emerging physical movement restrictions, should also be investigated. \*\*2009\*\*

## 10.11 RECOMMENDATIONS

### 10.11.1 Clinical practice recommendations

#### *Treatment for first episode psychosis*

10.11.1.1 For people with first episode psychosis offer:

- oral antipsychotic medication (see recommendations 10.11.1.2–10.11.1.13) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]

10.11.1.2 The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences). [2009; amended 2014]

#### *How to use oral antipsychotics*

10.11.1.3 Before starting antipsychotic medication, undertake and record the following baseline investigations:

- weight (plotted on a chart)
- waist circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity. [new 2014]

10.11.1.4 Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if:

- specified in the summary of product characteristics (SPC)
- a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
- there is a personal history of cardiovascular disease **or**
- the service user is being admitted as an inpatient. [2009]

10.11.1.5 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following:

- Discuss and record the side effects that the person is most willing to tolerate.

- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British national formulary (BNF) or SPC.
- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks. [2009; amended 2014]

**10.11.1.6** Monitor and record the following regularly and systematically throughout treatment, but especially during titration:

- response to treatment, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart)
- waist circumference annually (plotted on a chart)
- pulse and blood pressure at 12 weeks, at 1 year and then annually
- fasting blood glucose, HbA1c and blood lipid levels at 12 weeks, at 1 year and then annually
- adherence
- overall physical health. [new 2014]

**10.11.1.7** The secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. [new 2014]

**10.11.1.8** Discuss any non-prescribed therapies the service user wishes to use (including complementary therapies) with the service user, and carer if appropriate. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009]

**10.11.1.9** Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009]

- 10.11.1.10** 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 10.11.1.5. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC. [2009]
- 10.11.1.11** Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation'). [2009]
- 10.11.1.12** Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). [2009]
- 10.11.1.13** If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary. [2009]

### *Treatment of acute episode*

- 10.11.1.14** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:
- oral antipsychotic medication (see recommendations 10.11.1.2–10.11.1.13) in conjunction with
  - psychological interventions (family intervention and individual CBT , delivered as described in recommendations 9.4.10.3 and 9.7.10.3). [new 2014]
- 10.11.1.15** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 10.11.1.2–10.11.1.13). Take into account the clinical response and side effects of the service user's current and previous medication. [2009; amended 2014]

### *Behaviour that challenges*

- 10.11.1.16** Occasionally people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. The management of immediate risk should follow the relevant NICE guidelines (see recommendations 10.11.1.17 and 10.11.1.20). [2009]
- 10.11.1.17** Follow the recommendations in [Violence](#) (NICE clinical guideline 25) when facing imminent violence or when considering rapid tranquillisation. [2009]
- 10.11.1.18** After rapid tranquillisation, offer the person with psychosis or schizophrenia the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes. [2009]
- 10.11.1.19** Ensure that the person with psychosis or schizophrenia has the opportunity to write an account of their experience of rapid tranquillisation in their notes. [2009]

- 10.11.1.20** Follow the recommendations in [Self-harm](#) (NICE clinical guideline 16) when managing acts of self-harm in people with psychosis or schizophrenia. [2009]

### *Early post-acute period*

- 10.11.1.21** Inform the service user that there is a high risk of relapse if they stop medication in the next 1–2 years. [2009]
- 10.11.1.22** If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. [2009]
- 10.11.1.23** After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years. [2009]

### *Promoting recovery*

- 10.11.1.24** Review antipsychotic medication annually, including observed benefits and any side effects. [new 2014].
- 10.11.1.25** The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 10.11.1.2–10.11.1.13). [2009]
- 10.11.1.26** Do not use targeted, intermittent dosage maintenance strategies<sup>40</sup> routinely. However, consider them for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity. [2009]
- 10.11.1.27** Consider offering depot /long-acting injectable antipsychotic medication to people with psychosis or schizophrenia:
- who would prefer such treatment after an acute episode
  - where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. [2009]

### *Using depot/long-acting injectable antipsychotic medication*

- 10.11.1.28** When initiating depot/long-acting injectable antipsychotic medication:
- take into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics)
  - take into account the same criteria recommended for the use of oral antipsychotic medication (see recommendations 10.11.1.2–

---

<sup>40</sup> Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.

10.11.1.13), particularly in relation to the risks and benefits of the drug regimen

- initially use a small test dose as set out in the BNF or SPC. [2009]

### *Interventions for people whose illness has not responded adequately to treatment*

**10.11.1.29** For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment:

- Review the diagnosis.
- Establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration.
- Review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families.
- Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. [2009]

**10.11.1.30** Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic. [2009]

**10.11.1.31** For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 10.11.1.29 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine. [2009]

## **10.11.2 Research recommendations**

**10.11.2.1** More long-term, head-to-head RCTs of the efficacy and safety/tolerability and patient acceptability of the available antipsychotic drugs are required, in individuals in their first episode of schizophrenia, testing the risk-benefit of dosage at the lower end of the recommended dosage range. [2009]

**10.11.2.2** Large-scale, observational, survey-based studies, including qualitative components, of the experience of drug treatments for available antipsychotics should be undertaken. Studies should include data on service user satisfaction, side effects, preferences, provision of information and quality of life. [2009]



- 10.11.2.3** Quantitative and qualitative research is required to investigate the utility, acceptability and safety of available drugs for urgent sedation/control of acute behavioural disturbance (including benzodiazepines and antipsychotics), systematically manipulating dosage and frequency of drug administration. [2009]
- 10.11.2.4** Further work is required on the nature and severity of antipsychotic drug discontinuation phenomena, including the re-emergence of psychotic symptoms, and their relationship to different antipsychotic withdrawal strategies. [2009]
- 10.11.2.5** Direct comparisons between available oral antipsychotics are needed to establish their respective risk/long-term benefit, including effects upon relapse rates and persistent symptoms, and cost effectiveness. Trials should pay particular attention to the long-term benefits and risks of the drugs, including systematic assessment of side effects: metabolic effects (including weight gain), EPS (including tardive dyskinesia), sexual dysfunction, lethargy and quality of life. [2009]
- 10.11.2.6** Further RCT-based, long-term studies are needed to establish the clinical and cost effectiveness of available depot/long-acting injectable antipsychotic preparations to establish their relative safety, efficacy in terms of relapse prevention, side-effect profile and impact upon quality of life. [2009]
- 10.11.2.7** Further RCT-based, long-term studies are needed to establish the clinical and cost effectiveness of augmenting antipsychotic monotherapy with an antidepressant to treat persistent negative symptoms. [2009]
- 10.11.2.8** Controlled studies are required to test the efficacy and safety of combining antipsychotics to treat schizophrenia that has proved to be poorly responsive to adequate trials of antipsychotic monotherapy. [2009]
- 10.11.2.9** A randomised placebo-controlled trial should be conducted to investigate the efficacy and post effectiveness of augmentation of clozapine monotherapy with an appropriate second antipsychotic where a refractory schizophrenic illness has shown only a partial response to clozapine. [2009]
- 10.11.2.10** A randomised placebo-controlled trial should be conducted to investigate the efficacy and cost effectiveness of augmentation of antipsychotic monotherapy with lithium where a schizophrenic illness has shown only a partial response. The response in illness with and without affective symptoms should be addressed.[2009]

- 10.11.2.11** A randomised placebo-controlled trial should be conducted to investigate the efficacy and cost effectiveness of augmentation of antipsychotic monotherapy with sodium valproate where a schizophrenic illness has shown only a partial response. The response of illness in relation to behavioural disturbance, specifically persistent aggression, should be specifically addressed to determine if this is independent of effect on potentially confounding variables, such as positive symptoms, sedation, or akathisia. [2009]
- 10.11.2.12** Further controlled studies are required to test the claims that clozapine is particularly effective in reducing hostility and violence, and the inconsistent evidence for a reduction in suicide rates in people with schizophrenia. [2009]

# 11 ECONOMIC MODEL - COST EFFECTIVENESS OF PHARMACOLOGICAL INTERVENTIONS FOR PEOPLE WITH SCHIZOPHRENIA

## 11.1 INTRODUCTION

This chapter has not been updated. Sections of the guideline where the evidence has not been updated since 2009 are marked by asterisks (\*\*2009\*\* \_ \*\*2009\*\*).

### 11.1.1 Rationale for economic modelling – objectives

**\*\*2009\*\***The systematic search of economic literature identified a number of studies on pharmacological treatments for the management of schizophrenia which were of varying quality and relevance to the UK setting. Results were characterised, in most cases, by high uncertainty and various levels of inconsistency. The number of antipsychotic medications assessed in this literature was limited and did not include the whole range of drugs available in the UK for the treatment of people with schizophrenia. These findings pointed to the need for *de novo* economic modelling for this guideline. The objective of economic modelling was to explore the relative cost effectiveness of antipsychotic medications for people with schizophrenia in the current UK clinical setting, using up-to-date appropriate information on costs and clinical outcomes, and attempting to include a wider choice of antipsychotic drugs than that examined in the existing economic literature as well as to overcome at least some of the limitations of previous models. Details on the guideline systematic review of economic literature on pharmacological interventions for people with schizophrenia are provided in Chapter 10 (Section 10.9.1).

### 11.1.2 Defining the economic question

The systematic review of clinical evidence covered four major areas of treating people with schizophrenia with antipsychotic drugs: initial treatment for people with first-episode or early schizophrenia; treatment of people with an acute exacerbation or recurrence of schizophrenia; promoting recovery in people with schizophrenia that is in remission (relapse prevention); and promoting recovery in people with schizophrenia whose illness has not responded adequately to treatment (treatment resistance). In deciding which area to examine in the economic model, the following criteria were considered:

- quality and applicability (to the UK context) of relevant existing economic evidence
- magnitude of resource implications expected by use of alternative pharmacological treatments in each area

- availability of respective clinical evidence that would allow meaningful and potentially robust conclusions to be reached that could inform formulation of recommendations.

Based on the above criteria, the economic assessment of antipsychotic medications aiming at promoting recovery (preventing relapse) in people with schizophrenia that is in remission was selected as a topic of highest priority for economic analysis: relevant existing economic evidence was overall rather poor and not directly transferable to the UK context. Resource implications associated with this phase of treatment were deemed major because treatment covers a long period that can extend over a lifetime. Finally, respective clinical evidence was deemed adequate to allow useful conclusions from economic modelling because it covered most (but not all) of the antipsychotic medications available in the UK and was derived from a sufficient number of trials (17) providing data on 3,535 participants.

## **11.2 ECONOMIC MODELLING METHODS**

### **11.2.1 Interventions assessed**

The choice of interventions assessed in the economic analysis was determined by the availability of respective clinical data included in the guideline systematic literature review. Only antipsychotic medications licensed in the UK and suitable for first-line treatment aiming at preventing relapse in people with schizophrenia that is in remission were considered. Depot/long-acting injectable antipsychotic medications were not included in the economic analysis because they were not deemed suitable for first-line treatment of people with schizophrenia. Consequently, the following seven oral antipsychotic medications were examined: olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol. Quetiapine was not included in the economic analysis because no respective clinical data in the area of relapse prevention in people with schizophrenia that is in remission were identified in the literature. In addition, haloperidol was the only FGA evaluated because no clinical data on other FGAs were included in the guideline systematic review. Further clinical evidence on FGAs may exist, but may have not been identified because the guideline systematic search of the literature focused on clinical trials of SGAs. Non-inclusion of quetiapine and other FGAs is acknowledged as a limitation of the economic analysis.

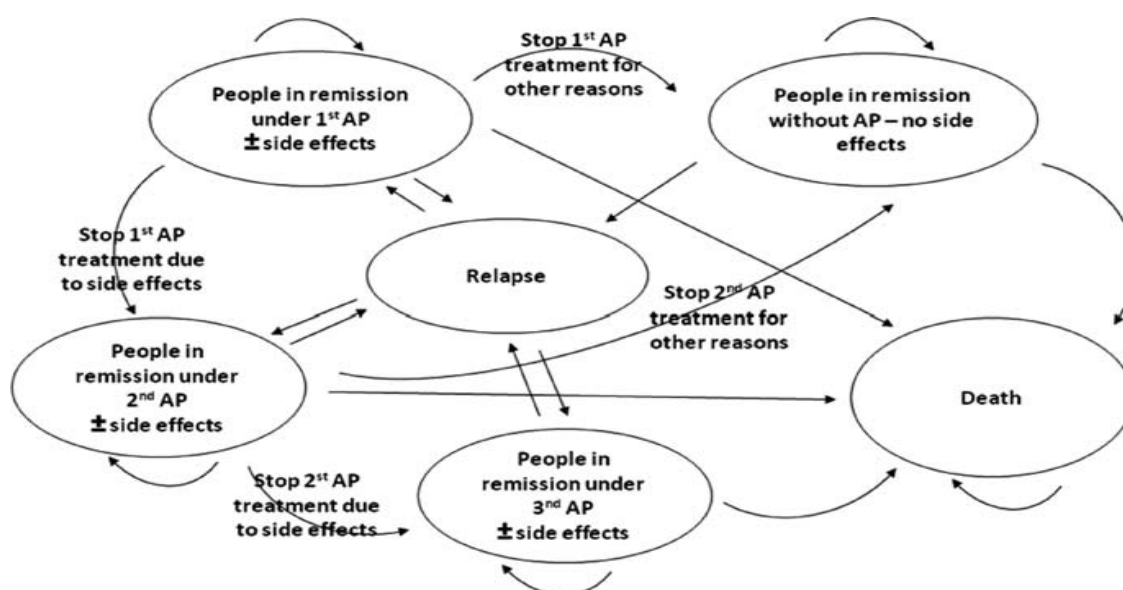
### **11.2.2 Model structure**

A decision-analytic Markov model was constructed using Microsoft Office Excel 2007. The model was run in yearly cycles. According to the model structure, seven hypothetical cohorts of people with schizophrenia that is in remission were initiated on each of the seven oral antipsychotic medications assessed (first-line antipsychotic). The age of the population was 25 years at the start of the model, as this is the mean age at onset of schizophrenia. Within each year, people either remained in remission, or experienced a relapse, or stopped the antipsychotic because of the presence of intolerable side effects, or stopped the antipsychotic for

any other reason (except relapse or presence of intolerable side effects), or died. People who stopped the first-line antipsychotic because of the development of intolerable side effects switched to a second-line antipsychotic. People who stopped the first-line antipsychotic for any other reason were assumed to stop abruptly and move to no treatment; these people remained without antipsychotic treatment until they experienced a relapse. People discontinuing treatment because of side effects or other reasons were assumed not to experience relapse in the remaining time of the cycle within which discontinuation occurred. All people experiencing a relapse stopped any antipsychotic drug that they had been receiving while in remission and were treated for the acute episode; after achieving remission, they either returned to their previous antipsychotic medication aiming at promoting recovery (50% of people achieving remission), or switched to a second-line antipsychotic drug (the remaining 50%). People initiated on a second-line antipsychotic experienced the same events as described above. People who stopped the second-line antipsychotic medication either because of intolerable side effects or following a relapse (50% of people) were switched to a third-line antipsychotic drug. No further medication switches were assumed after this point. This means that people under the third-line antipsychotic were assumed not to stop medication because of side effects or for other reasons, and all of them returned to this antipsychotic after treatment of relapses. It must be noted that discontinuation of an antipsychotic because of intolerable side effects was assumed to occur only during the first year of use of this particular antipsychotic. Discontinuation of an antipsychotic for other reasons was assumed to occur over each year of use, at the same rate. People under first-, second- or third-line antipsychotic medication might experience side effects that do not lead to discontinuation (tolerable side effects). All transitions in the model, for purposes of estimation of costs and QALYs, were assumed to occur in the middle of each cycle. Two different time horizons were examined (10 years and over the lifetime of the study population), to allow exploration of the impact of long-term benefits and risks of antipsychotic medications on their relative cost effectiveness over time. A schematic diagram of the economic model is presented in Figure 1.

The first-line antipsychotic described in the model structure was one of the seven oral antipsychotics evaluated in the analysis. The second-line antipsychotic following first-line olanzapine, amisulpride, zotepine, aripiprazole, paliperidone or risperidone was an FGA; the second-line antipsychotic following first-line haloperidol was an SGA. The third-line antipsychotic was in all cases a depot antipsychotic medication. In terms of costs, relapse and discontinuation and side effect rates, the FGA used as second-line treatment was assumed to be haloperidol; the SGA used as second-line treatment was assumed to be olanzapine; the depot antipsychotic (third-line treatment) was assumed to be flupentixol decanoate, as this is the most commonly used depot antipsychotic in UK clinical practice (NHS The Information Centre, 2008c).

**Figure 1: Schematic diagram of the economic model structure**



*Note.* AP = antipsychotic.

The aim of the consideration of three lines of treatment in the model structure was not to assess or recommend specific sequences of drugs. The model evaluated the relative cost effectiveness between the first-line antipsychotics only. The purpose of incorporating medication switching in the model structure was to assess the impact of lack of effectiveness in relapse prevention (expressed by relapse rates), intolerance (expressed by discontinuation rates because of side effects) and unacceptability (expressed by discontinuation rates because of other reasons) of the first-line antipsychotics on future costs and health outcomes, and to present a more realistic sequence of events related to treatment of people with schizophrenia with antipsychotic medication. The seven sequences of antipsychotic medications considered in the analysis are presented in Figure 2.

### 11.2.3 Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE, 2007). Costs consisted of drug acquisition costs, inpatient and outpatient secondary care costs, costs of primary and community healthcare, costs of treating side effects and related future complications, as well as costs of residential care. The measure of outcome was the QALY.

**Figure 2: Sequences of antipsychotic treatment assumed in the model for each of the seven hypothetical cohorts of people with schizophrenia followed**

First-line antipsychotic	Second-line antipsychotic	Third-line antipsychotic
Olanzapine	FGA	Depot antipsychotic medication
Amisulpride	FGA	Depot antipsychotic medication
Zotepine	FGA	Depot antipsychotic medication
Aripiprazole	FGA	Depot antipsychotic medication
Paliperidone	FGA	Depot antipsychotic medication
Risperidone	FGA	Depot antipsychotic medication
Haloperidol	SGA	Depot antipsychotic medication

### 11.2.4 Overview of methods employed for evidence synthesis

To populate the economic model with appropriate input parameters, the available clinical evidence from the guideline systematic review and meta-analysis needed to be combined in a way that would allow consideration of all relevant information on the antipsychotics assessed. The systematic review of clinical evidence in the area of relapse prevention identified 17 trials that made pair-wise comparisons between an SGA and another SGA, an FGA, or placebo. To take all trial information into consideration, without ignoring part of the evidence and without introducing bias by breaking the rules of randomisation (for example, by making ‘naive’ addition of data across relevant treatment arms from all RCTs as described in Glenny and colleagues (2005), mixed treatment comparison meta-analytic techniques were employed. Mixed treatment comparison meta-analysis is a generalisation of standard pair-wise meta-analysis for A versus B trials to data structures that include, for example, A versus B, B versus C and A versus C trials (Lu & Ades, 2004). A basic assumption of mixed treatment comparison methods is that direct and indirect evidence estimate the same parameter; in other words, the relative effect between A and B measured directly from an A versus B trial is the same with the relative effect between A and B estimated indirectly from A versus C and B versus C trials. Mixed treatment comparison techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments and, at the same time, allow simultaneous inference on all treatments examined in the pair-wise trial comparisons while respecting randomisation (Caldwell et al., 2005; Lu & Ades, 2004). Simultaneous inference on the relative effect a number of treatments is possible provided that treatments participate in a single ‘network of evidence’, that is, every treatment is linked to at least one of the other treatments under assessment through direct or indirect comparisons.

Mixed treatment comparison methods were undertaken to make simultaneous inference for the antipsychotic drugs included in the economic analysis on the following five parameters: probability of relapse, probability of treatment discontinuation because of intolerable side effects, probability of treatment discontinuation because of any other reason, probability of weight gain and probability of acute EPS. Data on the first three parameters were analysed together

using a mixed treatment comparison ‘competing risks’ logistic regression model appropriate for multinomial distribution of data. Data on probability of weight gain and probability of acute EPS were analysed using two separate logistic regression models for binomial distributions. All three models were constructed following principles of Bayesian analysis and were conducted using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4 (Lunn et al., 2000; Spiegelhalter et al., 2001).

### **11.2.5 Relapse and discontinuation data**

Data on (i) relapse, (ii) drug discontinuation because of intolerable side effects and (iii) drug discontinuation because of other reasons were taken from 17 RCTs included in the guideline systematic review of pharmacological treatments aiming at relapse prevention in people with schizophrenia that is in remission (details of this review are provided in Chapter 10, Section 10.4). All 17 RCTs reported data on the three outcomes considered in the analysis. The vast majority of the trials reported separately on the proportions of people that discontinued treatment because of relapse and of people discontinuing because of side effects, as well as of people discontinuing for any other reason; overall treatment failure was defined as the sum of these three outcomes. The outcomes were thus ‘competing’ or ‘mutually exclusive’, in the sense that within the time frame of the trials any person who did not remain under treatment and in remission (which would equal treatment success) was at risk of either relapsing or stopping treatment because of side effects, or stopping treatment because of other reasons. A small number of trials reported the numbers of people who experienced relapse within the time frame of analysis, without clarifying whether these people remained in the trial following relapse and could be potentially double-counted if they discontinued treatment because of side effects or other reasons at a later stage of the study. However, for the purpose of analysis of clinical data and to build the economic model, data on relapse, discontinuation because of side effects and discontinuation because of other reasons from all 17 RCTs were treated as competing, as described above. It must be noted that all 17 studies reported numbers of people that experienced relapse, but not the total number of relapses per such person. It is therefore not known whether some of the trial participants could have experienced more than one episode of relapse during the time frame of analyses. Consequently, clinical data have been analysed assuming that participants reported to have experienced relapse had only one episode of relapse over the time frame of each trial. A final limitation of the data analysis lay in the fact that the 17 RCTs used various definitions of relapse (described in Chapter 10, Sections 10.4.4 and 10.4.5) and therefore the reported relapse rates are not entirely comparable across studies.



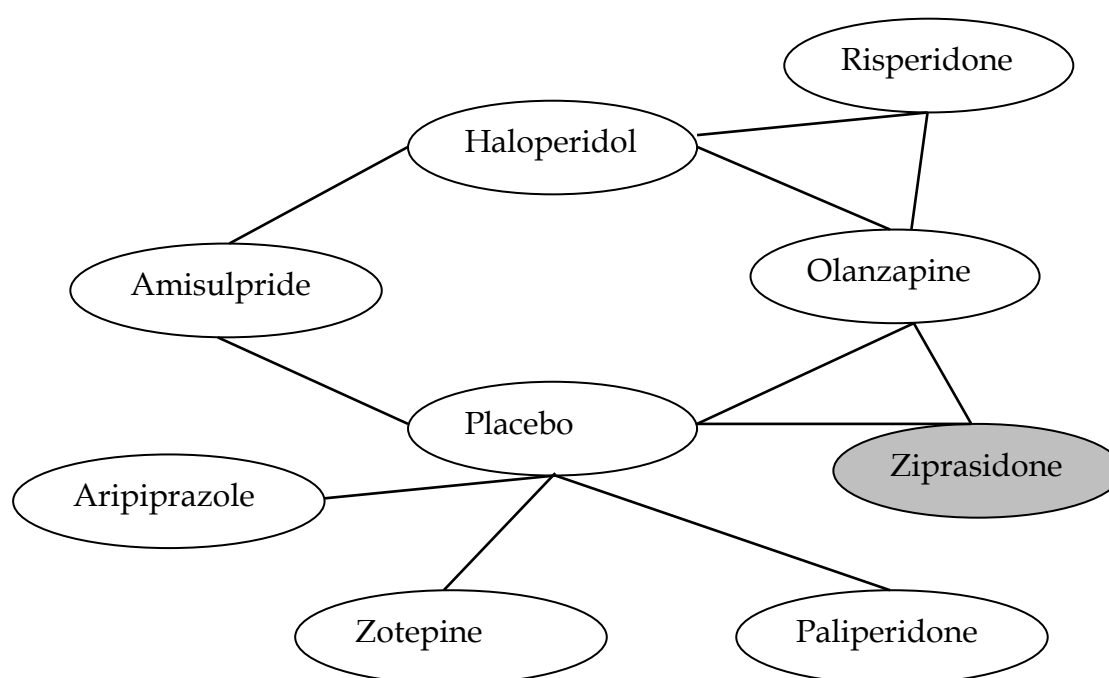
**Table 114: Summary of data reported in the RCTs included in the guideline systematic review on pharmacological relapse prevention that were utilised in the economic analysis**

Study	Time horizon (weeks)	Comparators	Number of people relapsing (m1)	Number of people stopping because of side effects (m2)	Number of people stopping because of other reasons (m3)	Number of people in each arm (n)
1.BEASLEY2003	42	Placebo (1) Olanzapine (2)	28 9	12 2	15 19	102 224
2.DELLVA1997 (study1)	46	Placebo (1) Olanzapine (2)	7 10	0 2	4 16	13 45
3.DELLVA1997 (study2)	46	Placebo (1) Olanzapine (2)	5 6	2 10	5 15	14 48
4.LOO1997	26	Placebo (1) Amisulpride (3)	5 4	5 1	39 26	72 69
5.Cooper2000	26	Placebo (1) Zotepine (4)	21 4	4 16	24 21	58 61
6.PIGOTT2003	26	Placebo (1) Aripiprazole (5)	85 50	13 16	12 18	155 155
7.Arato2002	52	Placebo (1) Ziprasidone (6)	43 71	11 19	7 28	71 206
8.KRAMER2007 <sup>a</sup>	47	Placebo (1) Paliperidone (7)	52 23	1 3	7 17	101 104

*Continued*

Study	Time horizon (weeks)	Comparators	Number of people relapsing (m1)	Number of people stopping because of side effects (m2)	Number of people stopping because of other reasons (m3)	Number of people in each arm (n)
9.SIMPSON2005	28	Olanzapine (2) Ziprasidone (6)	11 8	6 5	44 33	71 55
10.Tran1998 (a + b + c) <sup>b</sup>	52	Olanzapine (2) Haloperidol (8)	87 34	54 20	170 50	627 180
11.STUDY-S029	52	Olanzapine (2) Haloperidol (8)	28 29	9 14	26 25	141 134
12.Tran1997	28	Olanzapine (2) Risperidone (9)	20 53	17 17	36 18	172 167
13.Speller1997	52	Amisulpride (3) Haloperidol (8)	5 9	3 5	2 2	29 31
14.Csernansky2000	52	Haloperidol (8) Risperidone (9)	65 41	29 22	80 60	188 177
15.MARDER2003	104	Haloperidol (8) Risperidone (9)	8 4	0 3	4 4	30 33
<p><i>Note.</i> <sup>a</sup> Participants received treatment for up to 11 months (47 weeks)</p> <p><sup>b</sup> Data from the three RCTs with study ID Tran1998a+b+c are presented together because discontinuation data were not reported separately for each trial. The time horizon for a + b studies was 52 weeks. In study c, participants completed between 22 and 84 weeks of therapy. For modelling purposes, the time horizon in all three studies was assumed to be 52 weeks.</p>						

**Figure 3: Evidence network derived from data on relapse, treatment discontinuation because of intolerable side effects and treatment discontinuation for other reasons**



*Note.* Ziprasidone (in grey-shaded oval ) was considered in the mixed treatment comparison analysis because it allowed indirect comparison between olanzapine and placebo, thus strengthening inference. However, it was not included in the economic analysis because it is not licensed in the UK.

The time horizon of the RCTs ranged from 26 to 104 weeks. Two of the trials assessed ziprasidone versus placebo and versus olanzapine. Ziprasidone is not licensed in the UK and for this reason was not considered in the economic analysis; nevertheless, data from these RCTs were utilised in the mixed treatment comparison model because they allowed indirect comparison between olanzapine and placebo, thus strengthening inference. Table 114 provides a summary of the data utilised in the mixed treatment comparison competing risks model. The network of evidence resulting from the available data is shown in Figure 3

#### ***Mixed treatment comparisons – competing risks model for relapse and discontinuation data***

A random effects model was constructed to estimate for every antipsychotic drug evaluated the probabilities of relapse, treatment discontinuation because of intolerable side effects and treatment discontinuation because of other reasons over 52 weeks, using data from the 17 RCTs summarised in Table 114. The data for each trial  $j$  constituted a multinomial likelihood with four outcomes:  $m = 1$  relapse,  $2 =$  discontinuation because of intolerable side effects,  $3 =$  discontinuation because of other reasons and  $4 =$  none of these (treatment success). If  $r_{jm}$  is the number observed in each category and  $n_j$  is the total number at risk in trial  $j$ , then:

$$r_{j,m=1,2,3,4} \sim \text{Multinomial}(p_{j,m=1,2,3,4}, n_j) \text{ where } \sum_{m=1}^{m=4} p_m = 1$$

Each of the three outcomes  $m = 1, 2, 3$  was modelled separately on the log hazard rate scale. For outcome  $m$ , treatment  $k$  in trial  $j$ , and considering a trial  $j$  comparing treatments  $k$  and  $b$ ,

$$\theta_{j,k,m} = \mu_{j,m} + \delta_{j,b,k,m} I(b \neq k), m = 1, 2, 3$$

where  $d_{j,b,k,m}$  is the trial-specific log hazard ratio of treatment  $k$  relative to treatment  $b$ .  $\mu_{j,m}$  is the 'baseline' log hazard in that trial, relating to treatment  $b$ . The trial-specific log hazard ratios were assumed to come from a normal 'random effects' distribution:

$$\delta_{j,b,k,m} \sim \text{Normal}(d_{k,m} - d_{b,m}, \sigma_m^2)$$

The mean of this distribution is a difference between mean relative effects  $d_{k,m}$  and  $d_{b,m}$ , which are the mean effects of treatments  $k$  and  $b$  respectively relative to treatment 1, which is placebo, for outcome  $m$ . This formulation of the problem expresses the consistency equations were assumed to hold (Lu & Ades, 2006). The between- trials variance of the distribution was specific to each outcome  $m$ .

Vague priors were assigned to trial baselines in the estimation of relative effects and to mean treatment effects,  $m_j, d_{k,m} \sim N(0, 100^2)$ .

A competing risks model was assumed, with constant hazards  $\exp(\theta_{j,k,m})$  acting over the period of observation  $D_j$  in years. Thus, the probability of outcome  $m$  by the end of the observation period for treatment  $k$  in trial  $j$  was:

$$p_{j,k,m}(D_j) = \frac{\exp(\theta_{j,k,m}) [1 - \exp(-\sum_{m=1}^{m=3} D_j \exp(\theta_{j,k,m}))]}{\sum_{m=1}^{m=3} \exp(\theta_{j,k,m})}, \quad m = 1, 2, 3$$

To obtain absolute effects for use in the economic model requires an estimate of the baseline effect in the absence of treatment. While it is desirable to allow the baseline effects to be unconstrained so as to obtain unbiased estimates of relative effects, for the economic model in this guideline a baseline effect that represents the trial evidence was inputted. Therefore, a separate model was constructed for the response to placebo, based on the eight trials with a placebo arm. The response on each outcome was again modelled on a log hazard scale.

$$\xi_{j,m} \sim N(B, \omega_m^2), \quad B \sim N(0, 100^2)$$

$$p_{j,m}(D_j) = \frac{\exp(\xi_{j,m})[1 - \exp(-\sum_{m=1}^{m=3} D_j \exp(\xi_{j,m}))]}{\sum_{m=1}^{m=3} \exp(\xi_{j,m})}, \quad m = 1, 2, 3$$

Priors for the between-trials variation were constructed as follows. First, for the between-studies variation regarding placebo, each of the three outcomes was assigned vague inverse Gamma priors:  $1/\omega_m^2 \sim \text{Gamma}(0.1, 0.1)$ . Then, it was assumed that the variance of the treatment differences must be between zero (perfect correlation between arms) and unity (zero correlation between arms). Thus:

$$\sigma_m^2 = \omega_m^2 \sqrt{2(1-\rho)}, \quad \text{where } \rho \sim U(0,1)$$

For the economic analysis, the output from the model was the proportion of people reaching each outcome by 52 weeks on treatment. The absolute log hazard  $\Theta_{k,m}$  for outcome  $m$  on treatment  $k$  was based on the mean treatment effect relative to treatment 1 (that is, placebo) and a random sample  $X_{k,m}$  from the distribution of absolute log hazards on placebo:

$$X_m \sim N(\xi_m, \omega_m^2)$$

$$\Theta_{k,m} = X_m + d_{k,m}$$

$$P_{k,m} = \frac{\exp(\Theta_{k,m})[1 - \exp(-\sum_{m=1}^{m=3} \exp(\Theta_{k,m}))]}{\sum_{m=1}^{m=3} \exp(\Theta_{k,m})}, \quad m = 1, 2, 3$$

$$P_{k,4} = 1 - \sum_{m=1}^{m=3} P_{k,m}$$

Model parameters required for the economic analysis were estimated using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4 (Lunn et al., 2000; Spiegelhalter et al., 2001). The first 60,000 iterations were discarded and 300,000 further iterations were run; because of high autocorrelation observed in some model parameters, the model was thinned so that every 30th simulation was retained. Consequently, 10,000 posterior simulations were recorded. To test whether prior estimates had an impact on the results, two chains with different initial values were run simultaneously. Convergence was assessed by inspection of the Gelman–Rubin diagnostic plot.

The Winbugs code used to estimate the 52-week probabilities of (i) relapse, (ii) treatment discontinuation because of side effects and (iii) treatment discontinuation because of other reasons is provided in Appendix 26, followed by summary statistics

of a number of model parameters, including the log hazard ratios of all evaluated drugs relative to placebo on the three outcomes examined and the between-trials variation for each outcome. Results are reported as mean values with 95% credible intervals, which are analogous to confidence intervals in frequentist statistics. Table 115 presents the mean values and 95% credible intervals of the probabilities of each outcome for each of the drugs evaluated in the economic analysis, as well as the probability of each treatment being the best with respect to each of the outcomes considered. It can be seen that results for all antipsychotic drugs and all outcomes are characterised by high uncertainty, as expressed by wide 95% credible intervals.

Goodness of fit was tested using the deviance information criterion (DIC) tool. Three different models were tested: a fixed effects model, a random effects model assuming the same between-trials variance of distribution for all three outcomes and the random effects model described above, which allowed between-trials variance of distribution specific for each outcome. The data showed a considerably worse fit in the fixed effects model (DIC = 676.7) compared with the random effects model with common between-trials variance for all three outcomes (DIC = 661.6) and the random effects model with between-trials variance specific for each outcome (DIC = 659.9). Data fit well in both random effects models.

The probability of relapse and the probability of treatment discontinuation because of other reasons over 52 weeks were assumed to apply to every (yearly) cycle of the economic model. The probability of treatment discontinuation because of intolerable side effects over 52 weeks was assumed to apply only to the first year following initiation of a particular antipsychotic drug.

**Table 115: Results of mixed treatment comparison analysis – competing risks model**

Treatment	Probability of relapse over 52 weeks			Probability that treatment is best in reducing relapse over 52 weeks
	Mean	Lower CI	Upper CI	
Olanzapine	0.1996	0.0146	0.7222	0.078
Amisulpride	0.2988	0.0197	0.9042	0.043
Zotepine	0.1067	0.0023	0.5601	0.486
Aripiprazole	0.2742	0.0130	0.8531	0.061
Paliperidone	0.1625	0.0025	0.7008	0.270
Risperidone	0.2761	0.0182	0.8785	0.044
Haloperidol	0.3317	0.0262	0.9028	0.018
Placebo	0.4361	0.0913	0.8613	0.000
	Probability of discontinuation because of side effects over 52 weeks			Probability that treatment is best in reducing discontinuation because of side effects over 52 weeks
	Mean	Lower CI	Upper CI	
Olanzapine	0.0783	0.0021	0.4784	0.152
Amisulpride	0.0554	0.0006	0.3721	0.444
Zotepine	0.3821	0.0120	0.9750	0.011
Aripiprazole	0.1582	0.0026	0.7847	0.084
Paliperidone	0.3287	0.0039	0.9770	0.053
Risperidone	0.1032	0.0020	0.6735	0.134
Haloperidol	0.0922	0.0017	0.5386	0.116
Placebo	0.1094	0.0088	0.4047	0.006
	Probability of discontinuation because of other reasons over 52 weeks			Probability that treatment is best in reducing discontinuation because of other reasons over 52 weeks
	Mean	Lower CI	Upper CI	
Olanzapine	0.2730	0.0207	0.8596	0.030
Amisulpride	0.2435	0.0139	0.8324	0.123
Zotepine	0.2253	0.0074	0.8189	0.229
Aripiprazole	0.3520	0.0202	0.9218	0.046
Paliperidone	0.3848	0.0090	0.9479	0.105
Risperidone	0.1761	0.0086	0.7141	0.390
Haloperidol	0.2516	0.0151	0.8290	0.069
Placebo	0.2754	0.0273	0.7849	0.008
<i>Note.</i> Mean values and 95% credible intervals (CIs) of probabilities of (i) relapse, (ii) treatment discontinuation because of side effects and (iii) treatment discontinuation because of other reasons and probabilities of each treatment being the best in ranking for each of the above outcomes (data on ziprasidone not reported – ziprasidone not considered in ranking).				

### ***Probability of relapse under no treatment***

People discontinuing treatment because of other reasons and moving to no treatment were assumed to stop treatment abruptly, and were therefore at high risk of relapse, reaching 50%, in the first 7 months (Viguera et al., 1997). The annual probability of relapse for no treatment (following treatment discontinuation because of other reasons) was assumed to be equal to that estimated in the mixed treatment comparison analysis for placebo, with the exception of the first year following treatment discontinuation: for this year a higher probability of relapse was estimated, taking into account the data reported in Viguera and colleagues (1997).

### ***Probability of relapse for depot antipsychotic medication***

The annual probability of relapse for the third-line depot antipsychotic medication was taken from data reported in a Cochrane Review on flupentixol decanoate (David et al., 1999). The reported probability (29.77%) may seem rather high; however, this estimate was based on intention-to-treat analysis. Considering that the depot antipsychotic was the final line of treatment in the model and no further discontinuations (which indicate lower compliance) were allowed, the figure of 29.77% seemed reasonable and appropriate to use in the analysis, to reflect potential non-compliance associated with depot antipsychotic medication.

## **11.2.6 Side effect data**

The choice of side effects for consideration in the economic analysis was based on a number of criteria, including the number of people affected in the study population, the impact of side effects on the HRQoL, the magnitude of costs incurred by their management and the availability of respective clinical data specific to the treatment options assessed. Based on the above criteria, three side effects were modelled: weight gain, acute EPS and glucose intolerance/insulin resistance as a representative feature of the metabolic syndrome. It must be noted that acute EPS did not include cases of tardive dyskinesia; the latter differs from acute EPS as it has lasting effects and was not considered in the analysis. Omission of tardive dyskinesia and other neurological side effects, as well as other side effects of antipsychotic medication that may lead to impairments in quality of life (such as sexual dysfunction, increase in prolactin levels, and cardiovascular and gastrointestinal side effects), is acknowledged as a limitation of the economic analysis.

### ***Weight gain***

Data on rates of weight gain were derived from the guideline systematic review of side effects of antipsychotic medication (details of this review are provided in Chapter 10, Section 10.7). Only data reported as 'number of people experiencing an increase in weight of at least 7% from baseline' were considered for the economic analysis because this measure ensured a consistent and comparable definition of weight gain across trials.

Table 114 presents a summary of the data included in the guideline systematic review and utilised in the mixed treatment comparison analysis. Data were available



for six out of the seven antipsychotic medications evaluated in the economic analysis (that is, olanzapine, amisulpride, aripiprazole, paliperidone, risperidone and haloperidol). In addition, four trials that compared quetiapine with another antipsychotic drug were considered in the mixed treatment comparison analysis: two of the trials compared quetiapine with risperidone, one with haloperidol and one with olanzapine. Although quetiapine was not considered in the economic analysis because of lack of clinical data in the area of relapse prevention, quetiapine data on weight gain were considered in the respective mixed treatment comparison analysis as they allowed indirect comparisons across some antipsychotic medications, thus strengthening inference. Trials comparing an SGA with an FGA other than haloperidol were not considered in the mixed treatment comparison analysis as data on FGAs other than haloperidol were sparse; for this reason FGAs other than haloperidol have been treated as a class in the guideline meta-analysis. Nevertheless, such a methodology was considered inappropriate for mixed treatment comparison analysis. The network of evidence resulting from the available data is shown in Figure 4.

### **Mixed treatment comparisons – simple random effects model for data on weight gain**

A simple random effects model was constructed to estimate the relative effect between the  $k = 7$  antipsychotic drugs evaluated in terms of weight gain, using data from the 17 RCTs summarised in Table 116. The model is similar to that described by Hasselblad (1998). The data for each trial  $j$  comprised a binomial likelihood:

$$r_{jk} \sim \text{Bin}(p_{jk}, n_{jk})$$

where  $p_{jk}$  is the probability of experiencing weight gain in trial  $j$  under treatment  $k$ ,  $r_{jk}$  is the number of people experiencing weight gain in trial  $j$  under treatment  $k$  and  $n_{jk}$  is the total number of people at risk in trial  $j$  under treatment  $k$ .

Treatment effects were modelled on the log-odds scale and were assumed to be additive to the baseline treatment  $b$  in trial  $j$ :

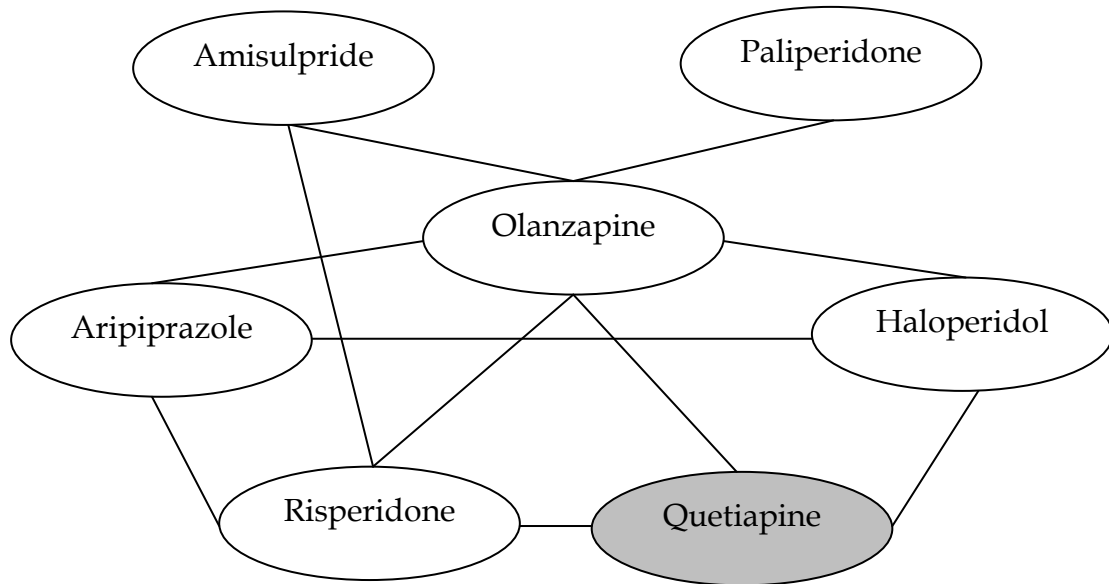
$$\begin{aligned} \text{logit}(p_{jk}) &= \mu_{jb} & \text{for } k = b; \\ \text{logit}(p_{jk}) &= \mu_{jb} + \delta_{jkb} & \text{for } k \neq b \end{aligned}$$

where  $\mu_{jb}$  is the log odds of weight gain for baseline treatment  $b$  in trial  $j$  and  $\delta_{jkb}$  is the trial-specific log-odds ratio of treatment  $k$  relative to treatment  $b$ .

**Table 116: Summary of data reported in the RCTs included in the guideline systematic review on weight gain ('increase in weight  $\geq 7\%$  from baseline') that were utilised in the economic analysis**

Study	Time horizon (weeks)	1. Haloperidol (r/n)	2. Olanzapine (r/n)	3. Aripiprazole (r/n)	4. Quetiapine (r/n)	5. Paliperidone (r/n)	6. Risperidone (r/n)	7. Amisulpride (r/n)
1.LIEBERMAN2003A	24	51/132	95/131	-	-	-	-	
2.KONGSAKON2006	24	30/94	51/113	-	-	-	-	
3.StudyS029	52	23/128	46/134	-	-	-	-	
4.KANE2002	4	10/103	-	11/203	-	-	-	
5.Arvanitis1997	6	2/52	-	-	20/157	-	-	
6.MCQUADE2004	26	-	58/155	21/154	-	-	-	
7.RIEDEL2007B	8	-	8/17	-	8/16	-	-	
8.DAVIDSON2007	6	-	25/115	-	-	13/118	-	
9.KANE2007A	6	-	16/123	-	-	6/118	-	
10.MARDER2007	6	-	23/109	-	-	8/112	-	
11.Conley2001	8	-	44/161	-	-	-	18/155	
12.MARTIN2002	24	-	66/186	-	-	-	-	39/186
13.POTKIN2003A	4	-	-	22/201	-	-	11/99	
14.CHAN2007B	4	-	-	2/49	-	-	4/34	
15.RIEDEL2005	12	-	-	-	3/22	-	1/22	
16.ZHONG2006	8	-	-	-	35/338	-	35/334	
17.Lecrubier2000	26	-	-	-	-	-	18/100	32/95

**Figure 4: Evidence network for data on weight gain (defined as an increase of at least 7% of baseline weight).**



By taking haloperidol (treatment A) as baseline, and the true mean treatment effects of the remaining six treatments B, C, D, *etc* relative to haloperidol as the basic parameters  $d_{AB}$ ,  $d_{AC}$ ,  $d_{AD}$ , the remaining functional parameters can be expressed in terms of these basic parameters, for example:

$$d_{BC} = d_{AC} - d_{AB}; \quad d_{BD} = d_{AD} - d_{AB}; \quad \text{etc}$$

The trial-specific log-odds ratios for every pair of treatments XY were assumed to come from normal random effects distributions:

$$\delta_{jXY} \sim N(d_{XY}, \sigma^2)$$

where  $d_{XY}$  is the true mean effect size between X and Y and  $\sigma^2$  the variance of the normal distribution, which was assumed to be common in all pairs of treatments. Vague priors were assigned to trial baselines, basic parameters and common variance:

$$\mu_{jb}, d_{AB}, d_{AC}, d_{AD}, \text{etc} \sim N(0, 100^2); \quad \sigma \sim \text{Uniform}(0,2)$$

The results of mixed treatment comparison analysis were recorded as odds ratios (ORs) of weight gain for each of the six antipsychotics (olanzapine, amisulpride, aripiprazole, quetiapine, paliperidone and risperidone) versus haloperidol (which was used as baseline). Posterior distributions were estimated using Markov chain Monte Carlo simulation methods implemented in Winbugs 1.4 (Lunn et al., 2000;

Spiegelhalter et al., 2001). The first 60,000 iterations were discarded and 300,000 further iterations were run; because of potentially high autocorrelation, the model was thinned so that every 30th simulation was retained. Consequently, 10,000 posterior simulations were recorded.

The Winbugs code used to estimate the ORs of weight gain for the six antipsychotic medications versus haloperidol is presented in Appendix 26, followed by summary statistics of a number of model parameters, including the ORs of each antipsychotic drug considered in the mixed treatment comparison model versus haloperidol and the between-trials variation.

Goodness of fit was tested using the residual deviance (resdev) and the deviance information criteria (DIC) tool. The simple random effects model demonstrated a better fit for the data (resdev = 45.06; DIC = 296.794) compared with a fixed effects model (resdev = 63.59; DIC = 306.519).

The probability of experiencing weight gain associated with haloperidol was calculated using data from RCTs included in the mixed treatment comparison analysis. The studies reporting increase in weight of at least 7% following use of haloperidol had time horizons ranging from 4 to 52 weeks. However, it was estimated that the rate of weight gain is not constant over time and that the majority of new cases of weight gain develop over the first 12 weeks following initiation of any particular antipsychotic drug. For this reason, only RCTs examining haloperidol with time horizons of up to 12 weeks were considered at the estimation of a weighted probability of weight gain for haloperidol. Rates of experiencing at least a 7% increase in weight reported in studies of duration shorter than 12 weeks were extrapolated to 12-week rates using exponential fit (assuming that the rate of experiencing an increase in weight of at least 7% remained stable over 12 weeks). The weighted average probability of weight gain for haloperidol was subsequently calculated from these estimates. The probabilities of weight gain ( $p_x$ ) for each of the other antipsychotic medications included in the mixed treatment comparison analysis were then estimated using the following formulae:

$$p_x = odds_x / (1 + odds_x)$$

and

$$odds_x = OR_{x,b} * p_b / (1 - p_b)$$

where  $p_b$  is the probability of weight gain for haloperidol,  $OR_{x,b}$  is the odds ratio for weight gain with each antipsychotic drug versus haloperidol as estimated in the mixed treatment comparison analysis, and  $odds_x$  is the odds of each antipsychotic to cause weight gain.

**Table 117: Increase in weight as a side effect of antipsychotic medications: ORs versus haloperidol, odds and absolute probabilities (mean values)**

Antipsychotic drug	OR versus haloperidol	Odds	Probability of weight gain	Source
Haloperidol	1	0.2500	0.2000	Probability based on extrapolation of data from RCTs with time horizon upto 12 weeks included in the guideline systematic review
Olanzapine	2.8631	0.7158	0.4172	ORs versus haloperidol taken from mixed treatment comparison analysis (simple random effects model)
Amisulpride	1.8604	0.4651	0.3175	
Aripiprazole	0.7373	0.1843	0.1516	
Paliperidone	1.0779	0.2695	0.2123	
Risperidone	1.0895	0.2724	0.2141	

provides the estimated probability of weight gain for haloperidol, the mean ORs of each antipsychotic drug examined in economic analysis versus haloperidol as derived from respective mixed treatment comparison analysis, as well as the estimated odds and probability of weight gain for each antipsychotic.

The drug-specific probabilities of experiencing weight gain derived from the above calculations were applied to the first year following initiation of a particular antipsychotic drug. In the following years, the probability of weight gain under this particular antipsychotic medication was assumed to be zero (for people at risk; that is, for those who had not already experienced weight gain).

### **Probability of experiencing weight gain under zotepine, depot antipsychotic medication and no treatment**

The probability of experiencing weight gain for zotepine was assumed to equal the respective probability for risperidone; the probability for the third-line depot antipsychotic medication was assumed to equal that of haloperidol. People under no treatment were assumed to experience no increase in their weight equalling or exceeding 7% of their initial weight.

### ***Acute extrapyramidal symptoms***

Data on rates of acute EPS were derived from the guideline systematic review of side effects of antipsychotic medication (details of this review are provided in Chapter 10, Section 10.7). Of the available data, those expressing 'need for anticholinergic medication' were considered for the economic analysis as this measure was thought to capture more accurately the presence of acute EPS.

Table 118 presents a summary of the data on acute EPS included in the guideline systematic review and utilised in the mixed treatment comparison analysis.

**Table 118: Summary of data reported in the RCTs included in the guideline systematic review on acute EPS ('need for anticholinergic medication') that were utilised in the economic analysis**

Study	Time horizon (weeks)	1. Haloperidol (r/n)	2. Risperidone (r/n)	3. Olanzapine (r/n)	4. Zotepine (r/n)	5. Amisulpride (r/n)	6. Quetiapine (r/n)	7. Aripiprazole (r/n)	8. Paliperidone (r/n)
1.Claus1991	12	6/22	4/22	-	-	-	-	-	-
2.Mesotten1991	8	12/32	9/28	-	-	-	-	-	-
3. Chouinard1993	8	15/21	29/68	-	-	-	-	-	-
4.Marder1994	8	31/66	72/256	-	-	-	-	-	-
5.Peuskens1995	8	67/226	201/907	-	-	-	-	-	-
6.Blin1996	4	7/20	5/21	-	-	-	-	-	-
7.Janicak1999	6	22/32	12/30	-	-	-	-	-	-
8.Heck2000	6	10/37	11/40	-	-	-	-	-	-
9.Emsley1995	6	63/84	50/99	-	-	-	-	-	-
10.SCHOOLER2005	52	68/137	48/116	-	-	-	-	-	-
11.Csernansky2000	52	33/188	16/177	-	-	-	-	-	-
12.MARDER2003	104	26/30	23/33	-	-	-	-	-	-
13.Jones1998	54	17/23	9/21	3/21	-	-	-	-	-
14.Tollefson1997	6	315/660	-	228/1336	-	-	-	-	-
15.KONGSAKON2006	24	30/94	-	24/113	-	-	-	-	-
16.LIEBERMAN2003A	24	65/125	-	21/125	-	-	-	-	-
17.Klieser1996	4	25/45	-	-	6/20	-	-	-	-

*Continued*

Table 38: (Continued)

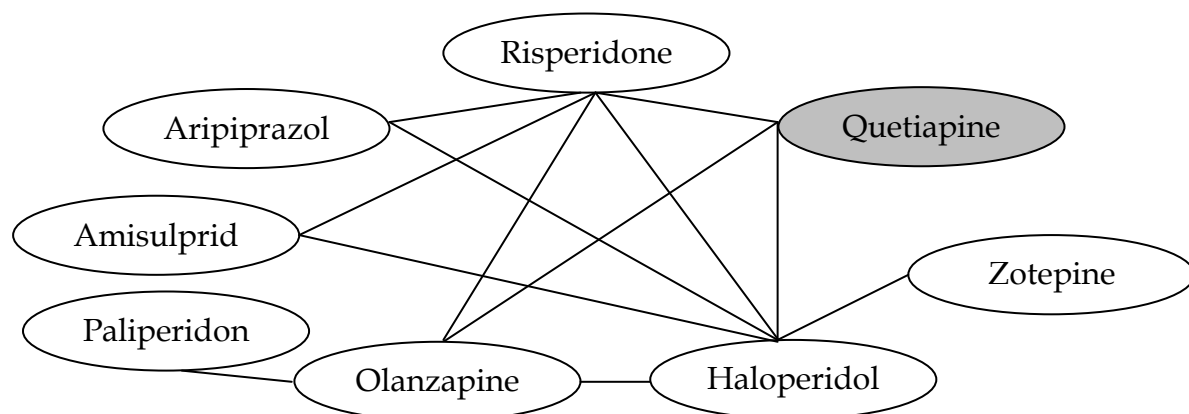
Study	Time horizon (weeks)	1. Haloperidol (r/n)	2. Risperidone (r/n)	3. Olanzapine (r/n)	4. Zotepine (r/n)	5. Amisulpride (r/n)	6. Quetiapine (r/n)	7. Aripiprazole (r/n)	8. Paliperidone (r/n)
18.Barnas1987	7	13/15	-	-	8/15	-	-	-	-
19.Petit1996	8	62/63	-	-	42/63	-	-	-	-
20.Delcker1990	6	13/20	-	-	-	11/21	-	-	-
21.Moller1997	6	54/96	-	-	-	28/95	-	-	-
22.Puech1998	4	26/64	-	-	-	45/194	-	-	-
23.Speller1997	52	25/31	-	-	-	10/29	-	-	-
24.Emsley1999	8	17/145	-	-	-	-	3/143	-	-
25.KANE2002	4	30/103	-	-	-	-	-	23/203	-
26.KASPER2003	52	245/430	-	-	-	-	-	196/853	-
27.Conley2001	8	-	61/188	53/189	-	-	-	-	-
28.Tran1997	28	-	55/167	34/172	-	-	-	-	-
29.Fleurot1997	8	-	26/113	-	-	35/115	-	-	-
30.Lecrubier2000	26	-	47/158	-	-	36/152	-	-	-
31.ZHONG2006	8	-	23/334	-	-	-	19/338	-	-
32.RIEDEL2005	12	-	9/22	-	-	-	2/22	-	-
33.CHAN2007B	4	-	14/34	-	-	-	-	12/49	-
34.SIROTA2006	26	-	-	6/21	-	-	5/19	-	-
35.KANE2007A	6	-	-	10/128	-	-	-	-	14/123
36.MARDER2007	6	-	-	13/109	-	-	-	-	10/112

Data on all seven antipsychotic medications evaluated in the economic analysis (olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol) were available. In addition, four trials that compared quetiapine with another antipsychotic drug were considered in the mixed treatment comparison analysis: two of the trials compared quetiapine with risperidone, one with haloperidol and one with olanzapine. Although quetiapine was not considered in the economic analysis owing to lack of clinical data in the area of relapse prevention, quetiapine data on acute EPS were considered in the respective mixed treatment comparison analysis as they allowed indirect comparisons across drugs, thus strengthening inference. Trials comparing an SGA with an FGA other than haloperidol were not considered in the mixed treatment comparison analysis as data on FGAs other than haloperidol were sparse; for this reason FGAs other than haloperidol have been treated as a class in the guideline meta-analysis. Nevertheless, such a methodology was considered inappropriate for mixed treatment comparison analysis. The network of evidence constructed based on the available data is demonstrated in Figure 5.

#### **Mixed treatment comparisons full random effects model for acute extrapyramidal side-effects data**

A full random effects model was constructed to estimate the relative effect between the  $k = 8$  antipsychotics evaluated in terms of development of acute EPS, using data from the 36 RCTs summarised in Table 118. The model is similar to that described above, utilised for the mixed treatment comparison analysis of data on weight gain, but takes into account the correlation structure induced by a three-arm trial (Jones, 1998) included in the 36 RCTs; this model structure relies on the realisation of

**Figure 5: Evidence network for data on acute EPS (expressed as need for anticholinergic medication)**



*Note.* Quetiapine (in grey-shaded oval) was considered in the mixed treatment comparison analysis because it allowed indirect comparisons between a number of medications, thus strengthening inference. However, it was not included in the economic analysis because no clinical data in the area of relapse prevention for people with schizophrenia that is in remission were available for quetiapine.



the bivariate normal distribution as a univariate marginal distribution and a univariate conditional distribution (Higgins & Whitehead, 1996):

$$\text{If } \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \sim N \left[ \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma^2 & \sigma^2/2 \\ \sigma^2/2 & \sigma^2 \end{pmatrix} \right]$$

$$\text{then } x_1 \sim N(\mu_1, \sigma^2), \text{ and } x_2 | x_1 \sim N\left(\mu_2 + \frac{1}{2}(x_1 - \mu_1), \frac{3}{4}\sigma^2\right)$$

The results of this mixed treatment comparison analysis were also recorded as ORs of developing acute EPS for each of the seven antipsychotic drugs (olanzapine, amisulpride, aripiprazole, zotepine, quetiapine, paliperidone and risperidone) versus haloperidol (which was again used as baseline). Posterior distributions were estimated using Markov chain Monte Carlo simulation methods implemented in Winbugs 1.4 (Lunn et al., 2000; Spiegelhalter et al., 2001). The first 60,000 iterations were discarded, and 300,000 further iterations were run; because of potentially high auto-correlation, the model was thinned so that every 30th simulation was retained. Consequently, 10,000 posterior simulations were recorded.

The Winbugs code used to estimate the ORs of developing acute EPS for the seven antipsychotic medications versus haloperidol is presented in Appendix 26, followed by summary statistics of a number of model parameters, including the OR of each antipsychotic drug considered in the mixed treatment comparison model versus haloperidol and the between-trials variation. The resdev of the model was 75.93. The probability of experiencing acute EPS for haloperidol was calculated using data from RCTs included in the mixed treatment comparison analysis. The studies reporting the need for anticholinergic medication following use of haloperidol had time horizons ranging from 4 to 104 weeks. However, it was estimated that the rate of developing acute EPS is not constant over time and that the majority of new cases of acute EPS develop over the first 8 weeks following initiation of any particular antipsychotic drug. For this reason, only RCTs examining haloperidol with time horizons of up to 8 weeks were considered at the estimation of a weighted probability of acute EPS for haloperidol. Rates of acute EPS reported in studies of duration shorter than 8 weeks were extrapolated to 8-week rates using exponential fit (assuming that the rate of development of acute EPS remained stable over 8 weeks). The weighted average probability of acute EPS for haloperidol was subsequently calculated from these estimates. The probability of acute EPS ( $p_x$ ) for each of the other antipsychotic medications included in the mixed treatment comparison analysis was then estimated using the following formulae:

$$p_x = \text{odds}_x / (1 + \text{odds}_x)$$

and

$$\text{odds}_x = \text{OR}_{x,b} * p_b / (1 - p_b)$$

where  $p_b$  is the probability of acute EPS for haloperidol,  $OR_{x,b}$  the odds ratio for acute EPS of each antipsychotic medication versus haloperidol as estimated in the mixed treatment comparison analysis, and  $odds_x$  the odds of each antipsychotic leading to development of acute EPS.

Table 119 provides the estimated probability of weight gain for haloperidol, the mean ORs of each antipsychotic drug examined in economic analysis versus haloperidol as derived from respective mixed treatment comparison analysis, as well as the estimated odds and probability of weight gain for each antipsychotic.

The drug-specific probabilities of developing acute EPS derived from the above calculations were applied to the first year following initiation of a particular antipsychotic drug. In the following years, the probability of developing acute EPS under this particular antipsychotic medication was estimated to be 10% of the probability applied to the first year.

#### **Probability of developing acute extrapyramidal side effects under depot antipsychotic medication and no treatment**

The probability of developing acute EPS under the third-line depot antipsychotic medication was taken from data reported in a Cochrane Review on flupentixol decanoate (David et al., 1999). People under no treatment were assumed to develop no acute EPS.

#### ***Glucose intolerance/insulin resistance and diabetes***

Glucose intolerance/insulin resistance was modelled as a representative feature of the metabolic syndrome, the incidence of which is high in people taking antipsychotic

**Table 119: Development of acute EPS as a side effect of antipsychotic medications: ORs versus haloperidol, odds and absolute probabilities (mean values)**

Antipsychotic drug	OR versus haloperidol	Odds	Probability of weight gain	Source
Haloperidol	1	1.1586	0.5367	Probability based on extrapolation of data from RCTs with time horizon up to 8weeks included in the guideline systematic review
Olanzapine	0.2631	0.3048	0.2336	ORs versus haloperidol taken from mixed treatment comparison analysis (full random effects model)
Amisulpride	0.3993	0.4626	0.3163	
Zotepine	0.1476	0.1710	0.1461	
Aripiprazole	0.2517	0.2916	0.2258	
Paliperidone	0.2983	0.3456	0.2569	
Risperidone	0.4743	0.5495	0.3546	

medication. The metabolic syndrome is a predictor of type-2 diabetes and coronary heart disease. Both conditions are associated with a number of events and complications that cause significant impairment in the HRQoL and incur substantial healthcare costs. Because there is a high correlation between the two conditions, it was decided to only model events (complications) resulting from the development of diabetes mellitus to avoid the double-counting of health events and the overestimation of the (negative) impact of metabolic syndrome on the cost effectiveness of antipsychotic drugs. Modelling health events as complications of diabetes was preferred to linking them to coronary heart disease because estimates of the incidence of diabetes complications have been reported in the literature, having been derived from a large prospective cohort study of people with diabetes mellitus in the UK (Stratton et al., 2000).

The relationship between specific antipsychotic medications, risk for metabolic syndrome and the development of type-2 diabetes has not been fully explored and relevant data that are appropriate for modelling are sparse. A systematic review of the metabolic effects of antipsychotic medications concluded that antipsychotics associated with greatest increases in body weight were also associated with a consistent pattern of clinically significant insulin resistance (Newcomer & Haupt, 2006). The authors noted that correlations between change in weight and change in plasma glucose values were weaker overall than correlations between weight change and change in insulin resistance, and that unchanged plasma glucose levels did not preclude clinically significant increases in insulin resistance. The results of the review indicated that the relative risk for diabetes mellitus during antipsychotic medication use generally matched the rank order of weight-gain potential for the different antipsychotics, although a significant minority of people taking antipsychotics might experience glucose dysregulation independent of weight gain. A systematic review and meta-analysis of studies comparing the risk for diabetes between SGAs and FGAs in people with schizophrenia and related psychotic disorders found that SGAs led to a greater risk for diabetes compared with FGAs (Smith et al., 2008). Besides being associated with impaired glucose levels and insulin resistance, antipsychotic drugs have been shown to lead directly to development of diabetes shortly after their initiation by people with schizophrenia (Saddichha et al., 2008; van Winkel et al., 2006; van Winkel et al., 2008).

Given that available data on the risk for glucose intolerance and/or diabetes associated with specific antipsychotic drugs are limited, the probability of developing glucose intolerance/insulin resistance (associated with greater future risk for developing diabetes) and the probability of developing diabetes directly in the first year of antipsychotic use were estimated as follows: first, estimates on these two probabilities specific to haloperidol were made, based on reported data in published literature. Second, drug-specific probabilities of weight gain, estimated as described in the previous section, were used to calculate relative risks of weight gain for each SGA included in the analysis versus haloperidol. Relative risks for weight gain were assumed to be equal to relative risks for developing glucose intolerance/insulin resistance and diabetes because existing evidence suggested a

high correlation between increase in weight and insulin resistance, as discussed above (Newcomer & Haupt, 2006). Finally, relative risks of each SGA versus haloperidol were multiplied by the haloperidol-specific estimated probabilities of developing glucose intolerance/insulin resistance and diabetes to obtain respective probabilities for each SGA assessed in the economic analysis. The resulting estimates, based on the correlation between glucose intolerance/risk for diabetes and weight gain, may be potentially conservative because an additional mechanism leading to glucose dysregulation, independent of weight increases, appears to exist (Newcomer & Haupt, 2006). On the other hand, the fact that the rank order of relative risk for diabetes has been shown to match the rank order of weight-gain potential for the different antipsychotics, according to findings of the same study, does not guarantee that the relative risk of developing intolerance/insulin resistance and diabetes of each SGA versus haloperidol is actually equal to their in-between relative risk of weight-gain. The described method for estimating absolute probabilities for developing intolerance/insulin resistance and diabetes for each SGA in the model was deemed necessary because of a lack of other appropriate data, but is acknowledged as a limitation of the economic analysis.

The estimated probability of directly developing diabetes during the first year of initiation of haloperidol was based on respective rates reported in the literature for people with schizophrenia under antipsychotic medication (van Winkel et al., 2008). Since these studies examined populations initiated on a number of antipsychotics, including SGAs, and the risk for developing diabetes is known to be higher for SGAs compared with FGAs (Smith et al., 2008), the probability of developing diabetes within the first year of initiation of haloperidol was estimated to be lower than the respective figures reported in the literature associated with use of antipsychotics generally. Similarly, the probability of glucose intolerance/insulin resistance within the first year of initiation of haloperidol was estimated taking into account relevant data identified in the guideline systematic review of clinical evidence. The resulting estimates for haloperidol that were used in the economic analysis were 2% (first year probability of developing diabetes) and 15% (first year probability of developing glucose intolerance/insulin resistance).

The resulting probabilities of developing diabetes/glucose intolerance for all antipsychotics following the methodology described above, and the ranking of antipsychotics in terms of risk for diabetes, were consistent with evidence suggesting that olanzapine is strongly associated with diabetic events while aripiprazole, risperidone and haloperidol are poorly associated with such events (Dumouchel et al., 2008).

The probability of developing diabetes directly was applied only to the first year of initiation of any particular antipsychotic. Similarly, it was assumed that development of glucose intolerance/insulin resistance occurred only within the first year of initiation of any specific drug. People who did not develop insulin resistance within the first year of initiation of a particular antipsychotic were assumed to develop no insulin resistance in the following years, provided that they remained on

the same drug. However, insulin resistance that developed within the first year of initiation of a specific antipsychotic was assumed to be permanent and to result in an increased risk for diabetes over a lifetime. The annual transition probability from impaired glucose tolerance to developing diabetes was taken from Gillies and colleagues (2008). It is acknowledged that applying the probabilities of developing diabetes and insulin resistance only to the first year of initiation of any particular antipsychotic is likely to be conservative and to underestimate the impact of the metabolic syndrome on the relative cost effectiveness of antipsychotics. On the other hand, insulin resistance that developed within the first year of initiation of a particular antipsychotic was assumed to be permanent and to lead to a lifetime risk of developing diabetes.

### **Complications from diabetes**

The probabilities of complications following development of diabetes were estimated based on data reported in the UKPDS (Stratton et al., 2000). This was a 20-year prospective study that recruited 5,102 people with type-2 diabetes in 23 clinical centres based in England, Northern Ireland and Scotland. The study reported incidence rates of complications for different levels of haemoglobin A1C concentration (Hgb A1C). Annual probabilities of complications were estimated based on the available data, assuming that 20% of people in the model had Hgb A1C 7 to <8%, 30% of people had 8 to <9%, 30% of people had 9 to <10% and 20% of people had  $\geq 10\%$ . These assumptions took account of the clinical experience of the GDG, according to whom, people with schizophrenia in general do not have good glycaemic control. Incidence of complications in Stratton and colleagues (2000) were provided as aggregate figures of fatal and non-fatal events for each complication. To estimate the probability of fatal and non-fatal events for each complication separately in the economic model, the reported overall incidence of deaths related to diabetes at each level of Hgb A1C was applied to the reported incidence of each complication at the same Hgb A1C level to estimate the proportion of fatal events reported for each complication.

### **11.2.7 Mortality estimates**

The risk of death is higher in people with schizophrenia than in the general population (McGrath et al., 2008). Transition to death in the model occurred as a result of suicide or other reasons, including increased physical morbidity characterising people with schizophrenia that leads to increased mortality. It was assumed that the risk of death was independent of specific antipsychotic drug use, owing to lack of sufficient data to support the opposite hypothesis. Instead, all people in the model were subject to increased mortality relative to the general population, common to all antipsychotic drugs. To calculate the number of deaths occurring each year, the increased standardised mortality ratio (SMR) observed in people with schizophrenia (McGrath et al., 2008) was multiplied by the age- and gender-specific mortality rates for people aged 25 years and above in the general population in England and Wales (Office for National Statistics, 2008). The number of deaths was calculated on the basis that the study population (people with schizophrenia) had a male to female ratio of 1.4 to 1 (McGrath, 2006).

Death was assumed to occur in the middle of every year (cycle); this means that over the year death occurred, people incurred half of the costs and gained half of the QALYs they were expected to incur and gain, respectively, had they not died.

### **11.2.8 Utility data and estimation of quality-adjusted life years**

To express outcomes in the form of QALYs, the health states of the economic model needed to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on, and perceptions of, HRQoL in the health states under consideration.

#### ***Systematic review of published utility scores for people with schizophrenia***

The systematic search of the literature identified six studies that reported utility scores for specific health states and events associated with schizophrenia (Chouinard & Albright, 1997; Cummins et al., 1998; Glennie, 1997; Lenert et al., 2004; Revicki et al., 1996; Sevy et al., 2001).

Chouinard and Albright (1997) generated health states using data on PANSS scores from 135 people with schizophrenia participating in a Canadian multicentre RCT of risperidone versus haloperidol. Cluster analysis identified three clusters that included 130 of the participants with mild, moderate and severe symptomatology. A health-state profile was described for each cluster, including additional information on adverse events, obtained by assessing the average scores of Extrapyramidal Symptom Rating Scale (ESRS) subscales of parkinsonism, dyskinesia and dystonia in each treatment group. Subsequently, 100 psychiatric nurses in the US were asked to assign utility values to each of the three health states using standard gamble (SG) methods.

Glennie (1997) described the development of health-state profiles specific to antipsychotic medications, according to average PANSS scores reported in risperidone trials included in a systematic review. The impairment in HRQoL caused by the need for hospitalisation and the presence of EPS were also considered. In this case, seven people with schizophrenia in Canada who were in a stable state were asked to value the generated health states using the SG technique.

Lenert and colleagues (2004) valued health states associated with schizophrenia constructed from the results of principal component analysis of PANSS scores; the scores were obtained from people with schizophrenia participating in a large multicentre effectiveness trial conducted in the US. This analysis led to the clustering of types of symptoms and the final development of eight health states describing different types and severity of schizophrenia symptoms. Moreover, the presence of common adverse events from antipsychotic medication was taken into account at valuation. The resulting health states were valued by a sample of 441 people from the general US population using the SG technique.

Revicki and colleagues (1996) developed five hypothetical health states (vignettes) describing various levels of schizophrenia symptoms, functioning and well-being in inpatient and outpatient settings, based on relevant descriptions available in the medical literature and expert opinion. The health states were subsequently valued by three different groups of people in the UK, using different valuation techniques: 49 people with schizophrenia in remission and their carers rated the health states using categorical rating scales (RS) and paired comparisons (PC); a number of psychiatrists valued the health states using categorical RS and SG techniques. The study reported the psychiatrist-derived utility scores using SG, as well as the utility scores derived from people with schizophrenia and their carers using PC.

Cummins and colleagues (1998) linked health states observed in people with schizophrenia participating in an international RCT of olanzapine versus haloperidol with specific health states generated using the IHRQoL. The methodology used to link these two different sets of health state profiles was not clearly described. IHRQoL is a generic measure of HRQoL, consisting of three dimensions: disability, physical distress and emotional distress (Rosser et al., 1992). The composite health states derived from this generic measure have been valued using the SG method. However, detailed description of the methods of valuation has not been made available and no other application of this instrument has been identified in the literature (Brazier, 2007b).

Finally, Sevy and colleagues (2001) reported valuations of people with schizophrenia for a large number of side effects resulting from antipsychotic medication, using SG methods. The purpose of the study was to assess the relationship between the utility values obtained and the study population's willingness to pay to remove such side effects. The resulting scores were reported unadjusted because death was not used as anchor value 'zero' and are therefore not appropriate for use in economic modelling.

Table 120 summarises the methods used to derive health states and subsequent utility scores associated with schizophrenia health states and events, as well as the results of the first five studies described above, because these reported utility scores that could potentially be used in the guideline's economic analysis.

In addition to the above studies, a number of studies reported utility scores for people with schizophrenia that were generated using generic preference-based measures of HRQoL (Kasckow et al., 2001; Knapp et al., 2008; König et al., 2007; Lewis et al., 2006b; Sciolla et al., 2003; Strakowski et al., 2005; Tunis et al., 1999). However, any utility scores reported in these studies expressed the overall HRQoL of the study population and were not linked to specific health states; consequently, they were not useful for economic modelling.

König and colleagues (2007) assessed and valued the HRQoL of people with schizophrenic, schizotypal or delusional disorders using the EQ-5D. They concluded

that EQ-5D had reasonable validity in this group of people, but its association with the positive subscale of PANSS was rather weak. For this reason it was suggested that EQ-5D be used in combination with disease-specific instruments in such populations so that all aspects of HRQoL be captured. The study did not report utility scores relating to specific health states experienced by the study population. Lewis and colleagues (2006b) evaluated the cost effectiveness of FGAs versus SGAs, and clozapine versus SGAs, in people with schizophrenia responding poorly to, or being intolerant of, current antipsychotic treatment in two RCTs conducted in the UK (CUtLASS Bands 1 and 2). Health benefits from treatment were determined by measuring the participants' HRQoL using the EQ-5D at various points in the trials.

Knapp and colleagues (2008) also obtained EQ-5D scores from outpatients with schizophrenia participating in a European multicentre observational study to evaluate the cost effectiveness of olanzapine versus other oral and depot antipsychotics. In both of the above economic studies, the obtained EQ-5D scores were not attached to specific health states and therefore could not be applied to the health states described in the guideline economic analysis.

Sciolla and colleagues (2003) assessed the HRQoL of outpatients with schizophrenia aged over 45 years using the 36-item Short-Form health survey (SF-36). The authors stated that SF-36 adequately measured the impairment in HRQoL associated with schizophrenia in middle aged and older people. Strakowski and colleagues (2005) and Tunis and colleagues (1999) reported SF-36 scores in people with schizophrenia who participated in two different clinical trials of olanzapine versus haloperidol; both studies reported SF-36 scores at baseline and at end of treatment for each treatment group. None of the three studies that used the SF-36 linked the obtained scores to specific health states associated with schizophrenia; thus the data reported were not useful in the guideline economic analysis.

Kasckow and colleagues (2001) measured the quality of life of inpatients and outpatients with schizophrenia using the Quality of Well-Being Scale (QWB). Although hospitalisation and high levels of positive symptoms were shown to be associated with lower QWB scores, no health states that could be used in the guideline economic analysis were specified and linked with QWB-generated utility scores.



**Table 120: Summary of studies reporting utility scores relating to specific health states and events associated with schizophrenia**

Study	Definition of health states	Valuation method	Population valuing	Results
<b>Chouinard &amp; Albright, 1997</b>	Based on cluster analysis of PANSS scores combined within formation from data on ESRS subscales of parkinsonism, dyskinesia and dystonia, all obtained from 135 people with schizophrenia in Canada who participated in a multicentre three-arm RCT comparing risperidone versus haloperidol versus placebo	SG	100 psychiatric nurses in the US	Mild health state: 0.61 Moderate healthstate: 0.36 Severe healthstate: 0.29
<b>Cummins et al., 1998</b>	Health states of people with schizophrenia participating in a RCT linked with health states generated using the IHRQoL	SG	Unclear	Response – no EPS: 0.960 Response – EPS: 0.808 Need for acute treatment/relapse – No EPS: 0.762 Need for acute treatment/relapse – EPS: 0.631
<b>Glennie, 1997</b>	Based on average scores from each of the three PANSS subscales (positive, negative and general psychopathology) reported in risperidone trials included in a systematic review; need for hospitalisation and presence of EPS also considered	SG	7people with stable schizophrenia in Canada	Mild delusional symptoms – Risperidone: 0.89 Mild delusional symptoms – haloperidol: 0.86 Moderate delusional symptoms: 0.82 Hospitalisation: -0.07 Presence of EPS: -0.07
<b>Lenert et al., 2004</b>	Based on principal component analysis followed by cluster analysis of PANSS scores (positive, negative and general psychopathology subscales) obtained from people with schizophrenia participating in	SG	441 people from US general population	Mild (all areas low): 0.88 Moderate type I (negative predominant): 0.75 Moderate type II (positive predominant): 0.74

*Continued*

Study	Definition of health states	Valuation method	Population valuing	Results
	An effectiveness trial in the US; presence of adverse events from medication also considered			Severe type I (negative predominant): 0.63 Severe type II (positive and cognitive predominant): 0.65 Severe type III (negative and cognitive predominant): 0.53 Severe type IV (positive predominant): 0.62 Extremely severe (all symptoms high): 0.42 Orthostatic hypotension: -0.912% Weight gain: -0.959% Tardive dyskinesia: -0.857% Pseudo-parkinsonism: -0.888% Akathisia: -0.898%
Revicki et al., 1996	Vignettes based on medical literature and expert opinion	SG	UK psychiatrists	Outpatient, excellent functioning: 0.83 Outpatient, good functioning: 0.73 Outpatient, moderate functioning: 0.70 Outpatient, negative symptoms: 0.60 Inpatient, acute positive symptoms: 0.56
		PC	49 people with schizophrenia in remission in the UK	Outpatient, excellent functioning: 0.77 Outpatient, good functioning: 0.57 Outpatient, moderate functioning: 0.49 Outpatient, negative symptoms: 0.30 Inpatient, acute positive symptoms: 0.19
		PC	Carers of people with schizophrenia in the UK	Outpatient, excellent functioning: 0.69 Outpatient, good functioning: 0.51 Outpatient, moderate functioning: 0.44 Outpatient, negative symptoms: 0.32 Inpatient, acute positive symptoms: 0.22

NICE recommends the EQ-5D as the preferred measure of HRQoL in adults for use in cost-utility analysis. NICE also suggests that the measurement of changes in HRQoL should be reported directly from people with the condition examined, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as time trade-off (TTO) or SG, in a representative sample of the UK population. At the same time, it is recognised that EQ-5D data may not be available or may be inappropriate for the condition or effects of treatment (NICE, 2008a).

None of the studies summarised in Table 120 derived utility values using EQ-5D scores valued from members of the UK general population. Three of the five studies generated health states based on analysis of condition-specific PANSS scores (Chouinard & Albright, 1997; Glennie, 1997; Lenert et al., 2004). Valuations in these three studies were made by healthcare professionals in the US (Chouinard & Albright, 1997), by people with schizophrenia in Canada (Glennie, 1997) or by members of the public in the US (Lenert et al., 2004). All three studies used the SG technique. Revicki and colleagues (1996) developed health states based on vignettes, valued by people with schizophrenia and their carers using RS or PC, or by psychiatrists using SG. Finally, Cummins and colleagues (1998) linked health states associated with schizophrenia with health states generated using the IHRQoL. Although the last study used a generic measure to describe health states associated with schizophrenia, the methodology adopted in developing and valuing health states was not clear.

A comparison of data from the three studies that analysed PANSS scores to generate utility scores illustrated that Glennie (1997) reported the most conservative difference in utility scores between health states (difference between moderate and mild states 0.04–0.07; no severe state valued); Chouinard and Albright (1997) reported the greatest differences in utility between health states (difference between moderate and mild states 0.25; between severe and mild states 0.32); and Lenert and colleagues (2004) reported moderate changes in utility between health states (difference between moderate and mild states 0.13–0.14; between severe and mild states 0.22–0.35; and between very severe and mild states 0.46). It was therefore decided to use utility data from Lenert and colleagues (2004) in the base-case analysis and data from the other two studies that utilised PANSS scores (Chouinard & Albright, 1997; Glennie, 1997) in sensitivity analysis. The data by Lenert and colleagues (2004) were selected for the base-case analysis for a number of reasons: they were comprehensive, covering a wide range of health states of varying types and severity of symptoms; the described health states were derived from principal component analysis of condition-specific PANSS scores; the methodology was described in detail; the valuations were made by members of the general population using SG (although the population was from the US and not the UK); detailed utility data for a number of adverse events associated with antipsychotic medication were also reported; the study provided comprehensive data for linking PANSS scores to specific health states and subsequently to utility scores so that, apart from modelling

exercises, these data may be used in cost-utility analyses conducted alongside clinical trials measuring PANSS scores, thus increasing comparability across economic evaluations of antipsychotic treatments for people with schizophrenia. There is at least one example where these data have been used in a cost-utility analysis undertaken alongside effectiveness trials (Rosenheck et al., 2006). Development of health states from condition-specific instruments, such as PANSS, may be appropriate for people with schizophrenia because these are likely to capture more aspects of the HRQoL relating to emotional and mental status; they may also be more sensitive for a given dimension (Brazier, 2007a). Generic measures, such as EQ-5D, could miss some dimensions of HRQoL associated with mental symptoms. EQ-5D has been demonstrated to associate weakly with the positive subscale of PANSS. For this reason, it has been suggested that EQ-5D be used in combination with disease-specific instruments in people with schizophrenia (König et al., 2007).

The data reported in Revicki and colleagues (1996) were not considered further because they were based on vignettes, were not valued by members of the public and, in two of the participating groups, valuations were not made using choice-based methods. Data from Cummins and colleagues (1998) were also excluded from further consideration because the methods used for their derivation were not clearly reported.

#### *Linking utility scores to health states of remission and relapse*

To link the model states of remission and relapse with the utility scores reported for PANSS-generated health states in Lenert and colleagues (2004), the GDG estimated that the HRQoL of people in remission (model state) corresponded by 40% to HRQoL in the (PANSS-generated) mild state and by 60% to HRQoL in the moderate state (30% in moderate state type I and 30% in moderate state type II); the HRQoL of people in relapse corresponded by 60% to HRQoL in the severe state type IV and by 40% to HRQoL in the very severe state.

The GDG estimated that the decrement in HRQoL of people in schizophrenia while in acute episode (relapse) lasted for 6 months.

#### *Utility scores for acute extrapyramidal symptoms and weight gain*

The utility scores for acute EPS and weight gain were also taken from Lenert and colleagues (2004). The reduction in HRQoL caused by acute EPS corresponded to that reported for pseudo-parkinsonism and was estimated to last for 3 months, after which significant improvement in acute EPS symptoms was estimated to occur (either spontaneously after dose adjustment or following treatment). The reduction in HRQoL caused by weight gain was permanent because an increase in weight following use of antipsychotic medication was estimated to remain over a lifetime.

#### *Utility scores for diabetes complications*

Disutility owing to complications from diabetes was taken from the UKPDS (Clarke et al., 2002). Utility scores in this study were generated using patient-reported EQ-

5D scores; these were subsequently valued using EQ-5D UK tariff values. Disutility of diabetes without complications was not considered in the economic model as it was estimated to be negligible when compared with the impairment in HRQoL caused by schizophrenia.

### **11.2.9 Cost data**

Costs associated with pharmacological treatment of people with schizophrenia and related events were calculated by combining resource-use estimates with respective national unit costs. Costs of the relapse and remission states consisted of relevant drug acquisition costs, outpatient, primary and community care costs, costs of treating acute episodes (relapse state only) and residential care costs. People under no treatment (following treatment discontinuation for reasons other than relapse or presence of intolerable side effects) were assumed to incur no costs until they experienced a relapse. Costs associated with baseline measurements and laboratory tests for monitoring purposes were omitted from the analysis, because they were estimated to be the same for all antipsychotic medications evaluated. All costs were uplifted to 2007 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index (Curtis, 2007). Costs were discounted at an annual rate of 3.5% annually, as recommended by NICE (NICE, 2008a).

#### ***Drug acquisition costs***

Drug acquisition costs were taken from BNF 56 (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2008), with the exception of the cost of risperidone which was taken from the Electronic Drug Tariff (NHS Business Services Authority & Prescription Pricing Division, 2008) because risperidone recently became available in generic form but BNF 56 has not captured this information. The daily dosage of antipsychotic drugs was based on the national average daily quantity (ADQ) values reported by the NHS (NHS The Information Centre, 2008a). In cases where no ADQ values were available, the average daily quantity was estimated based on BNF guidance. Some of the reported doses were slightly adjusted to match tablet/injection doses and usual injection intervals. The ADQs and the drug acquisition cost, as well as the monthly ingredient cost for each drug included in the analysis, are reported in Table 121. Annual drug acquisition costs for people experiencing relapse were different because use of antipsychotic medication for relapse prevention was assumed to be interrupted during the acute episode and replaced with another antipsychotic (olanzapine) over this period of relapse.

#### ***Outpatient, primary and community care costs***

Estimates on resource use associated with outpatient, primary and community care were based on data reported in a UK study (Almond et al., 2004). The study collected information on healthcare resource use from 145 people with schizophrenia randomly selected from psychiatric caseloads drawn from urban and suburban areas of Leicester. Of the sample, 77 had experienced a recent relapse, defined as re-emergence or aggravation of psychotic symptoms for at least 7 days during the 6 months prior to the study ('relapse group'); the remaining 68 had not experienced such a relapse in the 6 months before the initiation of the study ('non-relapse

group'). Healthcare resource use for each group over 6 months was collected prospectively from case notes and interviews with the study participants. The study also reported

**Table 121: ADQs, drug acquisition costs and estimated monthly ingredient costs of antipsychotic medications included in the economic model**

Drug	ADQ Unit	Unit cost (BNF 56, September 2008)	Monthly cost
Amisulpride	400 mg	Generic 400 mg, 60-tab = £114.45	£57.23
Haloperidol	8 mg	Generic 1.5 mg, 28-tab = £2.84; 5 mg, 28 = £7.71; 10 mg, 28 = £9.06	£14.35
Olanzapine	10 mg	Zyprexa 10 mg, 28-tab = £79.45; 15 mg, 28-tab = £119.18	£85.13
Aripiprazole	15 mg <sup>a</sup>	Abilify 15 mg, 28-tab = £101.63	£108.89
Paliperidone	9 mg <sup>a</sup>	Invega 9 mg, 28-tab = £145.92	£156.34
Risperidone	5 mg	Generic 1 mg, 60-tab = £28.38; 4 mg, 60-tab = £106.65 <sup>b</sup>	£67.52
Zotepine	200 mg	Zoleptil 100 mg, 90-tab = £94.55	£63.03
Flupentixol decanoate	3.6 mg	Depixol Conc. 100 mg/ mL, 1-mL amp = £6.25 (administered every 4 weeks)	£6.70
<i>Note.</i> <sup>a</sup> ADQ data available—daily dosage estimated based on BNF guidance. <sup>b</sup> Based on the Electronic Drug Tariff as of 1 December 2008 (NHS, Business Services Authority, 2008).			

inpatient care resource use for the two groups, but these data were not utilised in the economic model. It is acknowledged that the data reported in this study are not very recent (the study was conducted in the 1990s), but no more up-to-date data that were appropriate to inform the economic analysis were identified in the literature.

It was assumed that, over 1 year, people in the remission state in the model (including people who discontinued treatment because of side effects or any other reason for the cycle within which discontinuation occurred) consumed twice as much health resources as those reported for the 'non-relapse' group in Almond and colleagues (2004) over 6 months. Within a year, people in the relapse model state were assumed to consume the resources reported for the relapse group over 6 months and the resources reported for the non-relapse group over the remaining 6 months. Therefore, the annual resource use of outpatient, primary and community care for the relapse state consisted of the 6-month resource use reported for the relapse group (Almond et al., 2004) plus the 6-month resource use reported for the non-relapse group. Reported resource use in Almond and colleagues (2004) was combined with appropriate national unit costs (Curtis, 2007; Department of Health, 2008) to estimate total annual outpatient, primary and community care costs for people in the model states of remission and relapse. The reported resource use for the relapse and the non-relapse groups in Almond and colleagues (2004) as well as the respective UK unit costs are presented in Table 122. Based on the above

described methods and assumptions, the annual outpatient, primary and community care costs for the states of remission and relapse were estimated at £5,401 and £4,323, respectively (2007 prices).

### *Costs associated with management of acute episodes*

People experiencing an acute episode (relapse) were assumed to be treated either as inpatients or by CRHTTs. Glover and colleagues (2006) examined the reduction in hospital admission rates in England, following implementation of CRHTT. They reported that the introduction of CRHTT was followed by a 22.7% reduction in hospital admission levels. Based on this data, the economic analysis assumed that 77.3% of people with schizophrenia experiencing a relapse would be admitted to hospital, and the remaining 22.7% would be seen by CRHTTs. However, all people under long-term hospital care while in remission (see costs of residential care in next subsection) were assumed to be treated as inpatients when they experienced an acute episode.

The average cost of hospitalisation for people in acute episode was estimated by multiplying the average duration of hospitalisation for people with schizophrenia, schizotypal and delusional disorders (F20-F29, according to ICD-10) in England in 2006/07 (NHS The Information Centre, 2008b) by the national average unit cost per bed-day in a mental health acute care inpatient unit for adults in 2006/07 (Department of Health, 2008).

Regarding the management of people with schizophrenia experiencing an acute episode by CRHTTs, the GDG estimated that treatment lasted 8 weeks. This period was multiplied by the unit cost of each case treated by CRHTTs per care staff per week (Curtis, 2007) to provide a total cost associated with the management of acute episodes by CRHTTs.

All people experiencing an acute episode were assumed to interrupt the antipsychotic medication they were taking during remission and receive olanzapine at a dose of 15mg/day (Royal College of Psychiatrists, 2008) for the duration of the acute episode, which was assumed to be equal to the duration of hospitalisation for people with schizophrenia (as reported by the NHS, The Information Centre, 2008a (NHS The Information Centre, 2008b)). Olanzapine was chosen as a representative SGA for the treatment of acute episodes; its selection was made only for modelling purposes and does not necessarily suggest use of olanzapine instead of other available antipsychotic drugs for the treatment of acute episodes in people with schizophrenia.

Table 123 presents the resource use and respective unit costs associated with management of acute episodes in people with schizophrenia, and the percentage of people receiving each intervention.

### *Residential and long-term hospital care costs*

The percentage of people with schizophrenia living in private households, sheltered housing, group homes or under long-term hospital care were estimated using respective UK data (Mangalore & Knapp, 2007). The unit costs of residential care (sheltered housing and group homes) and long-term hospital care were taken from national UK sources (Curtis, 2007; Department of Health, 2008). Residential and long-term hospital care costs in the model were assumed to be independent of the choice of antipsychotic drug and were incurred over all of the time that people were not hospitalised for an acute episode. For this reason, the costs somewhat differed between remission and relapse health states. Residential care costs were assumed to be zero during management of acute episodes for those people treated as inpatients. Long-term hospital care costs were assumed to be zero during management of acute episodes because all people under this type of care were assumed to be treated as inpatients once they experienced an acute episode.

The type of accommodation and the costs associated with residential and long-term hospital care in people with schizophrenia in the economic model are reported in Table 124.



**Table 122: Resource use over 6 months and unit costs associated with outpatient, primary and community care for people with schizophrenia**

Service	Mean usage per person (Almond et al., 2004)		Unit cost (2007 prices)	Sources of unit costs; comments
	Non-relapse	Relapse		
Outpatient psychiatric visits	1.4	2.1	£140	Department of Health, 2008a; cost per face-to-face contact in outpatient mental health services
Outpatient other visits	0.1	0.3	£93	Department of Health, 2008a; cost per attendance in day care
Day hospital visits	2.3	2.1	£93	Department of Health, 2008a; cost per attendance in day care
Community mental health centre visits	2.4	1.4	£124	Department of Health, 2008a; cost per contact with CMHTs
Day care centre visits	5.9	0.9	£93	Department of Health, 2008a; cost per attendance in day care
Group therapy	0.4	0.1	£93	Department of Health, 2008a; cost per attendance in day care
Sheltered workshop	1.1	0	£49	Curtis, 2007. Sheltered work schemes: £8.1 gross cost per hour; 6 hours per contact assumed
Specialist education	2.9	0	£93	Department of Health, 2008a; cost per attendance in day care

Other (not specified)	0.6	0	£50	Assumption
Psychiatrist visits	2.5	2.3	£240	Department of Health, 2008a; cost per domiciliary visit by psychiatrist
Psychologist visits	0	0	£196	Department of Health, 2008a; cost per domiciliary visit by psychologist
GP visits	1.8	1.6	£58	Curtis, 2007; cost per home visit £55 including travel, qualification and direct care staff costs – 2006 prices
District nurse visits	0.1	0	£24	Curtis, 2007; cost per home visit for community nurse including qualification costs and travelling
CPN visits	12.6	5.2	£26	Curtis, 2007; cost per hour of client contact for community nurse specialist £75; assuming 20 minutes' duration of visit; including qualification costs and travelling
Social worker visits	0.1	0.4	£41	Curtis, 2007; cost per hour of face-to-face contact £124; assuming 20 minutes' duration of visit – qualification costs not available
Occupational therapist visits	0	0.8	£39	Curtis, 2007; cost of community occupational therapist per home visit including qualification and travelling costs
Home help/care worker	0.4	0.6	£19	Curtis, 2007; cost of care worker per hour of face-to-face week day programme – qualification costs not available

**Table 123: Hospital, and crisis resolution and home treatment team costs per person in acute episode (relapse)**

Treatment	Duration	Unit cost (2007 prices)	Total cost	% of people treated
Acute hospital	111 days (NHS, 2008a)	£259/day (Department of Health, 2008a)	£28,645	77.3 (Glover et al., 2006)
CRHTT	8 weeks (GDG estimate)	£264 per case per care staff per week (Curtis, 2007)	£2,112	22.7 (Glover et al., 2006)
Olanzapine 15mg/day	111 days (NHS, 2008a)	£4.26/day (BNF56)	£471	100 (assumption)

**Table 124: Type of accommodation and costs of residential and long-term hospital care in people with schizophrenia (remission state)**

Type of accommodation	% of people <sup>a</sup>	Unit cost (2007 price)	Source of unit cost	Weighted annual cost
Private household	77	0	N/A	0
Residential care (sheltered)	18	£478/week	Curtis, 2007	£4,486
Residential care (group home)	2	£107/week	Curtis, 2007	£112
Long-term hospital care	3	£249/day	Department of Health, 2008a	£2,727
Total weighted residential cost per person in remission				£7,325
<i>Note.</i> <sup>a</sup> Based on data reported in Mangalore & Knapp, 2007				

### *Costs incurred by switching between antipsychotic medications*

People moving to next-line treatment (because of intolerable side effects or relapse) were assumed to incur additional costs, associated with three visits to a consultant psychiatrist lasting 20 minutes each, at a total cost of £435 (the unit cost of a consultant psychiatrist was £435 per hour of patient contact, including qualification costs (Curtis, 2007)).

### *Costs of managing side effects and related complications*

Although acute EPS may be managed solely by dose adjustment or may improve spontaneously, people experiencing acute EPS were assumed to pay a visit to a

consultant psychiatrist, lasting 20 minutes, and receive procyclidine at a daily dose of 15 mg for 3 months.

All people experiencing weight gain were assumed to pay two visits to their GP for general advice. In addition, 20% of them received special advice from a dietician. These methods of management were consistent with levels I and II of interventions for people with weight gain recommended by the NICE clinical guideline on obesity (NICE, 2006b).

Resource use estimates and respective unit costs associated with management of acute EPS and weight gain in people with schizophrenia are reported in Table 125. The annual cost of diabetes without complications, consisting of anti-diabetic and antihypertensive drug treatment and inclusive of implementation costs was estimated based on published data from UKPDS (Clarke et al., 2005). Costs associated with management of complications from diabetes were taken from the same study.

Costs were uplifted to 2007 prices using the Hospital and Community Health Services Pay and Prices inflation index (Curtis, 2007). Costs and QALYs associated with each antipsychotic treatment were discounted at an annual rate of 3.5% as recommended by NICE (NICE, 2008a).

**Table 125: Resource use and respective unit costs of managing acute EPS and weight gain**

State-event	Resource use (GDG estimates)	Unit costs (2007prices)
<i>Acute EPS</i>		
Procyclidine	5mg/ day for 3 months	5mg, 28-tab = £3.35 (BNF56)
Psychiatrist	1 visit of 20 minutes	Cost per hour of patient contact: £435 (qualification costs included – Curtis, 2007)
<i>Weight gain</i>		
100% <sup>a</sup> general advice	2 GP visits	Cost per clinic visit:£52 (qualification and direct care staff costs included – Curtis, 2007)
20% <sup>a</sup> diet and exercise	3 visits to dietician over 6 months (duration of first visit 1 hour; Of next 2 visits 30 minutes)	Cost per hour of client contact: £32 (qualification costs included – Curtis, 2007)
<i>Note.</i> <sup>a</sup> % based on GDG estimates		

Table 126 reports the mean (deterministic) values of all input parameters utilised in the economic model and provides information on the distributions assigned to specific parameters in probabilistic sensitivity analysis.

Psychosis and schizophrenia in adults

**Table 126: Input parameters utilised in the economic model**

Input parameter	Deterministic value	Probabilistic distribution	Source of data-comments
<b>Annual probability of relapse</b>		<b>Distribution based on 10,000 mixed treatment comparison iterations</b> 95% credible intervals	
Olanzapine	0.1996	0.0146 to 0.7222	Mixed treatment comparison competing risks model-analysis of data included in the guideline systematic review; results for 52 weeks assumed to reflect annual probability; results for placebo assumed to apply to no treatment in all years except the first year following the move to no treatment
Amisulpride	0.2988	0.0197 to 0.9042	
Zotepine	0.1067	0.0023 to 0.5601	
Aripiprazole	0.2742	0.0130 to 0.8531	
Paliperidone	0.1625	0.0025 to 0.7008	
Risperidone	0.2761	0.0182 to 0.8785	
Haloperidol	0.3317	0.0262 to 0.9028	
No treatment-following years	0.4361	0.0913 to 0.8613	
Flupentixol decanoate	0.2977	<b>Beta distribution</b> ( $\alpha=39, \beta=92$ according to data reported in David and colleagues, 1999)	David et al., 1999. Meta-analysis of trials comparing flupentixol decanoate versus other depot antipsychotics; data on relapse
No treatment-first year following discontinuation of treatment	0.6062	<b>Distribution based on 10,000 mixed treatment comparison iterations</b> – results for placebo, adding the effect of abrupt discontinuation on the risk for relapse (Viguera et al., 1997)	Mixed treatment comparison competing risks model—a higher probability of relapse over the first 7 months (50%) was taken into account (Viguera et al., 1997)

*Continued*

Table 126 (*continued*)

Input parameter	Deterministic value	Probabilistic distribution	Source of data–comments
<b>Probability of discontinuation because of intolerable side effects–first year of initiation of a particular antipsychotic</b>		<b>Distribution based on 10,000 mixed treatment comparison iterations</b>	
		95% credible intervals	
Olanzapine	0.0783	0.0021 to 0.4784	Mixed treatment comparison competing risks model–analysis of data included in the guideline systematic review; results for 52 weeks assumed to apply to the first year within initiation of a particular antipsychotic only
Amisulpride	0.0554	0.0006 to 0.3721	
Zotepine	0.3821	0.0120 to 0.9750	
Aripiprazole	0.1582	0.0026 to 0.7847	
Paliperidone	0.3287	0.0039 to 0.9770	
Risperidone	0.0994	0.0020 to 0.6471	
Haloperidol	0.0922	0.0017 to 0.5386	
<b>Annual probability of discontinuation because of other reasons</b>		<b>Distribution based on 10,000 mixed treatment comparison iterations</b>	
		95% credible intervals	
Olanzapine	0.2730	0.0207 to 0.8596	Mixed treatment comparison competing risks model–analysis of data included in the guideline systematic review; results for 52 weeks assumed to reflect annual probability
Amisulpride	0.2435	0.0139 to 0.8324	
Zotepine	0.2253	0.0074 to 0.8189	
Aripiprazole	0.3520	0.0202 to 0.9218	
Paliperidone	0.3848	0.0090 to 0.9479	
Risperidone	0.1761	0.0086 to 0.7141	
Haloperidol	0.2516	0.0151 to 0.8290	

*Continued*

Table 126 (continued)

Input parameter	Deterministic value	Probabilistic distribution	Source of data-comments
<b>Weight gain – first year of initiation of a particular antipsychotic ORs versus haloperidol</b>		<b>Distribution based on 10,000 mixed treatment comparison iterations</b> 95%credible intervals	
Olanzapine	2.8631	1.7050 to 4.5090	Mixed treatment comparison simple random-effects model–analysis of data from guide line meta-analysis of side effects;only data reported as ‘increase in weight gain of $\geq 7\%$ from baseline’ were considered.
Amisulpride	1.8604	0.7345 to 4.0360	
Aripiprazole	0.7373	0.3498 to 1.3990	
Paliperidone	1.0779	0.4405 to 2.1640	
Risperidone	1.0895	0.5214 to 2.0850	
Zotepine	1.0895	As for risperidone	
<b>Probability of weight gain</b>			
Haloperidol	0.2000	<b>Beta distribution</b> ( $\alpha = 31, \beta = 124$ according to data reported in studies with time horizon up to 12 weeks included in the guideline meta-analysis of side effects)	OR of zotepine versus haloperidol assumed to be equal of that of risperidone versus haloperidol
Flupentixol decanoate	0.2000	As for haloperidol	Extrapolation of data reported in studies with time horizon up to 12 weeks included in the guideline meta-analysis of side effects;only data reported as ‘increase in weight gain of $\geq 7\%$ from baseline’ were considered.  Assumed to equal that for haloperidol

*Continued*

Table 126 (continued)

Input parameter	Deterministic value	Probabilistic distribution	Source of data-comments
<b>Acute EPS</b>			
<b>First year of initiation of a particular antipsychotic</b>		<b>Distribution based on 10,000 mixed treatment comparison iterations</b>	
<u>ORs versus haloperidol</u>		95% credible intervals	Mixed treatment comparison full random effects model – analysis of data from guide line meta-analysis of side effects; only data on ‘need for anticholinergic medication’ were considered
Olanzapine	0.2631	0.1832 to 0.3641	
Amisulpride	0.3993	0.2587 to 0.5836	
Zotepine	0.1476	0.0517 to 0.3132	
Aripiprazole	0.2517	0.1505 to 0.4002	
Paliperidone	0.2983	0.1179 to 0.6214	
Risperidone	0.4743	0.3680 to 0.5994	
<u>Probability of acute EPS</u>			
Haloperidol	0.5367	<b>Beta distribution</b> ( $\alpha = 928$ , $\beta = 801$ according to data reported in RCTs with time horizon up to 8 weeks included in the guideline meta- analysis of side effects)	Extrapolation of data reported in studies with time horizon up to 8 weeks included in the guideline meta-analysis of side effects; only data on ‘need for anticholinergic medication’ were considered
Flupentixol decanoate	0.4891	<b>Beta distribution</b> ( $\alpha = 45$ , $\beta = 47$ according to data reported in David and colleagues, 1999)	David et al., 1999. Meta-analysis of trials comparing flupentixol decanoate versus other depot antipsychotics; data on need for anti cholinergic medication
<b>Following years</b>			
<u>Probability of acute EPS</u>			
All antipsychotics	10% of first year estimate	N/ A (no distribution assigned)	GDG expert opinion

Continued



Table 126 (continued)

Input parameter	Deterministic value	Probabilistic distribution	Source of data—comments
Probability of diabetes—first year of initiation of a particular antipsychotic		Distribution based on 10,000 mixed treatment comparison iterations of data on weight gain	Probability of haloperidol estimated from data reported in van Winkel et al., 2006 and 2008 and considering the increased RR for diabetes of SGAs versus FGAs; the remaining probabilities were calculated by multiplying respective RRs for weight gain of each SGA versus haloperidol by the probability of diabetes for haloperidol
Olanzapine	0.0417	Relative risk of each SGA versus haloperidol for diabetes was assumed to equal their in-between relative risk for weight gain; the latter was deter-mined by the posterior distribution of ORs of weight gain for each SGA and haloperidol	
Amisulpride	0.0317		
Zotepine	0.0214		
Aripiprazole	0.0156		
Paliperidone	0.0212		
Risperidone	0.0214		
Haloperidol	0.0200	Beta distribution ( $\alpha= 2$ , $\beta= 98$ based on assumption)	
Flupentixol decanoate	0.0200	As for haloperidol	

*Continued*

Table 126 (continued)

Input parameter	Deterministic value	Probabilistic distribution	Source of data—comments
Probability of glucose intolerance— first year of initiation of a particular antipsychotic		Distribution based on 10,000 mixed treatment comparison iterations of data on weight gain	Probability of haloperidol estimated from data identified in the guideline systematic review; the remaining probabilities were calculated by multiplying respective RRs for weight gain of each SGA versus haloperidol by the probability of glucose intolerance for haloperidol
Olanzapine	0.3129	Relative risk of each SGA versus haloperidol for glucose intolerance was assumed to equal their in-between relative risk for weight gain; the latter was determined by the posterior distribution of ORs of weight gain For each SGA and haloperidol, respectively	
Amisulpride	0.2381		
Zotepine	0.1606		
Aripiprazole	0.1167		
Paliperidone	0.1592		
Risperidone	0.1606		
Haloperidol	0.1500	Beta distribution ( $\alpha$ = 15, $\beta$ = 85 based on assumption)	
Flupentixol decanoate	0.1500	As for haloperidol	
Annual transition probability of impaired glucose tolerance to diabetes	0.0196	Beta distribution Standard error 0.0025 (Gillies et al., 2008)	Gillies et al., 2008

*Continued*

**Table 126 (continued)**

Input parameter	Deterministic value	Probabilistic distribution	Source of data–comments
<b>Annual probability of diabetes complications</b> Fatal myocardial infarction Non-fatal myocardial infarction Non-fatal stroke Amputation Macrovascular events – heart failure Microvascular events – ischaemic heart disease	0.0042 0.0130 0.0039 0.0023 0.0040 0.0157	<b>Beta distribution</b> Determined from the numbers of people experiencing each of the complications at each level of Hgb A1C concentration in the UKPDS (Stratton et al., 2000)	Based on UKPDS data (Stratton et al., 2000), assuming that 20% of people with schizophrenia and diabetes in the model had Hgb A1C concentration 7 to <8%, 30% of people had 8 to <9%, 30% of people had 9 to <10% and 20% of people had ≥10%
<b>Standardised mortality ratio – all cause mortality</b>	2.6	N/A (no distribution assigned)	McGrath et al., 2008
<b>Mortality rates per 1000 people in general population by age</b>	25–34 years: 0.69 35–44 years: 1.29 45–54 years: 3.10 55–64 years: 7.53 65–74 years: 20.48 75–84 years: 59.36 ≥85 years: 164.02	N/A (no distribution assigned)	Office for National Statistics, 2008; mortality rates for England and Wales, 2005, estimated based on a male to female ratio 1.4 to 1, characterising people with schizophrenia (McGrath, 2006)
<b>Utility scores</b> Model health states Remission Relapse Death	0.799 0.670 0.000	<b>Beta distribution</b> Determined using the reported numbers of people valuing each PANSS-generated health state as in Lenert and colleagues (2004)	Lenert et al., 2004; linking between model states and states described in the study based on GDG estimates – see the main text for details. Duration of decrement in HRQoL caused by relapse: 6 months

**Table 126 (continued)**

Input parameter	Deterministic value	Probabilistic distribution	Source of data–comments
<u>Side effects</u>			
Acute EPS	–0.888%	Estimated from the number of people valuing the presence of each side effect, as reported in Lenert and colleagues (2004)	Lenert et al., 2004; acute EPS causes HRQoL reduction corresponding to that of pseudo-parkinsonism, lasting 3 months; weight gain causes permanent reduction in HRQoL
Weight gain	–0.959%		
<u>Diabetes complications</u>		95% credible intervals	
Myocardial infarction	–0.055	–0.067 to –0.042	Clarke et al., 2002; utility scores based on patient-reported EQ-5D scores, valued using EQ-5DUK tariff values
Stroke	–0.164	–0.222 to –0.105	
Amputation	–0.280	–0.389 to –0.170	
Macrovascular events – heart failure	–0.108	–0.169 to –0.048	
Microvascular events – ischaemic heart disease	–0.090	–0.126 to –0.054	
<b>Annual drug acquisition costs (remission state)</b>		N/ A (no distribution assigned)	BNF56 (British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2008), except risperidone cost, which was taken from the Electronic Drug Tariff (NHS, Business Services Authority, 2008). Average daily dosage taken from respective NHS data (NHS, The Information Centre, 2008c) and BNF guidance when no other data were available
Olanzapine	£1,036		
Amisulpride	£696		
Zotepine	£767		
Aripiprazole	£1,325		
Paliperidone	£1,902		
Risperidone	£821		
Haloperidol	£175		
Flupentixol decanoate	£81		

*Continued*

**Table 126 (continued)**

Input parameter	Deterministic value	Probabilistic distribution	Source of data-comments
<b>Annual costs of remission</b> Outpatient, primary and community care Residential and long-term hospital care Total (cost of antipsychotic medication for relapse prevention excluded)	£5,401 £7,325 £12,726	<b>Gamma distribution</b> Standard error of all costs: 70% of mean value (assumption)	Details on outpatient, primary and community care cost reported in Table 122; details on costs of residential and long-term hospital care reported in Table 124; 2007 prices
<b>Annual costs of relapse</b> Outpatient, primary and community care Residential and long-term hospital care Acute treatment (including olanzapine) Total (cost of antipsychotic medication for relapse prevention excluded)	£4,323 £5,421 £23,274 £33,018	<b>Gamma distribution</b> Standard error of all costs: 70% of mean value (assumption)	Details on outpatient, primary and community care cost reported in Table 122; details on costs of treating acute episode reported in Table 123; details on costs of residential and long-term hospital care reported in Table 124; 2007 prices
<b>Cost of switching between antipsychotics</b>	£435	Standard error: 70% of mean value (assumption)	3 visits to consultant psychiatrist, lasting 20 minutes each; unit cost from Curtis, 2007; 2007 prices

*Continued*

**Table 126 (continued)**

Input parameter	Deterministic value	Probabilistic distribution	Source of data-comments
<b>Cost of treating side effects</b>		<b>Gamma distribution</b>	Details on resource use and unit costs associated with acute EPS and weight gain reported in Table 125; 2007 prices
Acute EPS	£177	Standard error of all costs: 70% of the respective mean value (assumption)	
Weight gain	£117		
Diabetes (without complications) – annual	£199		UKPDS (Clarke et al., 2005); 2007 prices
Fatal myocardial infarction	£1,531		
Non-fatal myocardial infarction first year/following years	£5,407/£616		
Non-fatal stroke first year/following years	£3,144/£331		
Amputation first year/following years	£11,238/£401		
Macrovascular events-heart failure first year/following years	£418/£343		
Microvascular events-ischaemic heart disease first year/following years	£363/£271		
<b>Discount rate</b> (for both costs and outcomes)	0.035	N/A (no distribution assigned)	Recommended by NICE (NICE, 2008a)

### 11.2.10 Data analysis and presentation of the results

Two methods were employed to analyse the input parameter data and present the results of the economic analysis.

First, a 'deterministic' analysis was undertaken, where data are analysed as point estimates; results are presented as mean total costs and QALYs associated with each treatment option are assessed. Relative cost effectiveness between alternative treatment options is estimated using incremental analysis: all options are initially ranked from most to least effective; any options that are more expensive than options that are ranked higher are dominated (because they are also less effective) and excluded from further analysis. Subsequently, ICERs are calculated for all pairs of consecutive options. ICERs express the additional cost per additional unit of benefit associated with one treatment option relative to its comparator. Estimation of such a ratio allows consideration of whether the additional benefit is worth the additional cost when choosing one treatment option over another.

If the ICER for a given option is higher than the ICER calculated for the previous intervention in ranking, then this strategy is also excluded from further analysis, on the basis of extended dominance. After excluding cases of extended dominance, ICERs are recalculated. The treatment option with the highest ICER below the cost effectiveness threshold is the most cost-effective option.

A number of sensitivity analyses explored the impact of the uncertainty characterising model input parameters on the results of the deterministic analysis. The following scenarios were tested:

- Unit cost per bed-day in an adult mental health acute care inpatient unit of £235, according to the reported lower quartile of the NHS reference unit cost (Department of Health, 2008)
- Duration of hospitalisation for people experiencing an acute episode of 69 days, taken from an effectiveness trial of clozapine versus SGAs conducted in the UK (CUtLASS Band 2, (Davies et al., 2008)
- Combination of the two scenarios above.

The following three scenarios attempted to investigate the impact of hospitalisation costs on the results of the analysis:

- Use of alternative utility scores for schizophrenia health states, as reported in Chouinard and Albright (1997) and Glennie (1997)
- Probability of side effects assumed to be common for all antipsychotic drugs: probabilities of acute EPS, weight gain and, subsequently, glucose intolerance and diabetes were assumed to be the same for all drugs. This scenario aimed at exploring the importance of side effects in determining total QALYs, costs and relative cost effectiveness between antipsychotic medications over time
- Probability of relapse assumed to be common for all antipsychotic drugs. The objective of this sensitivity analysis was to explore whether

the effectiveness in preventing relapse was the driver of the cost effectiveness results, as expected.

In addition to deterministic analysis, a 'probabilistic' analysis was also conducted. In this case, most of the model input-parameters were assigned probability distributions (rather than being expressed as point estimates), to reflect the uncertainty characterising the available clinical and cost data. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. This exercise provided more accurate estimates of mean costs and benefits for each antipsychotic (averaging results from the 10,000 iterations) by capturing the non-linearity characterising the economic model structure (Briggs et al., 2006a).

The probabilistic distributions of data on relapse, discontinuation and side effects that were analysed using mixed treatment comparison techniques (that is, annual probability of relapse, probability of treatment discontinuation because of intolerable side effects and annual probability of treatment discontinuation because of any other reason, ORs of weight gain versus haloperidol and ORs of acute EPS versus haloperidol) were defined directly from random values recorded for each of the 10,000 respective mixed treatment comparison iterations performed in Winbugs. To maintain the correlation between the posterior estimates for (i) probability of relapse, (ii) probability of treatment discontinuation because of intolerable side effects and (iii) probability of treatment discontinuation because of any other reason, data from each of the common mixed treatment comparison simulations for these parameters were exported jointly and fitted into the Excel file of the economic model where the probabilistic analysis was carried out.

The probability of relapse and acute EPS for the depot antipsychotic, and of acute EPS and weight gain for haloperidol, were given a beta distribution. Beta distributions were also assigned to utility scores and rates of complications from diabetes. The estimation of distribution ranges in all these cases was based on available data in the published sources of evidence or from the guideline meta-analysis.

The probabilities of developing diabetes and glucose impairment following use of haloperidol were also given a beta distribution; the ranges of values attached to these parameters were based on assumptions.

All costs (except drug acquisition costs) were assigned a gamma distribution; to take account of their likely high skewness and variability, the standard errors associated with costs were assumed to equal 70% of the values used in deterministic analysis. Table 126 shows which input parameters were assigned distributions in the probabilistic analysis, and gives more details on the types of distributions and the methods employed to define their range.



Results of probabilistic analysis are presented in the form of cost-effectiveness acceptability curves (CEACs), which demonstrate the probability of each treatment option being the most cost effective among the strategies assessed at different levels of willingness-to-pay per unit of effectiveness (that is, at different cost-effectiveness thresholds the decision-maker may set). In addition, the cost effectiveness acceptability frontier (CEAF) is provided alongside CEACs, showing which treatment option among those examined offers the highest average net monetary benefit (NMB) at each level of willingness-to-pay (Fenwick et al., 2001). The NMB of a treatment option at different levels of willingness-to-pay is defined by the following formula:

$$\text{NMB} = E \cdot \lambda - C$$

where E and C are the effectiveness (number of QALYs) and costs associated with the treatment option, respectively, and  $\lambda$  is the level of the willingness-to-pay per unit of effectiveness.

## 11.3 RESULTS

### 11.3.1 Results of deterministic analysis

According to deterministic analysis, zotepine was the most cost-effective option among those assessed because it produced the highest number of QALYs and was associated with the lowest costs (dominant option). This result was observed for both time horizons of the analysis; that is, 10 years and lifetime.

Table 127 provides mean costs and QALYs for every antipsychotic drug assessed in the economic analysis, as well as the results of incremental analysis, over a time horizon of 10 years. The seven drugs have been ranked from the most to the least effective in terms of number of QALYs gained. Zotepine is associated with lowest costs and highest benefits (QALYs) and consequently dominates all other treatment options. It can be seen that paliperidone and olanzapine dominate all drugs except zotepine; therefore, if zotepine is not an option for the treatment of people with schizophrenia that is in remission, then the decision (solely in terms of cost effectiveness) would have to be made between paliperidone and olanzapine. The ICER of paliperidone versus olanzapine is £150,159/QALY; this figure is much higher than the cost effectiveness threshold of £20,000–£30,000/QALY set by NICE (NICE, 2008b). Therefore, at 10 years of antipsychotic medication use, according to the results of deterministic analysis, olanzapine is the second most cost-effective option following zotepine, and paliperidone is the third (because it dominates all other options). If paliperidone and olanzapine are excluded from analysis (in addition to zotepine), then four drugs remain for further analysis: two of them, aripiprazole and amisulpride, are dominated by haloperidol. The ICER of risperidone to haloperidol exceeds £1,600,000/QALY, and therefore haloperidol is the most cost-effective option among the four remaining drugs.

**Table 127: Mean costs and QALYs per person for each antipsychotic drug used for relapse prevention in people with schizophrenia that is in remission – time horizon of 10 years. Incremental analysis undertaken in steps, after excluding the most cost-effective option of the previous step, to enable ranking of medications in terms of cost effectiveness**

Antipsychotic drug	QALYs	Cost	Incremental analysis (cost per QALY gained)				
			All options	Excluding zotepine and olanzapine	Excluding paliperidone	Excluding haloperidol	Excluding aripiprazole
Zotepine	6.468	£139,170	<b>Dominant</b>				
Paliperidone	6.427	£142,173	Dominated	£150,159			
Olanzapine	6.420	£141,212	Dominated				
Risperidone	6.417	£149,112	Dominated	Dominated	£1,600,986	£204,529	£48,961
Haloperidol	6.413	£143,406	Dominated	Dominated			
Aripiprazole	6.400	£145,697	Dominated	Dominated	Dominated		
Amisulpride	6.392	£147,920	Dominated	Dominated	Dominated	Dominated	

By repeating this process in steps, and excluding in each new incremental analysis all options found to be cost effective in previous ones, it is possible to rank all medications in terms of cost effectiveness. This incremental analysis 'in steps' resulted in the following ranking of antipsychotics in terms of cost effectiveness: (1) zotepine; (2) olanzapine; (3) paliperidone; (4) haloperidol; (5) aripiprazole; (6) amisulpride; (7) risperidone.

Table 128 provides mean costs and QALYs for each antipsychotic drug assessed in the economic model as well as results of incremental analysis in steps over a lifetime. The seven drugs have again been ranked from the most to the least effective. Zotepine dominates all other options in this analysis, too. If zotepine is excluded from the analysis, then paliperidone dominates all other drugs except haloperidol and olanzapine. The ICER of paliperidone versus haloperidol is £11,458 per QALY; the ICER of haloperidol versus olanzapine is £41,129 per QALY. Consequently, haloperidol is excluded from consideration on the basis of extended dominance. The ICER of paliperidone versus olanzapine is £20,872 per QALY. These figures suggest that, if zotepine is not an option, then olanzapine is the second best option in terms of cost effectiveness (using the lower, £20,000/QALY, threshold set by NICE (2008b)), and paliperidone third (however, it must be noted that the figure of £20,872/QALY is very close to the lower threshold and if the upper NICE cost effectiveness threshold of £30,000/QALY is used, then paliperidone is ranked second best option in terms of cost effectiveness and olanzapine third). If incremental analysis in steps is undertaken, as show Table 128, then the ranking of antipsychotic medications in terms of cost effectiveness is the following: (1) zotepine; (2) olanzapine; (3) paliperidone; (4) haloperidol; (5) aripiprazole; (6) risperidone; (7) amisulpride.

A comparison of rankings in terms of QALYs between Table 127 and Table 128 shows that olanzapine and haloperidol appear in low places in the lifetime horizon (seventh and fifth, respectively), compared with their ranking at 10 years where they are ranked third and fourth, respectively. This finding is explained by the higher risk for weight gain and diabetes characterising olanzapine (olanzapine was the second-line antipsychotic in the cohort initiated on haloperidol); eventually, the (permanent) increase in weight and the incidence of complications from diabetes, which was higher in the cohorts receiving olanzapine as first or second-line treatment, reduced the overall HRQoL and the total number of QALYs gained relative to other treatment options. Nonetheless, the ranking of olanzapine and haloperidol in terms of cost effectiveness was not affected: they were ranked second and fourth cost-effective options, respectively, over 10 years, and this ranking order remained over a lifetime. It must be noted that, with the exception of the last two places, the ranking of antipsychotic medications in terms of cost effectiveness was not affected by the time horizon used.

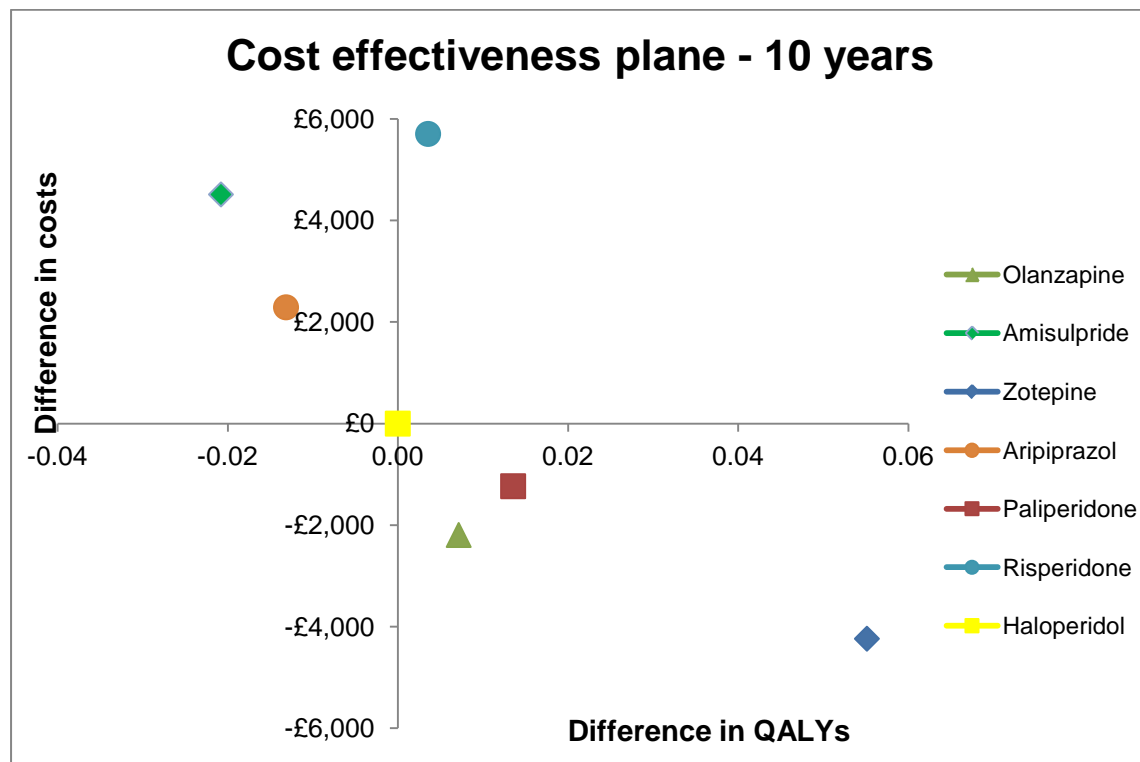
**Table 128: Mean costs and QALYs per person for each antipsychotic drug used for relapse prevention in people with schizophrenia that is in remission – lifetime horizon. Incremental analysis undertaken in steps, after excluding the most cost-effective option of the previous step, to enable ranking of medications by cost effectiveness**

Antipsychotic drug	QALYs	Cost	Incremental analysis (cost per QALY gained)					
			All options	Excluding zotepine	Excluding olanzapine	Excluding paliperidone	Excluding haloperidol	Excluding aripiprazole
Zotepine	16.849	£397,247	<b>Dominant</b>					
Paliperidone	16.804	£402,288	Dominated	£20,872	£11,458			
Risperidone	16.791	£409,083	Dominated	Dominated	Dominated	£191,056	£118,464	£12,809
Aripiprazole	16.767	£406,195	Dominated	Dominated	Dominated	Ext.domin.		
Haloperidol	16.753	£401,702	Dominated	Ext.domin.				
Amisulpride	16.733	£408,332	Dominated	Dominated	Dominated	Dominated	Dominated	
Olanzapine	16.729	£400,725	Dominated					

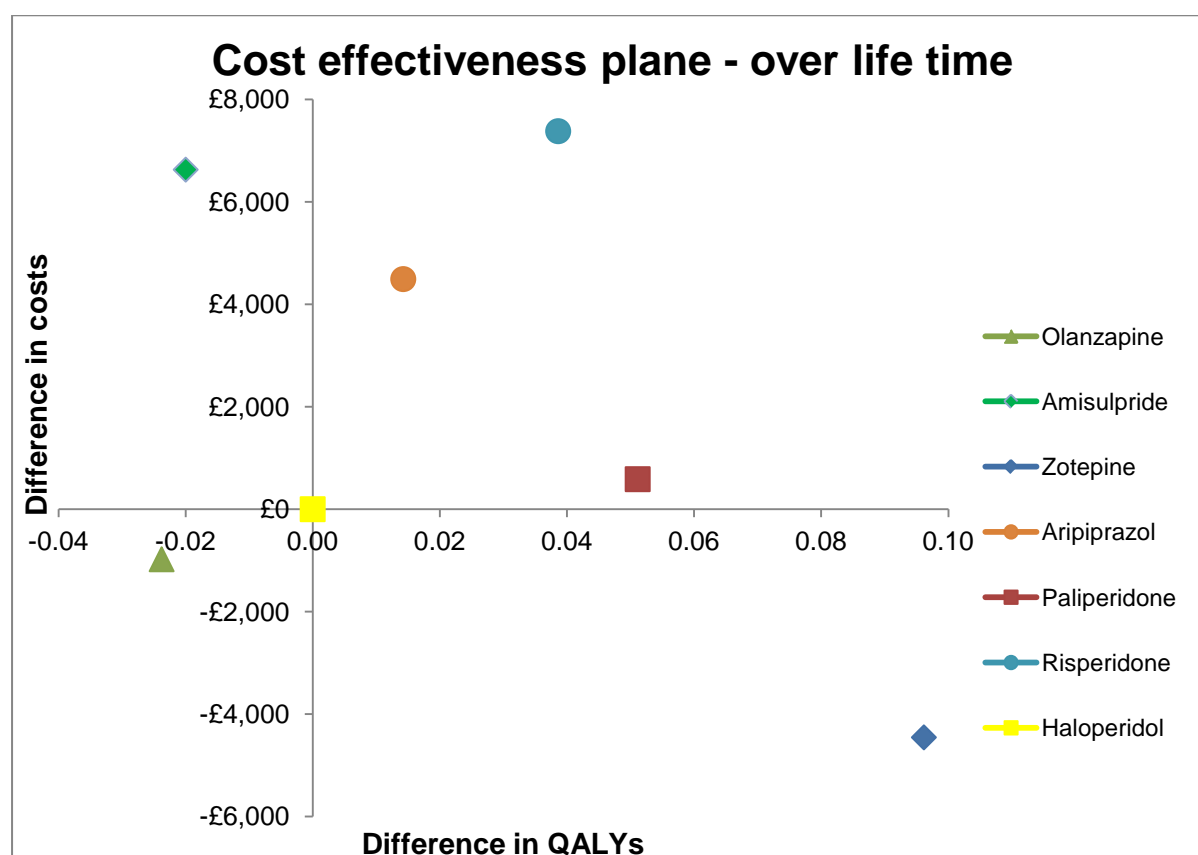
*Note.* Ext.domin. = extendedly dominated.

Figure 6 and Figure 7 present the cost effectiveness planes for the two time horizons of the analysis, showing the incremental costs and benefits (QALYs) of all SGAs versus haloperidol. In both cases, it can be seen that zotepine is in the southeast quadrant and has the highest number of QALYs and the lowest costs relative to all other options assessed.

**Figure 6: Cost-effectiveness plane of all treatment options plotted against haloperidol, at 10 years of antipsychotic medication use**



**Figure 7: Cost-effectiveness plane of all treatment options plotted against haloperidol, over a lifetime of antipsychotic medication use**



### *Results of deterministic sensitivity analysis*

Results were very sensitive to annual probabilities of relapse, as expected. When all antipsychotic medications were assumed to have equal probabilities of relapse, the ranking of medications in terms of effectiveness was significantly affected. In general, this ranking by effectiveness was predicted by the ranking of medications in terms of discontinuation to other reasons, with options with lower probabilities of discontinuation ranking more highly in terms of effectiveness. Regarding cost effectiveness, the ranking of treatment options at 10 years following incremental analysis in steps was: (1) haloperidol; (2) amisulpride; (3) olanzapine; (4) aripiprazole; (5) risperidone; (6) zotepine; (7) paliperidone. Over a lifetime, the ranking of antipsychotic medications in terms of cost effectiveness was: (1) risperidone; (2) amisulpride; (3) haloperidol; (4) olanzapine; (5) aripiprazole; (6) zotepine; (7) paliperidone. It is obvious that results were greatly affected by this scenario, with options that were ranked highly in base-case deterministic analysis, such as zotepine and paliperidone, occupying the last two places in ranking when relapse rates were assumed to be the same for all treatment options.

Results were, overall, robust under the other scenarios explored in sensitivity analysis. In all cases, zotepine was the most cost-effective option: zotepine remained dominant under all other hypotheses tested, with the exception of the scenario that

combined a low estimate of inpatient stay for people having an acute episode (69 days instead of 111, which was the estimate used in base-case analysis) with a lower respective unit cost. In this case, and over a time horizon of 10 years, zotepine dominated all treatment except olanzapine which became less costly. However, the ICER of zotepine versus olanzapine was £7,751/QALY; therefore, zotepine remained the most cost-effective option of those assessed.

Ranking of medications in terms of cost effectiveness did not change at 10 years under any scenario of those examined (with the exception of using common probabilities of relapse, as discussed above). However, over a lifetime, some of the tested scenarios did affect the ranking of antipsychotic medications. Table 129 provides the ranking of medications in terms of cost effectiveness for those scenarios that affected ranking over a lifetime (the scenario of using common probabilities of relapse has not been presented in this table, as it has been discussed above).

**Table 129: Ranking of antipsychotic medications in terms of cost effectiveness over a lifetime under: (1) base-case analysis; (2) use of a lower estimate of inpatient stay; (3) use of a lower estimate of inpatient stay and a lower unit cost of mental health inpatient bed-day; (4) use of utility scores reported in Glennie (1997); (5) assumption of common probabilities of side effects for all antipsychotic medications**

Base-case analysis	Scenario tested in sensitivity analysis			
1	2	3	4	5
Zotepine	Zotepine	Zotepine	Zotepine	Zotepine
Olanzapine	Paliperidone	Paliperidone	Paliperidone	Olanzapine
Paliperidone	Olanzapine	Haloperidol	Olanzapine	Haloperidol
Haloperidol	Haloperidol	Olanzapine	Haloperidol	Paliperidone
Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole
Risperidone	Amisulpride	Amisulpride	Risperidone	Amisulpride
Amisulpride	Risperidone	Risperidone	Amisulpride	Risperidone

It must be noted that using common probabilities of side effects (that is, acute EPS, weight gain, glucose intolerance and diabetes) for all antipsychotic medications did not significantly affect the results of the analysis. Ranking medications in terms of QALYs changed, as expected, with olanzapine being ranked in second place in both of the time horizons examined. However, the first two ranked places in terms of cost effectiveness were not affected, with zotepine remaining the most cost-effective option followed by olanzapine, as in base-case analysis.

### 11.3.2 Results of probabilistic analysis

Results of probabilistic analysis did not differ significantly from those of deterministic analysis: as in deterministic analysis, zotepine dominated all other options because it was associated with the lowest total costs and highest total

QALYs (that is, mean values from 10,000 iterations) compared with the other six antipsychotic medications assessed. Regarding the ranking of medications in order of cost effectiveness, this was the same for deterministic and probabilistic analysis over 10 years. Over a lifetime, cost-effectiveness ranking of antipsychotic drugs in probabilistic analysis differed from respective ranking in deterministic analysis to some extent; probabilistic analysis ranking was as follows: (1) zotepine; (2) olanzapine; (3) haloperidol; (4) paliperidone; (5) risperidone; (6) amisulpride; (7) aripiprazole.

Probabilistic analysis demonstrated that zotepine had the highest probability of being the most cost-effective option among all antipsychotic medications examined, at any level of willingness-to-pay per additional QALY gained of those explored; that is, from zero to £50,000 per QALY gained. However, this probability was low, ranging between 25 and 29% at 10 years, and 28 and 33% over a lifetime, and remained virtually unaffected by the cost-effectiveness threshold examined. The other antipsychotic medications had probabilities of being the most cost-effective options that ranged from approximately 5% (haloperidol) to 16% (paliperidone) and were also almost independent of the cost-effectiveness threshold and the time horizon examined. The cost effectiveness acceptability frontier coincided with the CEAC for zotepine, because zotepine produced the highest average net benefit at any level of willingness to pay.

Figure 8 and Figure 9 show the CEACs generated for each of the seven antipsychotic medications examined, over 10 years and a lifetime of antipsychotic medication use, respectively.

Table 130 and Table 131 show the probabilities of each antipsychotic medication being cost effective at various levels of willingness-to-pay per QALY gained.



Figure 8: Cost-effectiveness acceptability curves of all treatment options at 10 years of antipsychotic medication use

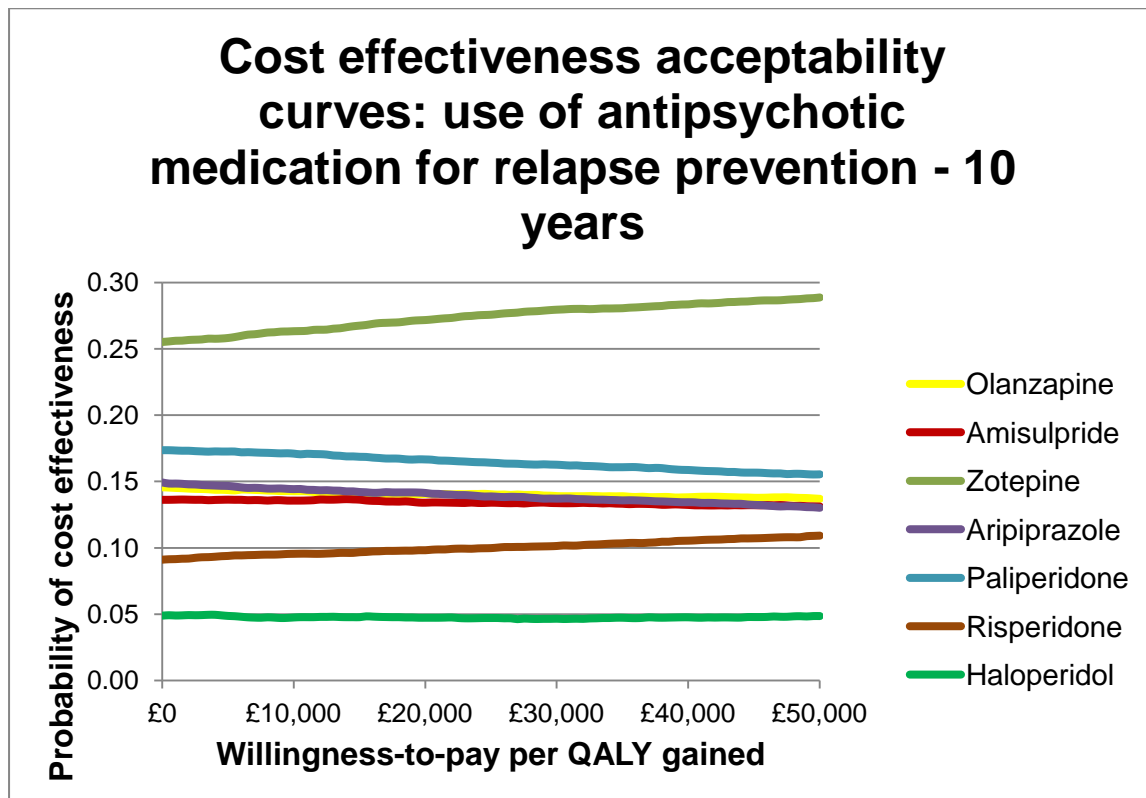
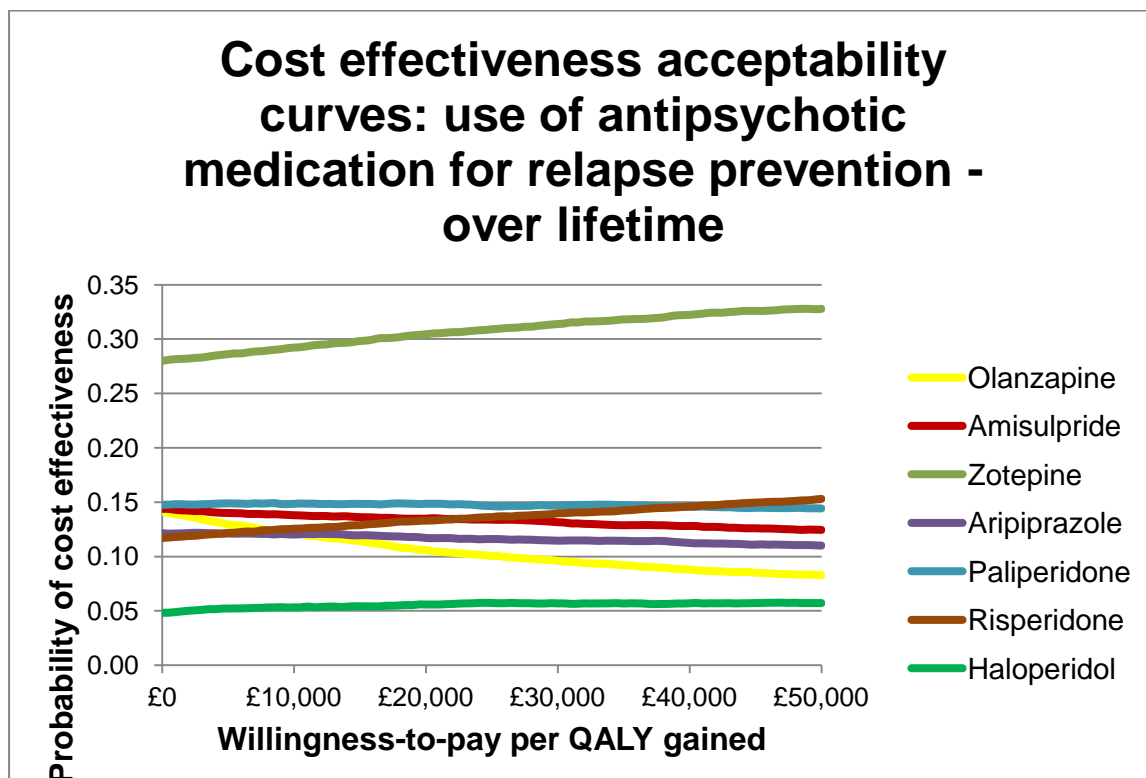


Figure 9: Cost-effectiveness acceptability curves of all treatment options over a lifetime of antipsychotic medication use



## 11.4 DISCUSSION OF FINDINGS - LIMITATIONS OF THE ANALYSIS

The results of the economic analysis suggest that zotepine is potentially the most cost-effective pharmacological treatment of those examined for relapse prevention in people with schizophrenia that is in remission. Zotepine dominated all other treatment options in deterministic analysis. In probabilistic analysis, use of zotepine yielded the maximum average net benefit and demonstrated the highest probability of being the most cost-effective option at any level of willingness-to-pay per unit of effectiveness. However, because of the high uncertainty characterising model input parameters, the probability of zotepine being the most cost-effective option was low at approximately 27 to 30% and remained virtually unaffected by the level of willingness-to-pay. The probability of zotepine being the most cost-effective antipsychotic medication at the NICE cost-effectiveness threshold of £20,000 per QALY was 27.17% at 10 years and 30.46% over a lifetime.

One of the major drawbacks of the economic analysis was the omission of a number of antipsychotic drugs that are potentially effective in preventing relapse in people with schizophrenia in remission. Quetiapine and FGAs other than haloperidol were not assessed in the economic analysis because no relevant clinical data in the area of relapse prevention were identified in the systematic review of relevant literature. The clinical data on relapse and discontinuation utilised in the economic model were limited in some cases: data on zotepine, which was shown to be the dominant option in deterministic analysis, were derived exclusively from a placebo-controlled RCT. Respective data on aripiprazole and paliperidone were also taken from two trials that assessed each of these two antipsychotic drugs versus placebo. Therefore, the results of the economic analysis should be interpreted with caution.

**Table 130: Probability of each antipsychotic intervention being cost effective at various levels of willingness-to-pay per QALY gained (WTP) – 10 years**

WTP	Olanzapine	Amisulpride	Zotepine	Aripiprazole	Paliperidone	Risperidone	Haloperidol
0	0.1457	0.1363	0.2552	0.1492	0.1736	0.0911	0.0489
£5,000	0.1436	0.1364	0.2582	0.1466	0.1726	0.0939	0.0487
£10,000	0.1427	0.1357	0.2633	0.1442	0.1710	0.0955	0.0476
£15,000	0.1410	0.1364	0.2675	0.1420	0.1686	0.0967	0.0478
£20,000	0.1407	0.1341	0.2717	0.1413	0.1666	0.0982	0.0474
£25,000	0.1404	0.1341	0.2757	0.1387	0.1641	0.0998	0.0472
£30,000	0.1390	0.1338	0.2795	0.1370	0.1626	0.1014	0.0467
£35,000	0.1389	0.1333	0.2806	0.1357	0.1607	0.1034	0.0474
£40,000	0.1381	0.1324	0.2835	0.1343	0.1586	0.1054	0.0477
£45,000	0.1377	0.1322	0.2861	0.1323	0.1566	0.1072	0.0479
£50,000	0.1369	0.1312	0.2887	0.1301	0.1553	0.1092	0.0486

**Table 131: Probability of each antipsychotic intervention being cost effective at various levels of willingness-to-pay per QALY gained (WTP) – over a lifetime**

WTP	Olanzapine	Amisulpride	Zotepine	Aripiprazole	Paliperidone	Risperidone	Haloperidol
0	0.1412	0.1440	0.2801	0.1216	0.1476	0.1172	0.0483
£5,000	0.1294	0.1402	0.2863	0.1213	0.1488	0.1218	0.0522
£10,000	0.1218	0.1381	0.2924	0.1203	0.1484	0.1257	0.0533
£15,000	0.1143	0.1363	0.2984	0.1196	0.1483	0.1289	0.0542
£20,000	0.1060	0.1349	0.3046	0.1171	0.1485	0.1331	0.0558
£25,000	0.1007	0.1340	0.3092	0.1161	0.1464	0.1364	0.0572
£30,000	0.0960	0.1316	0.3140	0.1146	0.1471	0.1399	0.0568
£35,000	0.0921	0.1288	0.3182	0.1145	0.1472	0.1425	0.0567
£40,000	0.0882	0.1281	0.3224	0.1125	0.1458	0.1461	0.0569
£45,000	0.0853	0.1260	0.3261	0.1109	0.1449	0.1497	0.0571
£50,000	0.0831	0.1245	0.3279	0.1100	0.1443	0.1531	0.0571

Moreover, definition of relapse varied across the 17 trials that provided data on relapse; this is another factor that should be taken into account when interpreting the economic findings. Data on relapse, discontinuation because of side effects and discontinuation because of other reasons were treated as mutually exclusive in analysis. Although the majority of the 17 RCTs that formed the evidence-base for the economic analysis reported these outcomes as such (that is, trial participants could either stay in remission, or relapse, or discontinue because of side effects, or discontinue because of other reasons), a small number of trials did not clarify whether some participants could have been double-counted in the reporting of outcomes and an assumption of mutual exclusiveness of such outcomes also in these studies had to be made. Results of the mixed treatment comparison analysis of clinical data on relapse prevention were characterised by high uncertainty, as demonstrated by the wide 95% credible intervals of the respective posterior distributions; this uncertainty was reflected in the results of the probabilistic economic analysis: the probability of zotepine being the most cost-effective option was roughly 27 to 30%, with the probabilities of the remaining options being cost effective ranging from around 5% (haloperidol) to 16% (paliperidone), regardless of the level of willingness-to-pay per QALY gained.

The mixed treatment comparison analysis of the available clinical data, including relapse and discontinuation rates as well as rates of side effects, overcame the major limitation characterising previous economic models that assessed the cost effectiveness of pharmacological treatments for people with schizophrenia: most of those analyses synthesised trial-based evidence by naive addition of clinical data across relevant treatment arms, thus breaking randomisation rules and introducing bias into the analysis (Glenny et al., 2005). On the other hand, mixed treatment comparison techniques enable evidence synthesis from both direct and indirect comparisons between treatments, and allow simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Caldwell et al., 2005; Lu & Ades, 2004).

The guideline economic analysis, in contrast to previous economic studies, considered a lifetime horizon (in addition to a time horizon of 10 years); this was deemed appropriate and relevant for the economic question, given the potential need for long-term (likely to be over a lifetime) use of antipsychotic drugs by people with schizophrenia in remission, and the nature of schizophrenia, which is often characterised by phases of remission alternating with phases of relapse over a lifetime. However, one limitation of the analysis was the extrapolation of relatively short-term clinical data over a lifetime because no appropriate long-term data were available to inform the economic model: clinical data on relapse and discontinuation were taken from trials with time horizons ranging between 26 and 104 weeks. The 52-week probability of relapse, the 52-week probability of treatment discontinuation because of intolerable side effects and the 52-week probability of treatment discontinuation because of any other reason were estimated in most cases by extrapolating the available clinical data; the estimated probability of relapse and of treatment discontinuation because of other reasons were then assumed to apply to

every yearly cycle in the model, over a lifetime of the hypothetical study cohorts. Although such an extrapolation of the data was required to populate the economic model, no robust evidence exists to confirm that such extrapolation accurately reflects the long-term effectiveness of antipsychotic medication and its impact on the course of schizophrenia in real life. If the effectiveness of antipsychotic drugs in preventing relapse is maintained over time, then the results of the economic analysis more closely reflect a realistic situation. If, however, the effectiveness of antipsychotic drugs in preventing relapse is reduced over time, then this analysis has overestimated the cost effectiveness of antipsychotic medication, especially of those treatments that have been demonstrated to be the most effective in preventing relapse in the short term, such as zotepine.

The economic model structure incorporated three side effects: acute EPS, weight gain, and diabetes/ glucose intolerance potentially leading to diabetes. The choice of side effects was based on their expected impact on the relative cost effectiveness of antipsychotic medications and the availability of relevant data. However, it should be emphasised that antipsychotic drugs are characterised overall by a wider range of side effects, such as other neurologic side effects including tardive dyskinesia, sexual dysfunction, increase in prolactin levels, as well as cardiovascular and gastrointestinal side effects, the omission of which may have affected the results of the economic analysis. In particular, lack of consideration of tardive dyskinesia, which has lasting effects and causes a significant impairment in HRQoL, is acknowledged as a limitation of the analysis. Inclusion of tardive dyskinesia in the model structure might disfavour haloperidol, given that clinical evidence indicates that haloperidol is associated with a higher risk for neurologic side effects.

To populate the economic model using the available data on side effects, a number of GDG estimates and further assumptions were required, including selection of data for analysis and extrapolation of available evidence over the time horizon of the analysis. Data on acute EPS were more comprehensive compared with data on weight gain and data on the risk for diabetes and glucose intolerance. Data on weight gain were not available for zotepine; for this reason the risk of weight gain for zotepine was assumed to be equal to the respective risk for risperidone. Data on the risk for diabetes and glucose intolerance associated with antipsychotic medication and appropriate for the economic analysis were very sparse and not available for all drugs assessed in the analysis. However, these parameters were considered to be important for inclusion in the model structure, as use of antipsychotic medication is associated with increased risk for development of diabetes, the complications of which have been shown to affect quality of life considerably and to incur substantial costs in the long term; therefore, to explore the impact of such parameters on the relative cost effectiveness of antipsychotic medications over time, a number of assumptions were made. It is acknowledged that the estimates used in the model regarding diabetes and glucose intolerance could be potentially conservative and may not fully reflect the negative effect of antipsychotic medication on glucose metabolism.

Deterministic analysis showed that although olanzapine was ranked second in terms of effectiveness (number of QALYs gained) at 10 years of antipsychotic medication use, it was placed last in the ranking when a lifetime horizon was considered. This change in ranking over time was probably caused by the eventual impairment in HRQoL of people taking olanzapine, owing to the estimated higher levels of permanent weight increase and the frequent presence of complications because of diabetes associated with use of olanzapine compared with other antipsychotic medications. Nevertheless, despite being the least effective option over a lifetime, olanzapine was still ranked second in terms of cost effectiveness among the antipsychotic drugs assessed in deterministic analysis. It must be emphasised that deterministic sensitivity analysis revealed that the probabilities of side effects used in the economic model had no significant impact on the overall conclusions of the incremental analysis, because assuming equal probabilities for side effects for all medications did not change their ranking in terms of cost effectiveness at 10 years and led to minor changes in ranking over a lifetime (zotepine and olanzapine were still ranked first and second most cost-effective options, respectively). However, if the estimates used in the model regarding diabetes and glucose intolerance are conservative and do not fully capture the negative impact of antipsychotic medication on HRQoL and associated costs, then the relative cost effectiveness of drugs with more significant metabolic implications, such as olanzapine, may have been overestimated.

Data on treatment discontinuation because of intolerable side effects and side-effect data were analysed separately. In probabilistic economic analysis, the probability of treatment discontinuation because of intolerable side effects was varied independently from the probability of developing each of the three side effects examined. However, there is a possible correlation between these probabilities; for example, treatment discontinuation because of intolerable side effects is likely to be related to the risk for acute EPS. Such potential correlation between these parameters has not been considered in the analysis. On the other hand, the correlations across probability of relapse, probability of treatment discontinuation because of intolerable side effects and probability of treatment discontinuation because of other reasons have been taken fully into account because data on these three parameters were analysed together in a competing risks mixed treatment comparison model. The posterior simulations resulting from this exercise were then exported jointly and fitted into the Excel file of the economic model where the probabilistic analysis was implemented.

The analysis adopted the perspective of the NHS and personal social services, as recommended by NICE. Costs associated with the pharmacological treatment of people with schizophrenia were estimated by combining data from the NHS and other national sources of healthcare resource utilisation, as well as information from published studies conducted in the UK, with national unit costs. A number of further GDG estimates and assumptions were required to inform the cost parameters of the economic model. The results of the economic analysis demonstrated that drug acquisition costs do not determine the relative cost effectiveness of antipsychotic

medications: haloperidol had the lowest probability of being cost effective in probabilistic analysis, despite the fact that it is by far the cheapest drug among those assessed. On the other hand, paliperidone was ranked highly in terms of cost effectiveness (the third best option in deterministic analysis at 10 years and over a lifetime; and the second highest probability of being cost effective in probabilistic analysis), despite having the highest acquisition cost. Although drug acquisition costs seem to be unimportant in determining cost effectiveness, it must be noted that the prices of a number of antipsychotic medications are expected to fall in the future because more drugs will be available in generic form.

Deterministic analysis showed that the probability of relapse was the key driver of cost effectiveness. It is not surprising, therefore, that zotepine, which was shown to be the most cost-effective option in both deterministic and probabilistic analyses, had the lowest average probability of relapse and the highest probability of being the most effective drug in reducing relapse in the mixed treatment comparison analysis; olanzapine and paliperidone, which were the second and third most cost-effective options in deterministic analysis, respectively, had the third and second lowest relapse rates, respectively, and were ranked third and second best drugs in reducing relapse, respectively (details of effectiveness ranking in mixed treatment comparison analysis are provided in Table 115). These findings indicate that it is the effectiveness of an antipsychotic drug in preventing relapse that primarily affects its cost effectiveness, especially considering that the rates of side effects were not shown to have any significant impact on the cost-effectiveness results; such a hypothesis seems reasonable, given that relapse prevention greatly improves the HRQoL of people with schizophrenia and, simultaneously, leads to a substantial reduction in hospitalisation rates and associated high costs. In fact, reduction in inpatient costs associated with the development of acute episodes affects the level of total costs associated with antipsychotic medication and the ranking of options in terms of cost effectiveness in the long term, as shown in sensitivity analysis.

Besides the health and social care costs that were considered in this analysis, according to the NICE recommended economic perspective, wider societal costs (such as costs borne to the criminal justice system, personal expenses of people with schizophrenia and their carers, productivity losses of people with schizophrenia, carers' time spent with people with schizophrenia, which may also translate to productivity losses for carers, as well as the emotional burden associated with schizophrenia) need to be taken into account when the cost effectiveness of antipsychotic medications is assessed.

## 11.5 CONCLUSIONS

The economic analysis undertaken for this guideline showed that zotepine may be potentially the most cost-effective antipsychotic medication among those assessed for relapse prevention in people with schizophrenia in remission. However, results were characterised by high uncertainty, and probabilistic analysis showed that no antipsychotic medication can be considered to be clearly cost effective compared



with the other options included in the assessment: the probability of each intervention being cost effective ranged from roughly 5% (haloperidol) to about 27 to 30% (zotepine), and was independent of the cost-effectiveness threshold used and the time horizon of the analysis (that is, 10 years or a lifetime). The probability of 27 to 30% assigned to zotepine, although indicative, is rather low and inadequate to lead to a safe conclusion regarding zotepine's superiority over the other antipsychotic medications assessed in terms of cost effectiveness. In addition, clinical data for zotepine in the area of relapse prevention (as well as for paliperidone and aripiprazole) came from a single placebo-controlled trial. Data on side effects were not comprehensive; in particular, data on the risk for diabetes and glucose intolerance associated with use of antipsychotic medications were sparse, so that the impact of the risk for diabetes and its complications on the relative cost effectiveness of antipsychotic drugs could not be determined accurately. It has to be noted, however, that the estimated rates of side effects considered in the analysis did not significantly affect the cost effectiveness results.

Further research is needed on the benefits and patterns of use of antipsychotic medications in the area of relapse prevention in people with schizophrenia that is in remission, as well as on the rates of associated long-term metabolic side effects, to address the uncertainty characterising the results of the economic analysis.

Moreover, clinical data in the area of relapse prevention are needed for quetiapine and FGAs other than haloperidol, to enable a more comprehensive assessment of the relative cost effectiveness of antipsychotic medications in relapse prevention for people with schizophrenia that is in remission.\*\*2009\*\*

# 12 TEAMS AND SERVICE-LEVEL INTERVENTIONS

## 12.1 INTRODUCTION

This chapter fully updates the review of teams and service-level interventions (developed as part of ‘community care’ in different parts of the world, as well as those specifically developed in the UK) from the 2002 and 2009 guidelines. The GDG recognised that much of the research in this area has followed changes in practice, often led by policy initiatives to move from hospital to community care, with mental health service providers developing different, previously untested, service configurations in the community as an alternative to relatively costly inpatient settings.

Some teams and services have been developed for the routine, non-acute provision of care for people with psychosis and schizophrenia in community settings, for example, community mental health teams (CMHTs), while others have focused much more on treatment during times of crisis that, previously, would have led to an inpatient admission, for example, crisis resolution and home treatment teams (CRHTTs). The latter have, in the main, been designed as alternatives to acute hospital care. Some services have, nevertheless, been designed to both support people day to day in the community, and provide some treatment and care either to prevent an impending crisis or even to avoid acute admission, for example, assertive community treatment (ACT). To reduce confusion and in the service of clarity, the GDG has synthesised the available evidence to provide guidance about the best team and service-level interventions for acute and non-acute care in community settings.

The GDG, therefore, considered and reviewed the evidence for non-acute community-based care and the evidence for acute or crisis community-based care separately. Although the provision of non-acute and acute/crisis care is not always clearly demarcated within mental health and social care services in practice, the trials contributing to these two reviews were nevertheless separated. The GDG also considered the importance of reducing the duration of untreated psychosis (DUP) for people with first episode psychosis because longer DUP has been reported to be associated with poorer outcomes (Marshall et al., 2005; Perkins et al., 2005), and much of the rationale for the emergence of early intervention services (EIS; also known as ‘early intervention in psychosis services’) was based on reducing DUP. The GDG utilised the review by Lloyd-Evans et al. (2011) to assess the effectiveness of programmes that aim to reduce DUP.

The chapter is thus divided into three sections. Section 12.2 discusses the interface between primary and secondary care in relation to service provision. Section 12.3 reviews non-acute community mental healthcare and includes an evaluation of EIS

and early detection programmes to reduce DUP, CMHTs and intensive case management (ICM – a recent term that encompasses ACT and case management). Section 12.4 reviews community-based alternatives to acute admission and includes CRHTTs, crisis houses and acute day hospital care.

In reviewing the evidence for the effectiveness of different services in the 2002 guideline, the GDG decided to focus on the RCT because this is the best design to evaluate the effectiveness of competing interventions. However, team and service-level interventions are essentially complex interventions including, for example, psychological interventions combined with specific team operating protocols and case load limits. The GDG has ensured that wherever meta-analyses have been performed, the definition of the team or service-level intervention has been examined carefully. Moreover, it is important to recognise that it is often difficult to establish with certainty, in a simple RCT, what aspects of the team or service-level intervention are the effective ingredients. In this regard, the GDG has played an important consensus-based role in grouping different types of intervention to allow meta-analysis and in interpreting the findings for each set of comparisons.

Individual randomisation is not possible in studies of early detection programmes, which by definition, target whole populations from which people with first episode psychosis might be referred to services. Therefore, the review of interventions to reduce DUP was not limited to RCTs.

Many of the studies have been undertaken outside the UK. Where the comparator is standard care, the GDG has taken this into consideration because ‘standard care’ is often different in important respects in other countries. Where UK studies have been available, the GDG has looked at UK sub-analyses alongside the full dataset analysis.

The GDG also considered the 2002 and 2009 guidelines in the area of primary care and the interface between primary and secondary care, both areas being the subject of a number of consensus-based recommendations. The GDG for the 2014 guideline has added to these recommendations, mainly in the area of physical health, and has also retained and modified some of the considerations made by the GDGs for the 2002 and 2009 guidelines, both within the text and the associated recommendations.

## **12.2 INTERFACE BETWEEN PRIMARY AND SECONDARY CARE**

### **12.2.1 Introduction**

This section focuses on the initial pathway to specialist help for a person presenting with first episode psychosis to primary care; and those with an established diagnosis managed either collaboratively between primary and secondary care, or wholly in primary care. The recommendations are based on an updated consensus-based narrative synthesis of the relevant sections of *Psychosis and Schizophrenia in Children and Young People* (NCCMH, 2013 [full guideline]; NICE, 2013a) and the 2009 adult guideline (NICE, 2009d).

### 12.2.2 First episode psychosis and its presentation

The emerging distress of a first episode of psychosis will cause many people, often supported by their families, to seek help from their GP. However, this is an infrequent event for an individual GP, who on average encounters around one to two patients per year with a suspected emerging psychosis (Simon et al., 2005); frequency is slightly increased in inner city areas. Notwithstanding this low frequency, GPs are the most common referral agents to specialist services, and, furthermore, their involvement is also associated with reduced use of the Mental Health Act (Burnett et al., 1999) making their role important in detecting psychosis and initiating the pathway to specialist care.

Psychosis is difficult for GPs to recognise, and there a number of reasons for this. It tends to occur for the first time when people are young: more than three quarters of men and two thirds of women who experience psychosis have their first episode before the age of 35. Indeed, most first episodes occur between late teens to late twenties, mirroring when many other lifetime mental disorders present for the first time (Kessler et al., 2007) and against a backdrop of increasing psychological distress for many young people -- for instance, 20% of young people will experience a diagnosable depressive episode by the age of 18 years (Lewinsohn et al., 1993). Moreover, serious disorders like psychosis often start off like milder and far more common mental health problems, and rarely present initially with clear cut psychotic symptoms. The challenge, therefore, for GPs in detecting psychosis promptly is to distinguish its presentation at an early undifferentiated phase and at an age when many people may first present with psychological difficulties. When asked how to improve detection of emerging first episode psychosis, GPs request better collaboration with specialist services and low-threshold referral services rather than educational programmes (Simon et al., 2005).

In view of the evidence presented in this guideline regarding suspected psychosis (that early treatment with CBT may decrease the likelihood of transition to psychosis whereas antipsychotics appear to be ineffective) and first episode psychosis (that there are benefits for being seen at an early stage), the GDG regarded the role of the GP in recognising and monitoring both suspected and likely symptoms of psychosis to be a clear focus for developing consensus-based recommendations.

The GDG therefore concluded that people presenting with symptoms of suspected or actual psychosis in primary care should be referred to EIS.

After the first episode, some people refuse to accept the diagnosis and sometimes also reject the treatment offered. Bearing in mind the consequences of a diagnosis of psychosis and schizophrenia, many people in this position, perhaps unsurprisingly, want a second opinion from another consultant psychiatrist. This is often requested through a person's GP if a person knows it is available.

### **12.2.3 People with an established diagnosis of psychosis and schizophrenia in primary care**

The GDG for the 2009 guideline made the following statements, which underpin a number of recommendations about primary care (the GDG for the 2014 guideline decided to only modify the related recommendations to improve the wording and to extend physical healthcare; see section below on physical health):

‘People with an established diagnosis of schizophrenia who are managed in primary care require regular assessment of their health and social needs. This should include monitoring of mental state, medication use and adherence, side effects, social isolation, access to services and occupational status. All such people should have a care plan developed jointly between primary care and secondary mental health services. Regular monitoring of physical health is also essential. With consent from service users, non-professional carers should also be seen at regular intervals for assessment of their health and social care needs. Carers should also be offered an assessment of their needs.

Advance statements and advance decisions about treatment should be documented in the service user’s notes. These should be copied from secondary services to the responsible GP. If no secondary service is involved in the service user’s care (because they have recently moved to the area, for example), the GP should ensure that any existing advance decisions or statements are copied to the secondary services to whom referral is made.

When a person with schizophrenia is planning on moving to the catchment area of a different NHS trust, their current secondary care provider should contact the new secondary and primary care providers, and send them the current care plan. People presenting to primary care services who are new to the area (not known to local services) with previously diagnosed psychosis should be referred to secondary care mental health services for assessment, subject to their agreement. The GP should attempt to establish details of any previous treatment and pass on any relevant information about this to the CMHT.

When a person with schizophrenia is no longer being cared for in secondary care, the primary care clinician should consider re-referral of the service user to secondary care. When referring a service user to secondary mental health services, primary care professionals should take the following into account:

- Previous history: if a person has previously responded effectively to a particular treatment without experiencing unwanted side effects and is considered safe to manage in primary care, referral may not be necessary.
- Views about referral: the views of the mental health service user should be fully taken into account before making a referral. If the service user wants to be managed in primary care, it is often necessary to work with the family and carers. Sharing confidential information about the service user with carers

raises many ethical issues, which should be dealt with through full discussion with the service user.

- Non-adherence to treatment: this may be the cause of the relapse, possibly as a result of lack of concordance between the views of the service user and of the healthcare professionals, with the former not recognising the need for medication. Alternatively, non-adherence might be the consequence of side effects. Finding the right antipsychotic drug specifically suited to the service user is an important aim in the effective management of schizophrenia.
- Side effects of medication and poor response to treatment: the side effects of antipsychotic drugs are personally and socially disabling, and must be routinely monitored. Side effects are also a cause of poor response to treatment. For about 40% of people given antipsychotics, their symptoms do not respond effectively.
- Concerns about comorbid drug and alcohol misuse: substance misuse by people with schizophrenia is increasingly recognised as a major problem, both in terms of its prevalence and its clinical and social effects (Banerjee et al., 2002). Monitoring drug and alcohol use is an essential aspect of the management of people with schizophrenia in primary and secondary care.
- Level of risk to self and others: people with schizophrenia, especially when relapse is impending or apparent, are at risk of suicide and are often vulnerable to exploitation or abuse. During an acute episode of illness, conflicts and difficulties may manifest themselves through social disturbances or even violence.'

The GDG for the 2014 guideline wished to add the following bullet point to this list:

- General social functioning and self-care: loss of employment/vocational activity, social withdrawal, self-neglect, and financial or housing difficulties can all be signs of or precursors to relapse. Social exclusion is a common feature in people with psychosis or schizophrenia diagnosis. Referral to secondary mental health services or other relevant agencies may be required.

The 2009 guideline concluded by saying: 'The identification of patients with schizophrenia in a well-organised computerised practice is feasible (Kendrick et al., 1991; Nazareth et al., 1993). The organisation and development of practice case registers is to be encouraged because it is often the first step in monitoring people with schizophrenia in general practice. There is evidence that providing payment incentives to GPs leads to improved monitoring of people with schizophrenia (Burns & Cohen, 1998). In 2004, as a part of the GP contract, the Quality and Outcomes Framework was introduced in English general practice as a voluntary process for all general practices – schizophrenia is one of the medical conditions to be monitored as part of this framework' (NCCMH, 2010 [full guideline]).

### *Physical health*

Since the 2009 guideline, the evidence base for physical ill health among people with psychosis and schizophrenia has continued to develop. In particular, more

understanding of why cardiovascular disease occurs at such high rates in people with schizophrenia makes it appropriate to review the existing recommendations relating to physical healthcare in primary care. New recommendations about lifestyle interventions to reduce the impact of cardiovascular risks are described in Chapter 10. In considering such interventions it is also necessary to reflect on the adequacy of screening for cardiovascular risk factors and, related to this, monitoring for adverse cardiometabolic effects from antipsychotic medication.

People with psychosis and schizophrenia are at considerably increased risk of poor physical health. Although suicide accounts for a quarter of all premature mortality in people with severe mental ill health, including schizophrenia, of all causes of premature death, cardiovascular disease is now the commonest in this group. This tendency is no doubt a result of a complex combination of social exclusion, poor diets, high rates of obesity, lack of physical activity and high rates of smoking, compounded by health risks linked to genetic vulnerabilities and adverse effects of antipsychotic medication. These various factors lead to more frequent disturbances of glucose and lipid metabolism, resulting in atherosclerosis. The rate of diabetes mellitus is two to three times higher than for the general population (almost entirely accounted for by type 2 diabetes). A European study screening people with schizophrenia who were not known to have diabetes, discovered 10% had type 2 diabetes and 38% were at high risk of type 2 diabetes; this population's average age was only 38 years (Manu et al., 2012).

Concerns about cardiovascular mortality more generally have attracted a public health focus in the UK over the last 2 decades. For instance, health promotion and disease management programmes for conditions like heart disease and diabetes have become established in primary care, further encouraged since 2006 through the primary care pay for performance scheme, the Quality and Outcomes Framework (NHS Employers, 2011). Although there have been reductions in cardiovascular morbidity and mortality in the general population, these benefits have not been enjoyed by people with severe mental illness – indeed the mortality gap between the general population and people with severe mental illness may still be widening (Brown et al., 2010). It is important to recognise, then, that some of the key antecedent risks for premature mortality in this group may emerge and become established early in the course of psychosis, perhaps even in or before the first episode.

People with first episode psychosis, exposed for the first time to antipsychotics, are particularly vulnerable to rapid weight gain (Alvarez-Jimenez et al., 2008; Kahn et al., 2008) and adverse cardiometabolic disturbance (Foley & Morley, 2011). The subsequent trajectory of weight gain and increasing metabolic disturbance, when combined with high rates of tobacco smoking even before the first episode begins (Myles et al., 2012), provide a potent mix of cardiovascular risk factors. Given that modifiable cardiovascular risk appears within months of commencing treatment (Foley & Morley, 2011), the onus should arguably shift towards a prevention and

early intervention approach to cardiovascular risk (Phutane et al., 2011). The GDG accepted this view.

A prerequisite for successful prevention is the implementation of guidelines such as the European screening and monitoring guidelines for diabetes and cardiovascular risk in schizophrenia (De Hert et al., 2009a). Yet despite numerous published screening recommendations, monitoring rates remain poor in adults (Buckley et al., 2005; Mackin et al., 2007b; Morrato et al., 2009; Nasrallah et al., 2006). This was recently also confirmed in the UK by the National Audit of Schizophrenia (Royal College of Psychiatrists, 2012). Importantly, this audit examined the implementation of recommendations for physical health monitoring set out in the 2009 guideline for people under the care of mental health services in community settings during the previous 12 months. Ninety-four per cent of mental health trusts across England and Wales participated in an audit of over 5,000 patients' case records making it very likely that its findings reflect current practice. On average, only 28% of this population (range by mental health trust of 13 to 69%) had a recorded assessment of the main risk factors for cardiovascular disease (BMI, smoking status and blood pressure, glucose and lipids) within the previous 12 months. The findings of the audit suggest inconsistent and often inadequate local monitoring arrangements and indicate a need to establish greater clarity over responsibilities and improve communication between primary and secondary care.

#### **12.2.4 Linking evidence to recommendations**

The GDG for the 2014 guideline reconsidered the 2002 and 2009 guidelines in the area of primary care and the primary and secondary care interface. It was agreed that although there is no robust evidence to guide recommendations in this area, the GDG for the 2014 guideline concurred with its predecessors that consensus-based recommendations (based on the considerations above but not restricted to them) should be developed to help guide primary and secondary care health and social care professionals in these areas. Service users with serious mental illness tend to be forgotten in primary care, by both primary and secondary care professionals, and there is a relatively low level of understanding of the role of primary care in the initial management of psychosis and schizophrenia, for example, when and if antipsychotic medication should be introduced. Moreover, the breadth and depth of initial assessments of people with psychosis and schizophrenia on entry to secondary care are very variable, as are the development and role of care plans. Service users commonly do not know that they have a care plan, especially when they first use secondary care services. Many service users like to return to primary care when they are stable, and primary care professionals are often unsure about their role in this context, nor about when to reengage secondary care and to re-refer. Finally, when service users move house, this often involves changing both primary and secondary care services. Service users frequently become lost to services at this point. The GDG for the 2014 guideline decided to follow the GDG for the 2009 guideline and include a recommendation about how to minimise loss from services at this point. Advance warning and relevant information from existing care providers should be given to the new providers.



It should be recognised that, of all parts of the care pathway for people with psychosis and schizophrenia, the role of primary care and the management of the primary-secondary care interface are areas of weakness and are relatively inaccessible to robust research. Primary care and its interface with secondary care are both important and yet lacking in evidence for best practice. In addition, there is no health economic evidence in these areas. As such, the following recommendations are intended to minimise harm, improve assessment, prevent service users becoming lost to services and ensure that when problems arise in primary care service users can gain access easily to the services they need.

At present, for most GPs, between one and two of the people on their list each year will develop a first episode psychosis. In these circumstances, referral to EIS appears to produce most benefit for the service user (for the review of EIS see Section 12.3.2). However, some GPs, on seeing a person with a psychotic presentation, consider the use of antipsychotics as a first step, while others are uncertain. In some situations, this may well be the right intervention, especially if the service user is very distressed or the psychosis is well advanced. However, given the increasing availability and preference for psychological treatments, the sometimes severe side effects that can occur with first exposure to antipsychotics, and the preparatory investigations that are usually necessary before starting these drugs, the GDG decided to recommend that antipsychotics should not be started in primary care without prior discussion with a consultant psychiatrist.

A further area of variable practice includes the assessment of service users on arrival in secondary care. Entering secondary care for the first time is a very important experience for service users and can colour future attitudes to secondary care. Professionals usually take this into account. However, this can lead to assessments being relatively brief and/or limited in content. It is also important to bear in mind that some drugs can precipitate a psychosis and that psychoses are often associated with coexisting physical and mental health problems. The GDG decided to adumbrate the key areas that should be covered in the assessment, so as to ensure that, even if these areas cannot be covered immediately, professionals in secondary care should aim for a genuinely comprehensive assessment over time. After all, psychosis and schizophrenia affects the whole of a person's life, including relationships, physical activity and health, education and employment, and their ability to pursue individual goals; and even where symptoms may be less severe, it is important to get a baseline of personal functioning at the point of admission to secondary care so as to track changes that may well come about through the acute episode and after recovery.

With these considerations in mind, the GDG recommended that the assessment in secondary care should include a full psychiatric assessment, as well as a full medical assessment for physical ill health and the possibility of organic factors influencing the development of the psychosis. Physical assessment should include smoking status, nutrition, physical activity and sexual health, all of which are commonly

affected either early on (for example 59% of people with a first episode of psychosis are already smoking) or certainly later (people with established schizophrenia have high rates of cardiovascular disease). People with psychosis and schizophrenia will experience considerable disruption to their social and psychological life. Assessment should include looking at their accommodation, their capacity to engage in cultural activities appropriate to their ethnicity, and to understand the burdens they have in terms of caring for others, including children or parents. It should also include evaluation of their social networks, relationships and possible personal trauma, and also neurodevelopmental considerations, especially for younger users of EIS who have an increased risk of presenting with social, cognitive and motor impairments. Psychosis will affect a person's quality of life, activities of daily living and access to employment, all of which need to be included in the assessment. It is common for people with psychosis to experience quite marked anxiety, depression and alcohol or drug (both street bought and prescribed) misuse; comorbidities can occur at any time but especially early on in the psychosis. Engaging service users is also a particular problem, especially in the early period. The GDG considered it helpful to make the assessment and development of a written care plan a focus for engagement by undertaking this jointly with the service user, wherever this is possible. The care plan should include all the issues identified in the assessment.

When a person presents for the first time, or even over the first few times, it may be quite clear that they have developed a psychosis, but not so clear whether they have schizophrenia, bipolar disorder or other affective psychosis, or another less common form of psychosis. This diagnostic problem is made all the more difficult by the coexistence of other mental health problems. Nevertheless, it usually becomes apparent that the psychosis is either a schizophrenic psychosis or an affective psychosis, and the relevant guidelines should be followed for the latter, whether this is the *Bipolar Disorder* (NICE, 2006a) or *Depression* (NICE, 2009a) guideline.

Most psychotic episodes resolve within 6 to 8 months, although it can take substantially longer for some people to reach stability. After a psychosis has resolved and the person is stable, it is common that service users wish to be discharged back to primary care. This transfer should be supported by secondary health and social care professionals who need to contact primary care and arrange transfer of care plans, if this has not occurred already. Primary healthcare professionals should ensure that, when a person first returns from secondary care services to primary care, they are added to a case register of all people with psychosis within their practice. This is a key step in ensuring that people with psychoses receive the right mental and physical healthcare within primary care.

It is important to recognise that antipsychotics can have quite severe and unpleasant side effects which, if carefully managed, can be minimised or even prevented. If they become excessive or intolerable, this can lead to service users stopping treatment altogether, sometimes suddenly, provoking relapse. It is, therefore, important to monitor side effects in primary care. It is also important to monitor psychotic symptoms in primary care, and to keep an eye on common accompaniments to

possible relapse such as an increase in alcohol consumption or drug taking. If there is concern in primary care, the care plan should be consulted. The care plan should include a crisis plan and the name of either the key clinician (which may be a consultant psychiatrist or psychologist or other secondary health or social care professional) and/or the care coordinator. Primary care professionals should not hesitate in making direct contact for advice and in making a referral. Key factors that should encourage referral include any factor associated with an increased likelihood of relapse, such as persisting psychotic symptoms (a poor response to treatment), a failure to continue with agreed treatment, intolerable or very unpleasant side effects, substance misuse and a risk of self-harm or harm to others. However, some service users and/or their carers will request re-referral to secondary care, usually because they want their drug regime reviewed because of side effects, such as excessive drowsiness or sexual side effects, or for specialist psychological treatments for psychosis. Requests for re-referral should be enabled and supported.

A comprehensive multidisciplinary assessment and close monitoring of people with psychotic symptoms would ensure timely detection and appropriate management of physical ill health. There is no health economic evidence in this area for people with psychosis and schizophrenia; however the GDG felt that since psychosis and schizophrenia affect the whole of a person's life, and people with these conditions are at considerable increased risk of poor physical health, that preventing ill health (including cardiovascular disease) and premature death, and minimising the adverse effects associated with antipsychotic medication, have clear potential to reduce healthcare costs and lead to improvements in health related quality of life.

### **12.2.5 Clinical practice recommendations**

**12.2.5.1** Do not start antipsychotic medication for a first presentation of sustained psychotic symptoms in primary care unless it is done in consultation with a consultant psychiatrist. [2009; amended 2014]

**12.2.5.2** Carry out a comprehensive multidisciplinary assessment of people with psychotic symptoms in secondary care. This should include assessment by a psychiatrist, a psychologist or a professional with expertise in the psychological treatment of people with psychosis or schizophrenia. The assessment should address the following domains:

- psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- physical health and wellbeing (including weight, smoking, nutrition, physical activity and sexual health)
- psychological and psychosocial, including social networks, relationships and history of trauma
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)

- social (accommodation, culture and ethnicity, leisure activities and recreation, and responsibilities for children or as a carer)
- occupational and educational (attendance at college, educational attainment, employment and activities of daily living)
- quality of life
- economic status. [2009; amended 2014]

**12.2.5.3** Routinely monitor for other coexisting conditions, including depression, anxiety and substance misuse particularly in the early phases of treatment. [2009; amended 2014]

**12.2.5.4** Write a care plan in collaboration with the service user as soon as possible following assessment, based on a psychiatric and psychological formulation, and a full assessment of their physical health. Send a copy of the care plan to the primary healthcare professional who made the referral and the service user. [2009; amended 2014]

**12.2.5.5** If the person's symptoms and behaviour suggest an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in [Bipolar disorder](#) (NICE clinical guideline 38) or [Depression](#) (NICE clinical guideline 90). [new 2014]

**12.2.5.6** Offer people with psychosis or schizophrenia whose symptoms have responded effectively to treatment and remain stable the option to return to primary care for further management. If a service user wishes to do this, record this in their notes and coordinate transfer of responsibilities through the care programme approach. [2009]

**12.2.5.7** Develop and use practice case registers to monitor the physical and mental health of people with psychosis or schizophrenia in primary care. [2009]

**12.2.5.8** When a person with an established diagnosis of psychosis and schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances), primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan. [2009]

**12.2.5.9** For a person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is:

- poor response to treatment
- non-adherence to medication
- intolerable side effects from medication
- comorbid substance misuse
- risk to self or others. [2009]

**12.2.5.10** When re-referring people with psychosis or schizophrenia to mental health services, take account of service user and carer requests, especially for:

- review of the side effects of existing treatments

- psychological treatments or other interventions. [2009]

**12.2.5.11** When a person with psychosis or schizophrenia is planning to move to the catchment area of a different NHS trust, a meeting should be arranged between the services involved and the service user to agree a transition plan before transfer. The person's current care plan should be sent to the new secondary care and primary care providers. [2009]

## **12.3 NON-ACUTE COMMUNITY MENTAL HEALTHCARE**

### **12.3.1 Introduction**

After the decline of the asylum and before the development of modern day community services, many mental health services provided a fairly typical medical arrangement based upon hospital care and outpatient clinics, with some facility for day care for people with a chronic illness and/or severe impairment. Prior to the development of community care, non-acute (routine, scheduled or planned) care took place predominantly in outpatient clinics or day services, and sometimes in hospital, in specific situations, for example, when medication changes in a well patient had the potential to destabilise their condition.

However, following an acute episode of psychiatric illness, discharging patients often proved problematic as there were little or no facilities to provide more supportive community-based help closer to people's homes. To enhance discharge, community psychiatric nurse roles, based on psychiatric wards and helping people settle in the community, were developed in the 1960s to provide an intermediate level of support away from hospital. By the mid 1990s community-based teams emerged to provide more routine care and to help avoid acute care when higher levels of support and treatment were needed. Although CMHTs became the routine, with consultant psychiatrists bridging the gap between non-acute community care and more clearly acute hospital care, there was surprisingly little evidence to suggest that CMHTs were any better or any worse than the previous arrangement of services. Nevertheless, service users generally prefer non-hospital-based solutions if they are given the choice.

With pressure on resources and national policy to move away from big hospitals, and a more explicit acceptance that service users wanted to access services for routine care in the community, new teams/services were formed, such as acute day hospitals, ACT, case management and ICM and later, EIS for people with early psychosis (for the first 3 years). This section of the guideline reviews the evidence for the clinical and cost effectiveness of EIS, CMHTs and ICM as providers of (predominantly) non-acute care, and also early detection programmes to reduce DUP. It should be remembered, however, that EIS will often accept patients with early schizophrenia in a crisis, usually with support from other acute, community-based services; and ICM often provides crisis care for some of their service users.

### 12.3.2 Early intervention services

#### *Introduction*

The NHS Plan (Department of Health, 2000) set out a requirement for mental health services to establish EIS. EIS are expected to provide care for: (a) people aged between 14 and 35 years with a first presentation of psychotic symptoms; and (b) people aged 14 to 35 years during the first 3 years of psychotic illness. The *Mental Health Policy Implementation Guide* (Department of Health, 2001) set out a wide range of tasks for EIS, including: reducing stigma and raising awareness of symptoms of psychosis; reducing DUP; promoting better engagement with treatment and services; providing evidence-based treatments; promoting recovery for young people who have experienced an episode of psychosis; and working across the traditional divide between CAMHS and AMHS, as well as in partnership with primary care, education, occupational therapy, social services, youth and other services. EIS was an innovation introduced over the last 10 to 15 years as a progressive, integrating service able to provide a broad range of effective treatments with the explicit aim of better engaging young people with psychosis, reducing time to treatment and minimising impairment. However, at the time of their national introduction, there was no RCT evidence for their effectiveness compared with standard care, either in the UK or elsewhere.

Early intervention is primarily concerned with identification and initial treatment of people with psychotic illnesses, such as schizophrenia. Identification may be directed either at people in the prodromal phase of the illness ('earlier early intervention', or prevention) or at those who have already developed psychosis ('early intervention'). Early identification of people with psychotic disorders may be especially relevant to specific groups, for example, African-Caribbean people who are at higher risk of developing a psychosis and presenting very late in the course of the illness. Central to the rationale for early identification is the concept of DUP. The sooner the psychosis is identified the sooner the psychosis can be treated. A number of researchers have reported that the longer the psychosis goes untreated, the poorer the prognosis becomes (Loebel et al., 1992; McGorry et al., 1996). This finding has led them to argue that new services are required to reduce the length of time that people with psychosis remain undiagnosed and untreated. The GDG therefore decided to examine the evidence for EIS or any other intervention, including public awareness campaigns and GP awareness and education programmes, to improve detection of psychosis with consequent reduction in DUP (see Section 12.3.3).

#### *Definition and aim of intervention/ service system*

EIS is defined as a service approach with focus on the care and treatment of people in the early phase (usually up to 5 years) of psychosis or schizophrenia, sometimes including the prodromal phase of the disorder. The service may be provided by a team or a specialised element of a team, which has designated responsibility for at least two of the following functions:

- early identification and therapeutic engagement of people experiencing a first episode of psychosis
- provision of age-appropriate, evidence-based pharmacological and psychosocial interventions during and following a first episode psychosis
- education of the wider community to reduce obstacles to early engagement in treatment.

### *Clinical review protocol (early intervention services)*

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 132 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis, and where data were lacking, the available evidence was synthesised using narrative methods.

**Table 132: Clinical review protocol summary for the review of early intervention services**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of early intervention services compared with treatment as usual or another intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of early intervention services in the treatment of psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Early intervention services
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Adverse events <ul style="list-style-type: none"> <li>◦ Suicide</li> </ul> </li> <li>• Functioning disability</li> <li>• Service use <ul style="list-style-type: none"> <li>◦ Hospitalisation (admissions, days)</li> <li>◦ In contact with services</li> </ul> </li> <li>• Response /relapse</li> <li>• Symptoms of psychosis <ul style="list-style-type: none"> <li>◦ Total symptoms</li> <li>◦ Positive symptoms</li> <li>◦ Negative symptoms</li> </ul> </li> <li>• Employment and education <ul style="list-style-type: none"> <li>◦ Competitive employment</li> <li>◦ Occupation (any)</li> <li>◦ Attendance at school/college</li> </ul> </li> <li>• Duration of untreated psychosis</li> <li>• Carer satisfaction</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	SR/ RCT: 2002 to June 2013
<i>Study design</i>	RCT
<i>Review strategy</i>	<p><i>Time-points</i></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><i>Sub-analysis</i></p> <p>Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>



### *Studies considered<sup>41</sup>*

Four RCTs (N = 800) met the eligibility criteria for this review: CRAIG2004B (Craig et al., 2004), GRAWE2006 (Grawe et al., 2006), KUIPERS2004 (Kuipers et al., 2004) and PETERSEN2005 (Petersen et al., 2005). All were published in peer-reviewed journals between 2004 and 2006 and were conducted in the UK or Europe. Further information about both included and excluded studies can be found in Appendix 15a.

All four eligible trials included sufficient data to be included in statistical analysis and compared EIS with standard care. The proportion of individual with psychosis and schizophrenia ranged from 93 to 100%. The length of treatment ranged from 52 to 104 weeks and only two trials had medium-term follow-up data. Table 133 provides an overview of the included trials.

**Table 133: Study information table for trials included in the meta-analysis of EIS versus any alternative management strategy**

	<b>Early intervention services versus any alternative management strategy</b>
<i>Total no. of trials (k); participants (N)</i>	k = 4; N = 800
<i>Study ID(s)</i>	CRAIG2004B GRAWE2006 KUIPERS2004 PETERSEN2005
<i>Country</i>	Denmark (k = 1) Norway (k = 1) UK (k = 2)
<i>Year of publication</i>	2004- 2006
<i>Mean age of participants (range)</i>	26.5 years (25.4 to 27.8 years)
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	98.31 % (93.22 to 100%)
<i>Mean percentage of women (range)</i>	34.52 % (23.73 to 40.95%)
<i>Length of follow-up (range)</i>	52 to 104 weeks
<i>Intervention type</i>	Croydon Outreach and Assertive Support Team (k = 1) Integrated Treatment (k = 2) Specialised care group - assertive outreach for early psychosis (k = 1)
<i>Comparisons</i>	Standard treatment (k = 4)

### *Clinical evidence for the review of early intervention services verses any control*

Evidence from each important outcome and overall quality of evidence are presented in Table 134. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

---

<sup>41</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

**Table 134: Summary of findings table for EIS versus any alternative management strategy**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: EIS					
Comparison: Any alternative management strategy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	EIS			
Adverse events (suicide, actual and attempted) - end of treatment	14 per 1000	4 per 1000 (1 to 24)	RR 0.27 (0.05 to 1.65)	691 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Adverse events (suicide, actual and attempted) - >12 months' follow-up	15 per 1000	11 per 1000 (2 to 48)	RR 0.74 (0.17 to 3.28)	547 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation) - end of treatment	674 per 1000	593 per 1000 (533 to 661)	RR 0.88 (0.79 to 0.98)	733 (3 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation, number of bed days) - end of treatment	N/A	Mean service use (hospitalisation, number of bed days - end of treatment) in the intervention groups was 0.18 standard deviations lower (0.33 to 0.03 lower)	N/A	683 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation, number of admissions) - end of treatment	N/A	Mean service use (hospitalisation, number of admissions - end of treatment) in the intervention groups was 0.46 standard deviations lower (0.8 to 0.12 lower)	N/A	136 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation) - >12 months' follow-up	446 per 1000	415 per 1000 (348 to 495)	RR 0.93 (0.78 to 1.11)	646 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation, number of bed days) - >12 months' follow-up	N/A	Mean service use (hospitalisation, number of bed days, >12 months's follow-up) in the intervention groups was 0.08 standard deviations lower (0.24 lower to 0.07 higher)	N/A	646 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (hospitalisation, number of admissions) - >12 months' follow-up	N/A	Mean service use (hospitalisation, number of admissions, >12 months' follow-up) in the intervention groups was 0.2 standard deviations lower (0.6 lower to 0.2 higher)	N/A	99 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use (contact - not in contact with index team) - end of treatment	158 per 1000	96 per 1000 (63 to 147)	RR 0.61 (0.4 to 0.93)	580 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Service use	370 per	155 per 1000	RR 0.42	144	⊕⊕⊕⊖

<i>(contact - not in contact with mental health service) - end of treatment</i>	1000	(85 to 288)	(0.23 to 0.78)	(1 study)	Moderate <sup>1</sup>
<i>Global state (relapse, full or partial) - end of treatment</i>	519 per 1000	337 per 1000 (239 to 482)	RR 0.65 (0.46 to 0.93)	172 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Global state (remission, full or partial) - end of treatment</i>	318 per 1000	210 per 1000 (102 to 442)	RR 0.66 (0.32 to 1.39)	181 (2 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Global state - functioning / disability (GAF) - end of treatment</i>	N/A	Mean global state (functioning/ disability [GAF], end of treatment) in the intervention groups was 0.32 standard deviations lower (0.51 to 0.14 lower)	N/A	467 (2 studies)	⊕⊕⊕⊖ Very low <sup>1,2,3</sup>
<i>Global state - functioning / disability (GAF) - &gt;12 months' follow-up</i>	N/A	Mean global state (functioning/ disability [GAF], >12 months' follow-up) in the intervention groups was 0.07 standard deviations lower (0.29 lower to 0.16 higher)	N/A	301 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Total symptoms (PANSS) - end of treatment</i>	N/A	Mean total symptoms (panss), end of treatment in the intervention groups was 0.52 standard deviations lower (0.92 to 0.11 lower)	N/A	99 (1 study)	⊕⊕⊕⊖ Low <sup>1,3</sup>
<i>Positive symptoms (PANSS or SAPS) - end of treatment</i>	N/A	Mean positive symptoms (PANSS or SAPS, end of treatment) in the intervention groups was 0.21 standard deviations lower (0.39 to 0.03 lower)	N/A	468 (2 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
<i>Negative symptoms (PANSS or SANS) - end of treatment</i>	N/A	Mean negative symptoms (PANSS or SANS, end of treatment) in the intervention groups was 0.39 standard deviations lower (0.57 to 0.2 lower)	N/A	468 (2 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
<i>Positive symptoms (PANSS) - &gt;12 months' follow-up</i>	N/A	Mean positive symptoms (PANSS, >12 months' follow-up) in the intervention groups was 0.06 standard deviations higher (0.16 lower to 0.29 higher)	N/A	301 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Negative symptoms (PANSS) - &gt;12 months' follow-up</i>	N/A	Mean negative symptoms (PANSS, >12 months' follow-up) in the intervention groups was 0.07 standard deviations lower (0.29 lower to 0.16 higher)	N/A	301 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Employment and education - end of treatment</i>	347 per 1000	250 per 1000 (187 to 337)	RR 0.72 (0.54 to 0.97)	436 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Employment and education - &gt;12 months' follow-up</i>	544 per 1000	577 per 1000 (501 to 669)	RR 1.06 (0.92 to 1.23)	547 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<p>Note. CI = confidence interval; RR = risk ratio; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p>					

<sup>1</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>2</sup> Evidence of serious heterogeneity of study effect size. <sup>3</sup> Suspicion of publication bias.

Moderate quality evidence from up to three trials (N = 733) showed that EIS was more effective than standard care in reducing hospitalisation, number of admissions, number of bed days, and contact with services at the end of the intervention. Two trials with 467 participants presented very low quality evidence showing a significant positive effect of EIS on functioning at the end of the intervention.

Moderate to low quality evidence from up to two trials (N = 181) showed that EIS significantly reduce relapse and have a beneficial effect on psychosis symptoms (total, positive and negative) at the end of the intervention. There was, however, no effect on remission (k = 2; N = 181)

One trial (N = 436) presented moderate quality evidence that those receiving EIS were significantly more likely to be in work or employment at the end of the intervention.

However, at follow-up exceeding 12 months, there was no evidence of any positive effects on either critical or non-critical outcomes. No data were available for carer satisfaction or DUP.

### *Clinical evidence summary*

Overall, the evidence suggests that EIS is effective across all service, clinical and social outcomes at post-treatment. However, there is no evidence that these positive effects are maintained at follow-up 12 months after leaving EIS.

### *Health economics evidence*

The systematic literature search identified six economic studies that assessed EIS for individuals with psychosis and schizophrenia (Cocchi et al., 2011; Hastrup et al., 2013; McCrone et al., 2010; McCrone et al., 2009d; Mihalopoulos et al., 2009; Serretti et al., 2009). Both studies by McCrone and colleagues were undertaken in the UK (McCrone et al., 2010; McCrone et al., 2009d), two studies were undertaken in Italy (Cocchi et al., 2011; Serretti et al., 2009), one in Denmark (Hastrup et al., 2013) and one in Australia (Mihalopoulos et al., 2009). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

McCrone and colleagues (2010) evaluated the cost effectiveness of EIS compared with standard care, defined as care by CMHTs, for 144 service users with psychosis. This was an economic evaluation undertaken alongside an RCT (CRAIG2004B)

conducted in the UK. The time horizon of the analysis was 18 months and the perspective of public sector payer was adopted. The study estimated NHS costs (primary, secondary and community care) and criminal justice costs incurred by arrests, court appearances and probation. The authors stratified costs, which enabled them to estimate costs from the NHS and PSS perspectives too. The resource use estimates were based on the RCT, hospital administrative system records, prison service annual reports and accounts, and other published sources. The unit costs were obtained from national sources. The measure of outcome for the economic analysis was improvement in Manchester Short Assessment of Quality of Life (MANSA) scores and vocational recovery. Vocational recovery was defined as a return to or taking up full-time independent employment or full-time education. EIS resulted in greater improvement in MANSA scores ( $p = 0.025$ ) and also in a greater proportion of service users achieving vocational recovery, although the latter outcome was not statistically significant. The mean cost per person over 18 months was £11,685 for EIS and £14,062 for standard care in 2003/04 prices, and excluding criminal justice sector costs the mean cost per person over 18 months was £11,682 for EIS and £14,034 for standard care. In both cases the cost difference was not statistically significant possibly because of the low number of participants in the study. Also, it was found at willingness to pay of £0 for someone making a vocational recovery the probability of EIS being cost effective is 0.76, and at willingness to pay of £0 for a unit difference in MANSA scores the probability of EIS being cost effective is 0.92. Results suggest that EIS provides better outcome at no extra cost, and thus is a cost-effective intervention for people with psychosis in the UK. The analysis was judged by the GDG to be directly applicable to this guideline review and the NICE reference case. The estimate of relative treatment effect was obtained from a single small RCT and some of the resource use estimates were derived from local sources, which may limit the generalisability of the findings. Also, the time frame of the analysis was under 2 years, which may not be sufficiently long enough to reflect all important differences in costs and clinical outcomes. Moreover, QALYs were not used, however in this case it was not a problem since the intervention was found to be dominant. Overall, given the limited availability of data this was a well-conducted study and was judged by the GDG to have only minor methodological limitations.

Another study by McCrone and colleagues (2009d) was a model-based cost analysis that compared EIS with standard care in service users with first episode psychosis. The authors stated that they were performing a cost-minimisation analysis, however this assumption was solely based on the authors' views that intervening early was unlikely to result in poorer health. Consequently, this was treated as a cost-analysis in the guideline systematic review. Standard care was defined as any specialised mental health provision that did not offer any intervention specifically intended to treat first episode psychosis. The analysis considered costs from the NHS and PSS perspectives and included costs associated with inpatient, outpatient and community care. Costs were reported for years one and three. It was found that EIS resulted in cost savings of £4,972 and £14,248 in years one and three, respectively (in 2006/07 prices). Overall the analysis was judged by the GDG to be directly

applicable to this guideline review and the NICE reference case. Probabilities of admissions, readmissions and transitioning along care pathways were derived from a single RCT, local audit data, routine data collected by the Department of Health and expert judgement; costs for the model were largely obtained from a single RCT, PSSRU and authors' assumptions; the definition of standard care was based on authors' assumptions and practice described in a single RCT. Nevertheless, the authors conducted a range of deterministic sensitivity analyses that indicated that when varying the model's assumptions EIS costs never exceed the costs of standard care. Also, probabilistic sensitivity analysis indicated that there is a far greater likelihood of cost savings associated with EIS and the results were fairly robust. The analysis was judged by the GDG to have only minor methodological limitations.

Two further studies (Cocchi et al., 2011; Serretti et al., 2009) conducted in Italy reported similar findings. Cocchi and colleagues (2011) evaluated the cost effectiveness of EIS compared with standard care (defined as any specialised mental health provision not offering interventions specifically aimed at treating the first episode psychosis). The analysis was based on two small cohort studies each with (n = 23) service users with schizophrenia and related disorders. The analysis was performed from the Italian NHS perspective and the primary outcome measure was improvement on the Health of the Nation Outcome Scale (HoNOS). Over the 5 years EIS resulted in cost savings and greater improvement on the HoNOS scale. However, the type of treatment did not produce a significant effect on HoNOS scores at the 5-year follow-up. The study was judged by the GDG to be partially applicable to this guideline review and the NICE reference case. The findings are based on a very small sample; and also cohort studies are prone to errors and bias. Moreover, the unit costs of resource use were obtained from previous publications and other local sources. Consequently, this analysis was judged by the GDG to have potentially serious methodological limitations. Similarly, a model-based cost analysis from the perspective of the Italian NHS by Serretti and colleagues (2009) compared EIS with standard care in service users with schizophrenia. Standard care was defined as care provided by community mental health centres. It was concluded that in year one EIS was a cost-saving strategy. The analysis was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case. In the analysis the efficacy data were based on various published sources. The resource utilisation associated with the standard care was derived from a retrospective prevalence-based multi-centre study and the resource utilisation associated with the intervention was based on various published sources and authors' assumptions. Moreover the source of unit costs was unclear. For these reasons the analysis was judged by the GDG to have potentially serious methodological limitations.

A recent cost-effectiveness analysis by Hastrup and colleagues (2013) based on a large RCT (PETERSEN2005) (n = 547) compared EIS with care provided by community mental health centres in service users with schizophrenia spectrum disorders from the public sector payer perspective. The mean total costs over 5 years were lower in the intervention group and the mean GAF score was higher, although

the differences were not statistically significant. Moreover, the probability EIS is cost effective at willingness to pay of €0 for an extra point increase on the GAF scale was estimated to be 0.953 and at willingness to pay of €2,000 it was 0.97. The study was judged by the GDG to be partially applicable to this guideline review and the NICE reference case. In the analysis, the estimate of relative treatment effect was derived from a single RCT based in Denmark; the estimates of the resource use were derived from the same RCT and national registers; the unit cost estimates were from national and local sources. The study may have limited generalisability to the NHS, but overall the analysis was well conducted and was judged by the GDG to have only minor methodological limitations.

Similarly in Australia, Mihalopoulos and colleagues (2009) compared EIS with standard care in service users with schizophrenia, bipolar disorder, depression with psychotic features, delusional disorder and psychosis. Standard care was defined as local inpatient and community-based care and the analysis was based on a small cohort study with historical controls (n = 65). According to the analysis, EIS resulted in significant annual cost savings from the public mental health service sector perspective and there were significantly greater improvements on the Brief Psychiatric Rating Scale (BPRS) during the long-term follow-up of up to 7.2 years. As a result EIS was identified as a dominant strategy. This study was judged by the GDG to be partially applicable to this guideline review and the NICE reference case. The findings are based on a small cohort study with historical controls. Also, the resource use estimates were derived from a variety of sources including clinical records, cohort study and other various nationwide sources and as a result findings may have limited generalisability to the NHS. For these reasons the analysis was judged by the GDG to have potentially serious methodological limitations.

### **12.3.3 Early detection programmes to reduce the duration of untreated psychosis**

#### ***Introduction***

Long DUP is associated with poor clinical outcomes for people with first episode psychosis (Marshall et al., 2005; Perkins et al., 2005) and poorer quality of life at first contact with services (Marshall et al., 2005). DUP of months or even years is common (Marshall et al., 2005; Norman et al., 2006); delays initiating help-seeking and slow health service response contribute to treatment delay (Malla et al., 2006). In UK government guidance (Care Services Improvement Partnership, 2005; Department of Health, 2001), and internationally (Bertolote & McGorry, 2005), professionals within EIS have been directed to ensure prompt access to treatment for people with first episode psychosis. Effective means to achieve this, however, are unclear.

#### ***Definition and aim of intervention/service system***

This review assesses the evidence for the effectiveness of early detection programmes, that is, any programme designed to reduce DUP and facilitate prompt access to treatment for people with first episode psychosis.

### *Clinical review protocol (early detection programmes)*

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 135 (the full review protocols and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 135: Clinical review protocol summary for the review of early detection programmes to reduce DUP**

<b>Component</b>	<b>Description</b>
<i>Review question(s)</i>	Are early detection programmes effective in reducing duration of untreated psychosis and improving pathways to care for people with first episode psychosis?
<i>Population</i>	People with first episode psychosis
<i>Intervention(s)</i>	<p><i>Included</i></p> <p>Early detection programmes designed to facilitate access to treatment for first episode psychosis (involving service reconfiguration and/or public education campaigns targeting health professionals, other community professionals, potential service users, or the public).</p> <p><i>Excluded</i></p> <p>This review was limited to early detection programmes designed to facilitate access to services and reduce duration of untreated psychosis for people with first episode psychosis. Psychosis prevention services for people with prodromal symptoms or at ultra-high risk of psychosis were excluded</p>
<i>Comparison</i>	Treatment as usual without early detection programme
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• DUP</li> <li>• Number of people with first episode psychosis accepted to services</li> <li>• Health status, experience of care, or referral pathways of people with first episode psychosis at admission to services.</li> <li>• Referral behaviours of groups targeted in early detection programmes</li> </ul>
<i>Electronic databases</i>	<p>CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process</p> <p>Topic specific: CINAHL, PsycINFO, IBSS</p>
<i>Date searched</i>	2009 to June 2013 (update search)
<i>Study design</i>	<p><i>Included studies</i></p> <p>Any study providing quantitative comparison of an early detection programme and treatment as usual (in EIS or other mental health services) – that is, cluster randomised trials, two-group non-randomised comparison studies, pre-post comparison studies.</p> <p><i>Review strategy</i></p> <p>Narrative synthesis of the included studies.</p>

### *Studies considered*

The GDG selected an existing systematic review (Lloyd-Evans et al., 2011) as the basis for this section of the guideline, with a new search conducted to update the



existing review. The review by Lloyd-Evans and colleagues included 11 studies evaluating eight early detection programmes: LEOCAT<sup>42</sup> (Power et al., 2007), REDIRECT<sup>43</sup> (Lester et al., 2009b), DETECT<sup>44</sup> (Renwick et al., 2008), EPPIC1<sup>45</sup> (McGorry et al., 1996; Yung et al., 2003), TIPS<sup>46</sup> (Joa et al., 2008; Johannessen et al., 2001; Melle et al., 2004), EPPIC2<sup>47</sup> (Krstev et al., 2004), EPIP<sup>48</sup> (Chong et al., 2005), PEPP<sup>49</sup> (Malla et al., 2005).

Two studies of two additional initiatives were identified by the guideline search: EASY<sup>50</sup> (Chen et al., 2011) and an untitled public education campaign (Yoshii et al., 2011).

In total, 13 studies of 10 early detection programmes met the eligibility criteria for this review. All were published in peer-reviewed journals between 1996 and 2012. Further information about both included and excluded studies can be found in Lloyd-Evans et al. (2011).

Of the 10 early detection programmes, five evaluated multi-focus public awareness campaigns (TIPS, EPPIC2, EPIP, PEPP, EASY), three evaluated GP education programmes (LEOCAT, REDIRECT, DETECT), one evaluated a specialist EIS (EPPIC1) and one evaluated an online education campaign for parents of high school students (Untitled; Yoshii et al., 2011). For a full description of the characteristics of the included and excluded studies, see Lloyd-Evans et al. (2011).

The studies included in this review employed varied study designs. Therefore, a meta-analysis of the included studies was not conducted and a narrative summary of the findings is provided below.

### *Clinical evidence for the review of early detection programmes verses any control*

Significant reductions in mean or median DUP were reported for two out of five multi-focus public awareness campaigns. The Norwegian TIPS programme reported a reduction in median DUP from 16 to 5 weeks. The Singapore EPIP programme reported reductions in mean DUP from 32 to 13 months and in median DUP from 12 to 4 months. Three multi-focus campaigns made no significant difference to DUP. Two GP education campaigns and one introduction of an EIS led to no significant reduction in DUP.

---

<sup>42</sup> Lambeth Early Onset Crisis Assessment Team.

<sup>43</sup> BiRmtingham Early Detection In untREated psyChosis Trial.

<sup>44</sup> Dublin East Treatment and Early Care Team.

<sup>45</sup> Early Psychosis Prevention and Intervention Centre (1).

<sup>46</sup> Treatment and Intervention in Psychosis.

<sup>47</sup> Early Psychosis Prevention and Intervention Centre (2).

<sup>48</sup> Early Psychosis Intervention Program.

<sup>49</sup> Prevention and Early Intervention in Psychosis Program.

<sup>50</sup> Early Assessment Service for Young People with Psychosis program.

No clear effect was observed in the number of people with first episode psychosis referred to services following an early detection programme. Studies of multi-focus public awareness programmes and a GP education programme reported no significant change in number of new referrals accepted.

Four studies evaluated pathways to care. For one GP education programme, and one multi-focus public awareness programme, no significant difference with comparison groups was found in the source of the referral. However, one UK GP education programme found that patients from GP practices receiving the intervention were less likely to have contact with A&E departments in their pathway to mental health services. One multi-focus public awareness programme reported that during the campaign, people were significantly more likely to self-refer and less likely to be referred via the police than in the historical comparison period.

People from areas exposed to a multi-focus public awareness programme were found to have significantly less severe symptoms at first contact with services than those from comparison groups in the Norwegian TIPS Project and the Australian EPPIC programme. No significant difference in service users' symptom severity was found between intervention and comparison areas in the Canadian multi-focus public awareness programme. The REDIRECT study found no significant difference in symptom severity or premorbid adjustment between people admitted from areas included in a GP education campaign and comparison areas.

All three studies of GP education initiatives included in this review found some evidence of impact of the initiative on GPs' referral behaviour. DETECT and LEOCAT reported that GPs receiving education were more likely to refer people with first episode psychosis to mental health services than GPs in a comparison group. REDIRECT found that the time from service users' first contact with GPs to referral to EIS was significantly shorter in duration for people from GP surgeries in the intervention arm of the study. One study reported a significant increase in help-seeking behaviour in parents of junior and high school students following a web-based educational programme. No change in DUP or number of referrals resulting from changes in referrers' behaviour was demonstrated in any of these studies.

### *Clinical evidence summary*

GP education programmes and setting up specialist EIS by themselves had no impact on DUP. Overall, there is no compelling evidence that any types of early detection programme are effective in reducing DUP or increasing numbers of people with first episode psychosis presenting to services.

## **12.3.4 Community mental health teams**

### *Introduction*

One of the earliest service developments in community-based care was that of the community mental health team (CMHT) (Merson et al., 1992). CMHTs are multidisciplinary teams, comprising all the main professions involved in mental

health, including psychiatry, psychology, nursing, occupational therapy and social work. Having developed in a relatively pragmatic way, CMHTs became the mainstay of community-based mental health work in most developed countries (Bennett & Freeman, 1991; Bouras et al., 1986), as well as in many others (Isaac, 1996; Pierides, 1994; Slade et al., 1995). Nevertheless, concerns about CMHTs have been raised, particularly regarding the incidence of violence (Coid, 1994), the quality of day-to-day life for people with serious mental illness and their carers, and the impact on society (Dowell & Ciarlo, 1983). In addition, CMHTs have changed very considerably over time in terms of how they are configured, what they provide, their role and their integration within the wider systems of mental health and social care.

### *Definition and aim of intervention/service system*

The GDG judged that the definitions used for the first (2002) guideline for CMHTs and the comparator standard care or usual care were still applicable:

- **\*\*2002\*\***CMHT care was management of care from a multidisciplinary, community-based team (that is, more than a single person designated to work within a team)
- standard care or usual care must be stated to be the normal care in the area concerned, non-team community care, outpatient care, admission to hospital (where acutely ill people were diverted from admission and allocated to CMHT or inpatient care) or day hospital care.**\*\*2002\*\***

The review specifically focused upon CMHT management, and therefore excluded studies that involved any additional method of management in the CMHT.

### *Clinical review protocol (community mental health teams)*

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline can be found in Table 136 (the full review protocols and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 136: Clinical review protocol summary for the review of community mental health teams**

<b>Component</b>	<b>Description</b>
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of community mental health teams compared with treatment as usual or another intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of community mental health teams in the treatment of psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Community mental health teams
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Service use <ul style="list-style-type: none"> <li>○ Hospitalisation: mean number of days per month in hospital</li> <li>○ Not remaining in contact with psychiatric services</li> <li>○ Use of services outside of mental health provision (that is, emergency services)</li> </ul> </li> <li>• Social functioning</li> <li>• Employment status</li> <li>• Accommodation status</li> <li>• Quality of life</li> <li>• Mental state <ul style="list-style-type: none"> <li>○ General symptoms</li> <li>○ Total symptoms</li> <li>○ Positive symptoms</li> <li>○ Negative symptoms</li> </ul> </li> <li>• Satisfaction <ul style="list-style-type: none"> <li>○ Participant satisfaction</li> <li>○ Carer satisfaction</li> </ul> </li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	SR/RCT: 2002 to June 2013
<i>Study design</i>	RCT
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings</p> <p><b>Sub-analysis</b> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>

## Studies considered<sup>51</sup>

Three RCTs (N = 344) met the eligibility criteria for this review: GATER1997 (Gater et al., 1997), MERSON1992 (Merson et al., 1992), TYRER1998 (Tyrer et al., 1998). The included trials were published between 1992 and 1998. All were conducted in the UK. Further information about both included and excluded studies can be found in Appendix 15a.

Of the included trials, two involved a comparison of a CMHT with standard hospital treatment and one compared CMHTs with traditional psychiatric services. The proportion of individuals with psychosis and schizophrenia ranged from 38 to 100%. The length of follow-up ranged from 12 to 104 weeks. Table 137 provides an overview of the included trials.

This review did not combine data from the three included trials in statistical analysis. MERSON1992 and TYRER1998 could not be combined in meta-analysis because in TYRER1998 the service was seeing discharged psychiatric patients who, presumably, were more likely to be readmitted to hospital and be more severely ill than those in the other two trials. This would appear to be confirmed by the very high admission rates in TYRER1998. Further, GATER1997 could not be included in meta-analysis due to the possibility of unit of analysis error as the study used a cluster randomisation design and there is no indication of accounting for inter-class-correlation. Further information about the cluster design was requested from the authors. The findings from all three included trials are thus described narratively.

**Table 137: Study information table for trials of community mental health teams versus standard care**

	Community mental health teams versus standard care
Total no. of trials (k); participants (N)	k = 3; N = 344
Study ID(s)	GATER1997 MERSON1992 TYRER1998
Country	UK (k = 3)
Year of publication	1992 to 1998
Mean age of participants (range)	38.07 years (32 to 44.13 years) <sup>1</sup>
Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)	64.49% (38% to 100%)
Mean gender % women (range)	50.79% (41.57 to 60%) <sup>1</sup>
Length of follow-up (range)	12 to 104 weeks
Intervention type	Community focused multidisciplinary team (EIS) (k = 1) Community team (k = 2)
Comparisons	Standard hospital treatment (k = 2) Traditional psychiatric service (k = 1)
Note. <sup>1</sup> TYRER1998 did not report data.	

<sup>51</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

### *Clinical evidence for community mental health teams*

Two trials (MERSON1992, TYRER1998) reported that CMHTs did not have a significant benefit over standard care on the number of participants admitted to hospital, use of A&E services, contact with primary care or contact with social care at both short- and medium-term follow-up. Additionally, one study (GATER1997) did not find any difference between CMHTs and standard care in the number of participants in contact with mental health services at medium-term follow-up. There was no significant difference between groups in psychological health and social functioning (MERSON1992). No study reported data for quality of life, mental state or satisfaction.

### *Clinical evidence summary*

Despite the fact that CMHTs became the mainstay of community mental healthcare, there is surprisingly little evidence to show that they are an effective way of organising services. Moreover, the trials of CMHTs included here are very unlikely to reflect the enormous diversity of community mental healthcare today, most of which has absorbed the practices used by more recently developed services such as ACT, outreach services, ICM and even early intervention. As such, evidence presented here for or against the effectiveness of CMHTs in the management of psychosis and schizophrenia is insufficient to make any evidence-based recommendations.

### *Health economics evidence*

The systematic search of the economic literature undertaken for the 2014 guideline, identified only one eligible study on CMHTs for individuals with psychosis and schizophrenia (McCrone et al., 2010). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

McCrone and colleagues (2010) evaluated the cost effectiveness of CMHTs compared with EIS for 144 service users with psychosis. This was an economic evaluation based on an RCT (CRAIG2004B) conducted in the UK. The time horizon of the analysis was 18 months and the public sector payer perspective was adopted, although the authors reported stratified costs and this allowed estimation of costs from the NHS and PSS perspective. CMHTs resulted in lower quality of life scores on the MANSA scale ( $p = 0.025$ ) and fewer service users achieving vocational recovery ( $p = ns$ ) compared with EIS. The mean cost per person over 18 months was £14,062 for CMHTs and £11,685 for EIS in 2003/04 prices, and excluding criminal justice sector costs the mean cost per person over 18 months was £14,034 for CMHTs and £11,682 for EIS. In both cases the cost difference was not statistically significant possibly because of the low number of participants in the study. Results suggest that

CMHTs lead to worse health outcomes and potentially higher healthcare costs. Consequently, EIS is a preferred treatment strategy compared with CMHTs. For more details and discussion of the findings see Section 12.3.2.

### **12.3.5 Intensive case management**

#### *Introduction*

In existence for at least 40 years, assertive community treatment (ACT) and intensive case management (ICM) are approaches to caring for people with severe mental illness (typically schizophrenia or bipolar disorder) who require intensive community support and have frequent admissions. Although in the 2002 and 2009 guidelines, these interventions were treated as discrete approaches, for the purposes of the 2014 guideline they are considered together as they are similar: both use an assertive outreach model of care (that is, persisting with service users who are not engaging) and both specify that practitioners should carry limited caseloads. The main difference is that ACT requires team members to share responsibility for the teams' clients, whereas ICM puts greater emphasis on the primacy of the individual case manager. A further difference is that ACT has been more precisely defined than ICM, for example, in terms of requirements for daily team meetings and for certain professionals to be included in the team, but has also become less distinct from it, as case managers have increasingly adopted a team-based approach and other elements of the ACT model (Marshall, 2008).

Early Cochrane reviews in this area attempted to draw a categorical distinction between trials of ACT and ICM on the basis of the label that the trialists had given to the intervention (Marshall et al., 2000; Marshall & Lockwood, 2000). ACT and ICM trials were then analysed in separate meta-analyses. However, it became increasingly obvious that such labels bore little relationship to actual practice in the trial. Later reviews, including Cochrane reviews (Burns et al., 2007b; Dieterich et al., 2010), therefore abandoned this blunt categorical approach and instead obtained ratings of fidelity to the ACT model for ACT and ICM interventions, based on data obtained directly from trialists. Trials of ACT and ICM were then combined in the same meta-analysis and fidelity to the ACT model used as an explanatory covariate whenever outcomes showed significant heterogeneity. The GDG accepts this approach, which has a sounder empirical basis than earlier reviews and takes account of the complexity of the changes in community care over time and across countries.

The question of control conditions is also problematic because standard care has been evolving from a clinic-based approach to a team-based community model, incorporating strong elements of case management (such as the UK care programme approach [CPA]). In accordance with the most recent Cochrane review (Dieterich et al., 2010), the GDG has distinguished two types of control: standard care, which refers to a clinic-based approach to follow-up; and non-intensive case management, which refers to a case management approach to follow-up, where the caseload size is large.

### *Definition and aim of intervention/ service system*

The definitions used in this review for ICM, non-intensive case management (non-ICM) and standard care used in the Cochrane review (Dieterich et al., 2010) and adopted for this guideline, are as follows:

*ICM:*

Where the majority of people received a package of care shaped either on:

- the ACT model, being based on the Training in Community Living project and the Program of Assertive Community Treatment (PACT) (Stein & Test, 1980), or
- the assertive outreach model (Witheridge, 1991; Witheridge et al., 1982), that is, a multidisciplinary team-based approach, practicing 'assertive outreach' and providing 24 hours' emergency cover (McGrew & Bond, 1995), or
- the case management model (Intagliata, 1982) however it was described in the trial
- report with a caseload up to and including 20 people.

*Non-ICM:* Where the majority of people received the same package of care as described for ICM (above) but with a caseload of over 20 people.

*Standard care:* Where the majority of people received a community or outpatient model of care not specifically shaped on either the model of ACT and case management, and not working within a specific designated named package or approach to care.

### *Clinical review protocol (intensive case management)*

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 138 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.



**Table 138: Clinical review protocol summary for the review of intensive case management**

<b>Component</b>	<b>Description</b>
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of intensive case management compared with non-intensive case management or standard treatment?
<i>Objectives</i>	To evaluate the clinical effectiveness of intensive case management in the treatment of psychosis and schizophrenia
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Intensive case management
<i>Comparison</i>	i) Non-intensive case management ii) Standard care
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Service use <ul style="list-style-type: none"> <li>○ Hospitalisation: mean number of days per month in hospital</li> <li>○ Not remaining in contact with psychiatric services</li> <li>○ Use of services outside of mental health provision (that is, emergency services)</li> </ul> </li> <li>• Functional disability</li> <li>• Quality of life</li> <li>• Satisfaction <ul style="list-style-type: none"> <li>○ Participant satisfaction</li> <li>○ Carer satisfaction</li> </ul> </li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO,
<i>Date searched</i>	SR/RCT: 2002 to June 2013
<i>Study design</i>	RCTs
<i>Review strategy</i>	<p>Time-points</p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p>Sub-analysis</p> <p>Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK only studies.</p>

## *Studies considered*<sup>52</sup>

The GDG selected an existing Cochrane review (Dieterich et al., 2010) as the basis for this section of the guideline, with a new search conducted to update it. The Cochrane review included 38 RCTs (N = 7,328) that met eligibility criteria for this guideline: Aberg-Wistedt-Sweden (Aberg-Wistedt et al., 1995), Audini-UK (Audini et al., 1994), Bjorkman-Sweden (Bjorkman et al., 2002), Bond-Chicago1 (Bond et al., 1990), Bond-Indiana1 (Bond et al., 1988), Bush-Georgia (Bush et al., 1990), Chandler-California1 (Chandler et al., 1996), Curtis-New York (Curtis et al., 1992), Drake-NHamp (Drake & McHugo, 1998), Essock-Connecticut1 (Essock & Kontos, 1995), Essock-Connecticut2 (Essock et al., 2006), Ford-UK (Ford et al., 1995), Hampton-Illinois (Hampton et al., 1992), Harrison-Read-UK (Harrison-Read et al., 2002), Herinckx-Oregon (Herinckx et al., 1997), Holloway-UK (Holloway & Carson, 1998), Jerrell-SCarolina1 (Jerrell, 1995), Johnston-Australia (Johnston et al., 1998), Lehman-Maryland1 (Lehman et al., 1997), Macias-Utah (Macias et al., 1994), Marshall-UK (Marshall et al., 1995), McDonel-Indiana (McDonel et al., 1997), Morse-Missouri1 (Morse et al., 1992), Morse-Missouri3 (Morse et al., 2006), Muijen-UK2 (McCrone et al., 1994), Muller-Clemm-Canada (Muller-Clemm, 1996), Okpaku-Tennessee (Okpaku & Anderson, 1997), OPUS-Denmark (Jørgensen et al., 2000), Pique-California (Pique, 1999), Quinlivan-California (Quinlivan et al., 1995), REACT-UK (Killaspy et al., 2006), Rosenheck-USA (Rosenheck et al., 1993), Salkever-SCarolina (Salkever et al., 1999), Shern-USA1 (Shern et al., 2000), Solomon-Pennsylvania (Solomon et al., 1994), Sytema-Netherlands (Sytema et al., 2007), Test-Wisconsin (Test et al., 1991), UK-700-UK (Burns et al., 1999). No additional RCTs were identified by the guideline search. All 38 studies were published in peer-reviewed journals between 1988 and 2007. Further information about included studies can be found in Appendix 15a. Further information about excluded studies can be found in Dieterich et al. (2010).

All included trials included sufficient data to be included in the meta-analysis. Of the 38 included trials, 26 trials compared ICM with standard care, 11 trials compared ICM with non-ICM and one study evaluated both comparisons. Table 139 provides an overview of the trials included in each comparison.

Two sub-analyses were conducted. The first used 13 trials with a large proportion ( $\geq 75\%$ ) of participants with a primary diagnosis of psychosis or schizophrenia. The second analyses included UK only based trials ( $k = 8$ ).

---

<sup>52</sup>Changes have not been made to the study ID format used in the Cochrane review utilised in this section.

**Table 139: Study information table for trials comparing ICM with standard care and ICM with non-ICM**

	<b>ICM versus standard care</b>	<b>ICM versus non-ICM</b>
<i>Total no. of trials (k); participants (N)</i>	k = 27; N = 4865	k = 12; N = 2560
<i>Study ID(s)</i>	Aberg-Wistedt-Sweden Audini-UK Bjorkman- Sweden Bond-Chicago1 Bond-Indiana1 Chandler-California1 Curtis-New York Ford-UK Hampton-Illinois Herinckx-Oregon Holloway-UK Jerrell-SCarolina1 Lehman-Maryland1 Macias-Utah Marshall-UK Morse-Missouri1 Morse-Missouri3 Muijen-UK2 Muller-Clemm-Canada OPUS-Denmark Pique-California Quinlivan-California Rosenheck-USA Shern-USA1 Solomon-Pennsylvania Sytema-Netherlands Test-Wisconsin	Bush-Georgia Drake-NHamp Essock-Connecticut1 Essock-Connecticut2 Harrison-Read-UK Johnston-Australia McDonel-Indiana Okpaku-Tennessee Quinlivan-California REACT-UK Salkever- SCarolina UK-700-UK
<i>Country</i>	Canada (k = 1) Denmark (k = 1) Netherlands (k = 1)	Australia (k = 1) UK (k = 3) USA (k = 8)

	Sweden (k = 2) UK (k = 5) USA (k = 17)	
<i>Year of publication</i>	1988 to 2007	1990 to 2006
<i>Mean age of participants (range)</i>	37.14 years (23 to 48 years) <sup>1</sup>	37.81 years (34 to 41.54 years) <sup>4</sup>
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	67.36% (30 to 100%) <sup>2</sup>	69.67% (23 to 88.89%)
<i>Mean gender % women (range)</i>	37.34% (0 to 59%) <sup>3</sup>	42.24% (25.6 to 57%)
<i>Length of follow-up (range)</i>	26 to 156 weeks	17 to 156 weeks
<i>Intervention type</i>	<p>ACT according to the Stein &amp; Test model (k = 15)</p> <p>ACT according to the Stein &amp; Test model staffed by consumers (k = 1)</p> <p>Case management approach provided by a community support team (k = 1)</p> <p>Case management based on the Strength Model (k = 2)</p> <p>Case management from team of social service case managers (k = 1)</p> <p>Choices programme (k = 1)</p> <p>Clinical case management based on ACT principles (Training in Community Living programme) (k = 2)</p> <p>ICM according to the 'Clinical Case Management Model' developed by Kanter (k = 1)</p> <p>ICM (not following any specific model of case management) (k = 1)</p> <p>ICM provided by an individual forensic case manager (k = 1)</p> <p>Intensive broker case management Model (k = 1)</p> <p>Intensive outreach case management (k = 1)</p> <p>Modified ACT (k = 1)</p> <p>Programme assertive community treatment (PACT) adaptation (k = 1)</p>	<p>Employment oriented case management (k = 1)</p> <p>ACT according to the Stein &amp; Test model (k = 3)</p> <p>Clinical case management according to the Stein &amp; Test model (Training in Community Living programme) (k = 2)</p> <p>Generalist model of ACT (k = 1)</p> <p>Enhanced community management based on ACT principles (Stein model) (k = 1)</p> <p>ACT teams with special training in substance misuse treatment (k = 1)</p> <p>ACT (McGrew &amp; Bond, 1995) (k = 1)</p> <p>PACT (k = 1)</p> <p>ICM (k = 1)</p>
<i>Comparisons</i>	<p>Psychosocial rehabilitation programme (k = 1)</p> <p>Routine care from psychiatric services (k = 6)</p> <p>Routine outpatient care (k = 2)</p> <p>Services as usual (k = 6)</p>	<p>Standard case management from a community mental health centre (k = 2)</p> <p>Non-ICM provided by the mental health services (k = 1)</p>

	<p>Services offered by the public mental health system (k=1)</p> <p>Standard care provided by CMHTs (k = 6)</p> <p>Standard care provided by community psychiatric nursing service (k = 2)</p> <p>Standard care provided from a variety of agencies (k = 1)</p> <p>Standard care provided from a drop-in centre (k = 2)</p>	<p>Generalist model, but providing case managers mobile (k = 1)</p> <p>Standard care providing case management at a lower level of intensity and rehabilitation services (k = 1)</p> <p>Traditional case management programme (k = 1)</p> <p>Clinical Case Management (k = 2)</p> <p>Locality-based community psychiatric services (k = 1)</p> <p>Non-ICM, incorporating most of the ACT principles, but providing less individual service for substance misuse (k = 1)</p> <p>Services offered by CMHT (according to the CPA) (k = 1)</p> <p>Case management (k = 1)</p>
<p><i>Note.</i> CMHT = community mental health team; ICM = intensive case management; SC = Standard care; non-ICM = non-intensive case management; CPA = care programme approach.</p> <p><sup>1</sup>Chandler-California<sup>1</sup>, Jerrell-SCarolina<sup>1</sup>, Macias-Utah, Muller-Clemm-Canada and Pique-California did not report data.</p> <p><sup>2</sup>Pique-California and Shern-USA<sup>1</sup> did not report data.</p> <p><sup>3</sup>Pique-California did not report data.</p> <p><sup>4</sup>Bush-Georgia<sup>1</sup> did not report data.</p>		

## *Clinical evidence for intensive case management*

### **Intensive case management versus standard care**

Evidence from each important outcome and overall quality of evidence are presented in Table 140. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Low quality evidence from 24 trials (N = 3,595) showed that ICM was more effective than standard care in reducing the average number of days in hospital per month, and keeping in contact with psychiatric services at medium- and long-term follow-up.

Low quality evidence from a single study (N = 125) found a positive effect of ICM on self-reported quality of life at short-term follow-up. However, this effect was not found at either medium- or long-term follow-up.

Moderate quality evidence from up to five trials (N = 818) showed that ICM was more effective than standard care in improving global functioning at both short- and long-term but not medium-term follow-up.

Very low to high quality evidence from up to two trials (N = 500) showed that participants receiving ICM were more satisfied with the intervention than those receiving standard care at all follow-up points.

No studies reported usable data on carer satisfaction.

#### *Sub-analysis (psychosis and schizophrenia only)*

The sub-analysis of trials with a sample of  $\geq 75\%$  people with psychosis and schizophrenia upheld the positive effect found in the main analysis of ICM on both the average number of days in hospital and self-reported quality of life. Consistency with the main analysis was also found for remaining in contact with psychiatric services at medium-term follow-up. However, unlike the main analysis, no significant difference for remaining in contact with psychiatric services was reported at long-term follow-up. Moreover, no difference between groups was observed for satisfaction with services at short-term follow-up or for functioning at any follow-up point. See Appendix 16 for the related forest plots.

#### *Sub-analysis (UK only)*

Unlike the main analysis, the UK only sub-analysis found no significant effect of ICM in reducing the average number of days hospitalised when compared with standard care ( $k = 5$ ;  $N = 369$ ). The sub-analysis findings did not differ from the main analysis in finding a benefit of ICM on both remaining in contact with psychiatric services and satisfaction at short-term follow-up, and no effect of ICM on quality of life. However, unlike the main analysis, participant satisfaction at long-term follow-

was not significantly different between ICM and standard care. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 140: Summary of findings tables for ICM compared with standard care**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: ICM					
Comparison: Standard care					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	ICM			
Service use (average number of days in hospital per month) - by about 24 months	N/A	Mean service use (average number of days in hospital per month - by about 24 months) in the intervention groups was 0.86 lower (1.37 to 0.34 lower)	N/A	3,595 (24 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Not remaining in contact with psychiatric services - short term follow-up	Study population		RR 0.54 (0.28 to 1.05)	95 (1 study)	⊕⊕⊕⊖ Very low <sup>3,4</sup>
	383 per 1000	207 per 1000 (107 to 402)			
Not remaining in contact with psychiatric services - medium term follow-up	Study population		RR 0.51 (0.36 to 0.71)	1,063 (3 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
	246 per 1000	126 per 1000 (89 to 175)			
Not remaining in contact with psychiatric services - long term follow-up	Study population		RR 0.27 (0.11 to 0.66)	475 (5 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	303 per 1000	82 per 1000 (33 to 200)			
Not remaining in contact with psychiatric services - total	Study population		RR 0.43 (0.3 to 0.61)	1,633 (9 studies)	⊕⊕⊕⊖ Very low <sup>2,5</sup>
	270 per 1000	116 per 1000 (81 to 165)			
Quality of life - by short term follow-up	N/A	Mean quality of life (by short term follow-up) in the intervention groups was 0.53 lower (0.97 to 0.09 lower)	N/A	125 (1 study)	⊕⊕⊕⊖ Low <sup>4,6</sup>
Quality of life - by medium term follow-up (LQoLP)	N/A	Mean quality of life (by medium term follow-up - LQoLP) in the intervention groups was 0.09 lower (0.78 lower to 0.6 higher)	N/A	52 (1 study)	⊕⊕⊕⊖ Low <sup>4,6</sup>
Quality of life - by medium term follow-up (MANSA)	N/A	Mean quality of life (by medium term follow-up-MANSA) in the intervention groups was 0.2 lower (0.69 lower to 0.29 higher)	N/A	81 (1 study)	⊕⊕⊕⊖ Moderate <sup>4</sup>

Quality of life - by long term follow-up (LQoLP)	N/A	Mean quality of life (by long term follow-up - LQoLP) in the intervention groups was 0.23 higher (0.08 lower to 0.55 higher)	N/A	113 (2 studies)	⊕⊕⊕⊖ Low <sup>1,4</sup>
Quality of Life - by long term follow-up (QOLI)	N/A	Mean quality of life (by long term follow-up - QOLI) in the intervention groups was 0.09 lower (0.42 lower to 0.24 higher)	N/A	132 (2 studies)	⊕⊕⊕⊖ Low <sup>1,4</sup>
Participant satisfaction - by short term follow-up	N/A	Mean participant satisfaction (by short term follow-up) in the intervention groups was 6.2 lower (9.8 to 2.6 lower)	N/A	61 (1 study)	⊕⊕⊕⊖ Very low <sup>6,7,8</sup>
Participant satisfaction - by medium term follow-up	N/A	Mean participant satisfaction (by medium term follow-up) in the intervention groups was 1.93 lower (3.01 to 0.86 lower)	N/A	500 (2 studies)	⊕⊕⊕⊕ high
Participant satisfaction - by long term follow-up	N/A	Mean participant satisfaction (by long term follow-up) in the intervention groups was 3.23 lower (4.14 to 2.31 lower)	N/A	423 (2 studies)	⊕⊕⊕⊖ Moderate <sup>9</sup>
Global functioning (GAF) - by short term follow-up	N/A	Mean global functioning (GAF- by short term follow-up) in the intervention groups was 2.07 lower (3.86 to 0.28 lower)	N/A	797 (4 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Global functioning (GAF) - by medium term follow-up	N/A	Mean global functioning (GAF- by medium term follow-up) in the intervention groups was 0.09 lower (3.28 lower to 3.11 higher)	N/A	722 (3 studies)	⊕⊕⊕⊖ Very low <sup>1,2,4</sup>
Global functioning (GAF) - by long term follow-up	N/A	Mean global functioning (GAF- by long term follow-up) in the intervention groups was 3.41 lower (5.16 to 1.66 lower)	N/A	818 (5 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>

Note. CI = confidence interval; RR = risk ratio; LQoLP = Lancashire Quality of Life Profile; MANSA = Manchester Short Assessment of Quality of Life; GAF = Global Assessment of Functioning; QOLI = Quality of Life Inventory.

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Most information is from studies at moderate risk of bias.

<sup>2</sup> Evidence of serious heterogeneity of study effect size.

<sup>3</sup> Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect.

<sup>4</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>5</sup> Most information is from studies at high risk of bias.

<sup>6</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.

<sup>7</sup> Concerns regarding applicability - different populations.

<sup>8</sup> Optimal information size not met.

<sup>9</sup> Concerns regarding size of effect.



## Intensive case management versus non-intensive case management

Evidence from each important outcome and overall quality of evidence are presented in Table 141. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

Low quality evidence from 12 studies (N = 2,220) showed no difference between ICM and non-ICM in the average number of days spent in hospital. Further low quality evidence from a single trial (N = 73) did show a benefit of ICM over non-ICM in remaining in contact with psychiatric services at medium-term follow-up. However, this effect was not found at long-term follow-up (k = 3; N = 1,182). Moreover, there was no difference between ICM and non-ICM in quality of life, participant satisfaction or global functioning at any follow-up points.

No studies reported usable data on carer satisfaction.

### *Sub-analysis (psychosis and schizophrenia only)*

The sub-analysis findings did not differ from the main analysis, reporting no benefit of ICM over non-ICM for service use outcomes, quality of life, participant satisfaction or global functioning.

### *Sub-analysis (UK only)*

The sub-analysis findings did not differ from the main analysis reporting no benefit of ICM over non-ICM for service use outcomes, quality of life, participant satisfaction or global functioning.

**Table 141: Summary of findings tables for ICM compared with non-ICM**

Patient or population: Adults with psychosis and schizophrenia Intervention: ICM Comparison: Non-ICM					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non-ICM	ICM			
Service use (average number of days in hospital per month) - by about 24 months	N/A	Mean service use (average number of days in hospital per month - by about 24 months) in the intervention groups was 0.08 lower (0.37 lower to 0.21 higher)	N/A	2,220 (12 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
Not remaining in contact with psychiatric services - medium term follow-up	Study population		RR 0.27 (0.08 to 0.87)	73 (1 study)	⊕⊕⊕⊖ Low <sup>2,3</sup>
	306 per 1000	82 per 1000 (24 to 266)			
Not remaining in contact with psychiatric services - long term	Study population		RR 0.82 (0.34 to 1.98)	1,182 (3 studies)	⊕⊕⊕⊖ Very low <sup>1,2,4</sup>
	111 per 1000	91 per 1000 (38 to 220)			

Quality of life - by short term follow-up	N/A	Mean quality of life (by short term follow-up) in the intervention groups was 0.02 higher (0.39 lower to 0.43 higher)	N/A	203 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
Quality of life - by medium term follow-up	N/A	Mean quality of life (by medium term follow-up) in the intervention groups was 0.04 higher (0.35 lower to 0.43 higher)	N/A	203 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
Quality of life (LQoLP) - by long term follow-up	N/A	Mean quality of life (LQoLP - by long term follow-up) in the intervention groups was 0.03 lower (0.16 lower to 0.1 higher)	N/A	526 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
Quality of life (MANSA) - by long term follow-up	N/A	Mean quality of life (MANSA - by long term follow-up) in the intervention groups was 0.1 lower (0.39 lower to 0.19 higher)	N/A	166 (1 study)	⊕⊕⊕⊕ Moderate <sup>5</sup>
Quality of life (overall life satisfaction - QOLI) - by long term follow-up	N/A	Mean quality of life (overall life satisfaction - QOLI - by long term follow-up) in the intervention groups was 0.1 lower (0.45 lower to 0.25 higher)	N/A	203 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
Participant satisfaction (patient need - CAN)- by long term follow-up	N/A	Mean participant satisfaction (patient need - CAN - by long term follow-up) in the intervention groups was 0.29 lower (0.69 lower to 0.11 higher)	N/A	585 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
Global functioning (HoNOS) - short term follow-up	N/A	Mean global functioning (HONOS - short term follow-up) in the intervention groups was 0.60 higher (1.8 lower to 3 higher)	N/A	118 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
Global functioning (HoNOS) - long term follow-up	N/A	Mean global functioning (HONOS- long term follow-up) in the intervention groups was 0.40 lower (1.77 lower to 0.97 higher)	N/A	239 (1 study)	⊕⊕⊕⊕ Low <sup>2,3</sup>
<p>Note. CI = confidence interval; RR = risk ratio; LQoLP = Lancashire Quality of Life Profile; MANSA = Manchester Short Assessment of Quality of Life; QOLI = Quality of Life Inventory; CAN = Camberwell Assessment of Need interview; HoNOS = Health of the Nation Outcomes Scales.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Most information is from studies at moderate risk of bias.</p> <p><sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p> <p><sup>3</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.</p> <p><sup>4</sup> Evidence of very serious heterogeneity of study effect size.</p> <p><sup>5</sup> Optimal information size not met</p>					

### *Clinical evidence summary*

When compared with standard care worldwide, ICM was found to be effective at both reducing duration spent in hospital and improving retention in care. Furthermore, participants consistently reported being more satisfied with the service. The benefits of ICM on functioning and quality of life are however less definitive, with inconsistent findings across follow-up points.

Notably, when analysing UK only studies, results did not demonstrate a benefit of ICM over standard care. The large effect on duration of hospitalisation was no longer reported and satisfaction data proved inconsistent across time. However, UK only data do suggest that ICM retains people within the service better than standard care.

When ICM is compared with a non-ICM intervention, there is inconclusive evidence about the additional benefits of a more intensive approach to case management.

### *Health economics evidence*

The economic review identified four eligible studies that met the inclusion criteria for this guideline. Two studies were conducted in the UK (Harrison-Read et al., 2002; McCrone et al., 2009c), one study in the US (Slade et al., 2013), one study in Germany (Karow et al., 2012) and one in Australia (Udechuku et al., 2005). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

The two UK studies were both based on RCTs. Harrison-Read and colleagues (2002) conducted a cost minimisation analysis comparing ICM, defined as enhanced community management, versus standard care. Standard care included local psychiatric services. The authors adopted a cost-minimisation approach since the effectiveness analysis of trial results found no differences in clinical outcomes. The study was based on a medium-sized RCT ( $n = 193$ ) (Harrison-Read-UK) in people with schizophrenia and related diagnoses. The time horizon of the analysis was 2 years and the NHS and PSS perspective was adopted. The authors considered inpatient, outpatient and community care costs. In year one ICM resulted in a cost increase of £441 ( $p = ns$ ) and in year two in a cost saving of £347 ( $p = ns$ ) in 1995/96 prices, leading to an overall cost increase of £94 over 2 years. The authors concluded that ICM did not lead to any important clinical gains or reduced costs of psychiatric care. Even though the study did not consider QALYs, the authors did not find differences in clinical outcomes, consequently the study was judged by the GDG to be directly applicable to this guideline review and the NICE reference case. The analysis derived some of the unit cost estimates from local sources, which may limit the generalisability of the findings to the NHS. However, overall this was a well-conducted analysis with only minor methodological limitations.

McCrone and colleagues (2009c) assessed the cost effectiveness of ICM compared with standard care. ICM was defined as assertive community management and standard care as care from CMHTs. The study population comprised service users with schizophrenia, schizoaffective disorder, bipolar disorder and other psychotic

illnesses. The analysis was based on a relatively large RCT (KILLASPY2006) ( $n = 251$ ). The time horizon of the analysis was 18 months and the societal perspective was adopted. However, NHS and PSS costs were reported separately. The analysis considered: inpatient, outpatient and community care costs; criminal justice costs incurred by probation, incarceration, lawyers, courts and police; and informal care costs. The RCT did not find clinical outcomes to be significantly different between the two groups. However, the authors hypothesised that interventions similar in effectiveness may differ in terms of process and acceptability. Consequently, the primary outcome measure of the analysis was satisfaction with services as measured on Gerber and Prince's scale. ICM resulted in a cost increase of £3,823 in 2003/04 prices excluding informal care and costs accruing to the criminal justice system. Including costs from the societal perspective ICM resulted in a cost increase of £4,031. Cost differences were not statistically significant. Also, it was found that ICM led to a significantly higher satisfaction score of 79.4 versus 71.7 ( $p < 0.05$ ) on Gerber and Prince's satisfaction scale. As a result, the authors concluded that there was no difference between the interventions in terms of costs, however ICM resulted in greater levels of service user satisfaction and engagement, and as such is the preferred community treatment. However, the cost-effectiveness acceptability curve showed that for the ICM to be cost effective in 95% of service users, society would need to be willing to pay £2,500 for one additional unit improvement in the satisfaction score, which is unlikely to represent 'good value for money'. Overall the study was judged by the GDG to be partially applicable to this guideline review and the NICE reference case. The authors did not attempt to estimate QALYs and the use of satisfaction scores as an outcome measure made it difficult to interpret the cost effectiveness results and to compare the findings with other studies. Nevertheless, this was a well-conducted study and was judged by the GDG to have only minor methodological limitations.

A recent cost analysis by Slade and colleagues (Slade et al., 2013) in the US based on a large observational study ( $n = 6,030$ ) compared ICM (defined as ACT) with care without an ACT component. The study population comprised service users with schizophrenia and bipolar disorder. The analysis was performed from a mental health service payer perspective and adopted a 1-year time horizon. Mean annual costs were estimated to be \$28,881 versus \$27,250 for ICM and standard care groups, respectively ( $p = 0.038$ ). The study was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case. The analysis was based on a pre- and post-observational study. These studies are prone to bias because of the inability to control for confounding factors. However, the authors used an extensive regression approach to control for a range of confounders. Overall this was a well-conducted cost analysis and was judged by the GDG to have only minor methodological limitations.

A recent cost-utility study by Karow and colleagues (2012) based on a prospective cohort study ( $n = 120$ ) in people with schizophrenia spectrum disorders in Germany compared ICM (defined as ACT) with standard care. Standard care included inpatient care, care at day clinic and outpatient centre, and care by private

psychiatrists. The public sector payer perspective was adopted and the time horizon of the analysis was 1 year. The analysis included costs associated with admissions, outpatient visits, medications and intervention provision. The primary outcome measure was the QALY. The quality of life was assessed with the EQ-5D descriptive system and the EQ-5D index scores from the UK were used. ICM resulted in a cost saving of €2,502 ( $p = \text{ns}$ ) in 2007 prices and an increase in QALYs of 0.1 ( $p < 0.01$ ) at 1 year's follow-up. Consequently, ICM was found to be the dominant strategy. Also, the probability of ICM being cost effective at a willingness to pay of €50,000 per QALY gained was estimated to be 0.995. The analysis was based on a relatively small cohort study and was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case because it was conducted in Germany and the definition of standard care was very different from the UK. Nevertheless this was a well-conducted study and was judged by the GDG to have only minor methodological limitations.

A cost analysis by Udechuku and colleagues (2005) in Australia based on a pre- and post-observational study ( $n = 31$ ) found ICM (defined as ACT) to be cost saving when compared with care without an ACT component. The study population comprised service users with schizophrenia, schizoaffective disorder and bipolar affective disorder. The analysis was performed from the mental health service payer perspective and adopted a 1-year time horizon. The analysis was judged by the GDG to be only partially applicable to this guideline review and the NICE reference case. Also, it was based on a small pre- and post-observational study. Consequently, it was judged by the GDG to have potentially serious methodological limitations.

### **12.3.6 Linking evidence to recommendations (non-acute community mental healthcare)**

#### *Relative value placed on the outcomes considered:*

The GDG agreed that the main aim of the EIS, CMHTs and ICM community-based care is to provide evidence-based treatments in a community setting and thereby to prevent or reduce admissions. However, each team or service-level intervention has certain nuances in the aim and content of the intervention, and the patient population they target, which influences which critical outcomes are relevant for each team/service intervention. The GDG therefore decided on the following critical outcomes.

#### **EIS:**

- Adverse events (for example, suicide)
- Functional disability
- Service use
- Response/relapse
- Symptoms of psychosis
- Employment and education
- DUP
- Satisfaction with services (service user and carer)

CMHTs:

- Service use
- Social functioning
- Employment and accommodation
- Quality of life
- Symptoms of psychosis and mental health
- Functional disability
- Satisfaction with services (service user and carer)

ICM:

- Loss to services
- Service use
- Quality of life
- Satisfaction with services (service user and carer)

### *Trade-off between clinical benefits and harms*

#### **Early intervention services**

EIS is a way of providing more intensive, personalised care for people in the first 3 years following first episode psychosis. From this review, EIS is better than comparators (standard care or a CMHT) on a range of outcomes, including reduced relapse rates, reduced hospital stay, improvement in symptoms and quality of life and, importantly, EIS is preferred to standard services. EIS provided a range of evidence-based interventions not routinely provided by other services (that is, family intervention and CBT).

The review of psychological treatments for the 2009 guideline suggested that family intervention for people with early psychosis reduces relapse rates but does little to reduce symptoms, whereas CBT for psychosis reduced symptoms and improved quality of life but did nothing to alter relapse rates. EIS teams included in the review all provided family intervention and CBT. The GDG considered this and took the view that although EIS providers often cite small caseloads and other factors, such as team ethos, as the key ingredients leading to positive outcomes, the inclusion of evidence-based psychological and pharmacological treatments in the context of such small caseloads was probably a more likely explanation for the success of EIS.

Importantly, the review for this 2014 guideline included data not previously available on the effects of EIS over 12 months after the end of treatment, which suggests that the impact of EIS is lost by this stage. In practice, EIS currently discharge people with early psychosis to CMHTs and other community services at the end of 3 years. Therefore, to maintain benefits, service users should either remain within EIS for longer periods or community teams (CMHT and ACT) for people with established schizophrenia will need to provide the same evidence-based treatments available in EIS, such as pharmacological, psychological and arts therapies and support for employment provided within an integrated team.

## **Implications for all teams and services for people with psychosis and schizophrenia**

Following the review of EIS, the GDG considered the implications for all teams providing services for psychosis and schizophrenia. EIS, more than any other service developed to date, is associated with improvements in a broad range of critical outcomes, including relapse rates, symptoms, quality of life and a better experience for services. EISs reviewed here all included family interventions and CBT for psychosis. The GDG took the view that, not only should EIS provide the full range of evidence-based treatments recommended in this guideline, but all teams and services should do so, irrespective of the orientation or type of team or service considered. Thus, ICM teams, inpatient teams and CRHTTs should provide, or give access to, pharmacological interventions, psychological interventions and any other treatments recommended in this guideline. Moreover, EIS has a very modern orientation to service user experience, which the GDG considered was encapsulated by the existing NICE guidance and quality standard on *Service User Experience in Adult Mental Health* (NICE, 2011) which covers community and hospital settings. The GDG therefore decided to recommend that all teams providing care for people with psychosis and schizophrenia should not only provide evidence-based treatments, but they should also comply with *Service User Experience in Adult Mental Health* in the way in which they deliver care.

### **Community mental health teams**

The review for CMHTs included three trials, of which one was a cluster randomised trial. The trial population was recruited from various sources, that is, those being discharged from inpatient or outpatient treatment. Comparators were also mixed and included participants receiving outpatient, inpatient and home treatment. Trials included in the review were UK based (one in Manchester and two in London) but were conducted in the 1990s. For people with severe mental illness, the GDG found no evidence of a difference in effectiveness between CMHTs and standard care for various symptom-related, service use and functioning outcomes. The most the GDG could conclude from this is that in the mid-1990s CMHTs showed no superiority over other ways of delivering care. The evidence is inconclusive and of historical interest only.

### **Intensive case management**

The dataset used for the review of ICM (24 trials of ICM, including ACT) was relatively large compared with those used for other reviews of team and service-level interventions. ICM was defined as a team-based approach using assertive case management/care programming. In comparison with standard care, ICM was found to be more effective than standard care for various critical outcomes including reducing time spent in hospital, better engagement with services (from a proxy measure of dropout from the trials), better quality of life and functioning, as well as greater satisfaction with services. Furthermore, ICM was found to be equally as effective as standard care for relapse rates and symptoms of psychosis, which suggests that ICM is not harmful for people with psychosis and schizophrenia. However, this benefit was not consistently found at longer follow-up points.

When compared with non-ICM (ICM defined as a caseload of 15 or less and non-ICM as a caseload of more than 15), although no differences were observed in symptoms, ICM was more effective at service user engagement at short-term follow-up but this effect was not observed at longer follow-up points.

In a UK only sub-analysis most beneficial effects were no longer observed but ICM was still beneficial for engagement and satisfaction with services compared with standard care, which suggests that it is well tolerated and liked by service users. UK data also suggest that ICM is no better than case management in the outcome of interest. The lack of benefit of ICM could reflect the difficulty in reducing already low bed numbers in the UK and that other outcomes, such as people's views and satisfaction with services, may be more appropriate to evaluate (Priebe et al., 2009). The GDG also considered the qualitative data on the adaptation of ICM in the UK, the CPA, which suggests service users do not value this approach and see it as bureaucratic and defensive.

### *Trade-off between net health benefits and resource use:*

#### **Early intervention services**

The UK-based economic evidence for EIS is based on two studies. One concluded that EIS provides better outcome at no extra cost, and thus is cost effective at 18 months. Similarly, in the other UK study EIS was found to be cost saving over 3 years. The UK findings are supported by international evidence. However, weak long-term clinical evidence associated with EIS means that there is uncertainty in the results. Nevertheless, the GDG judged that the costs of providing such interventions are justified by potential cost savings because of reduced relapse rates and shorter hospital stays, and expected clinical benefits and improvements in the quality of life of people with psychosis and schizophrenia.

#### **Community mental health teams**

The economic evidence for CMHTs is limited to one UK-based study. CMHTs resulted in increased healthcare costs and poorer health outcomes compared with EIS and consequently were not shown to be cost effective. Nevertheless, results should be treated with caution since the difference in costs between interventions was not significant and the clinical evidence pertaining to CMHTs is inconclusive.

#### **Intensive case management**

The economic evidence for ICM for individuals with psychosis and schizophrenia is mixed. One UK study did not find any important clinical gains or cost savings. In another UK study the costs of ICM were comparable to costs associated with standard care and it resulted in greater levels of client satisfaction and engagement with services. The international evidence on ICM is encouraging and although the standard care in these studies is quite likely to be different from that in the UK, all of the studies found ICM to be the preferred treatment strategy. Overall, the GDG



judged that the costs of providing ICM are justified by the expected savings arising from shorter hospital stays and better engagement with the services.

### *Quality of the evidence*

The quality of the evidence base for these reviews ranged from very low to moderate. Reasons for downgrading concerned risk of bias, high heterogeneity or lack of precision in confidence intervals. Heterogeneity was a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent. Furthermore, sub-analysis for UK-based studies resulted in more consistent findings, which suggests some variance between UK-based and other studies in the content of both the active intervention and the standard care comparator.

### *Overview of the evidence*

The GDG took the view that the key to effectiveness for EIS is the provision of evidence-based therapeutic interventions by competent practitioners. The GDG, therefore, suggest that integrated, therapeutic community-based teams providing evidence-based pharmacological, psychological and arts-based interventions, with support for education and employment, consistent with other reviews in this guideline, should be provided for people with psychosis and schizophrenia across the age range. Particular care should be taken when engaging people with early psychosis. The GDG felt that EIS or a specialist integrated community-based team should initiate and continue treatment and care. The team should not have a focus on risk-management but aim to engage the service user in services, and provide support in an atmosphere of optimism and hope. The GDG also considered that CMHTs represent an early stage in the evolution of community psychiatric care in the UK and that the evidence suggests that team-based care is possible, not harmful. The GDG considered the evidence for ICM and concluded that if engagement with, and retention within, services is a clinical propriety, it appears to have some advantages. Furthermore, the evidence suggests that smaller caseloads may not be necessary, but this was likely to depend upon the severity of illness and level of impairment of service users; finally the GDG judged that the CPA should be replaced with a lower intensity, less bureaucratic and defensive case management approach.

## **12.3.7 Clinical practice recommendations**

**12.3.7.1** Use this guideline in conjunction with [Service user experience in adult mental health](#) (NICE clinical guidance 136) to improve the experience of care for people with psychosis or schizophrenia using mental health services, and:

- work in partnership with people with schizophrenia and their carers
- offer help, treatment and care in an atmosphere of hope and optimism

- take time to build supportive and empathic relationships as an essential part of care. [ 2009, amended 2014]

**12.3.7.2** All teams providing services for people with psychosis or schizophrenia should offer a comprehensive range of interventions consistent with this guideline. [2009]

**12.3.7.3** Early intervention in psychosis services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person's age or the duration of untreated psychosis. [new 2014]

**12.3.7.4** People presenting to early intervention in psychosis services should be assessed without delay. If the service cannot provide urgent intervention for people in a crisis, refer the person to a crisis resolution and home treatment team (with support from early intervention in psychosis services). Referral may be from primary or secondary care (including other community services) or a self- or carer-referral. [new 2014]

**12.3.7.5** Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should:

- offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline
- be competent to provide all interventions offered
- place emphasis on engagement rather than risk management
- provide treatment and care in the least restrictive and stigmatising environment possible and in an atmosphere of hope and optimism in line with [Service user experience in adult mental health](#) (NICE clinical guidance 136). [new 2014]

**12.3.7.6** Early intervention in psychosis services should aim to provide a full range of pharmacological, psychological, social, occupational and educational interventions for people with psychosis, consistent with this guideline. [2014]

**12.3.7.7** Consider extending the availability of early intervention in psychosis services beyond 3 years if the person has not made a stable recovery from psychosis or schizophrenia. [new 2014]

**12.3.7.8** Consider intensive case management for people with psychosis or schizophrenia who are likely to disengage from treatment or services. [new 2014]

## **12.3.8 Research recommendation**

**12.3.8.1** How can the benefits of early intervention in psychosis services be maintained once service users are discharged after 3 years? (see Appendix 10 for further details) [2014]

## 12.4 ALTERNATIVES TO ACUTE ADMISSION

### 12.4.1 Introduction

#### *Home-based alternatives to acute admission*

Diverting patients from admission has been one of the central purposes of innovations in mental health service delivery for many decades; whereas it is only relatively recently that preventing admission has become a focus of interest in the rest of healthcare in the UK. The principal drivers for this have been the unpopularity of overcrowded psychiatric wards, the involuntary aspects of mental healthcare within hospitals and their high costs. Other arguments for home treatment have been that patients' autonomy and social functioning may be better preserved when they are not admitted, that resolving the crisis at home may allow skills for coping with future crises in the community to be enhanced, and intervening with social triggers for crises and involving social networks is more readily achieved (Johnson & Needle, 2008).

Innovative services assessing and treating service users at home in crises have been established and evaluated in several countries since Arie Querido first established a programme to avert psychiatric admissions in Amsterdam in the 1930s (Hoult, 1991; Johnson, 2013; Polak et al., 1979; Querido, 1935). Some of these services have been free-standing crisis management teams, where patients were admitted at the time of threatened admission to hospital and discharged once the crisis has resolved. Several of the earlier innovative teams involving acute home treatment were hybrids of the crisis team and ICM models, recruiting patients to home treatment at the time of a crisis but then retaining them on caseloads in the longer term (Marks et al., 1994; Stein & Test, 1980).

#### *Community residential alternatives*

Staying at home during a crisis is preferred by many service users, but not always practical or desirable. The risk of harm to self or others is too great for some patients to be left alone for extended periods of time without supervision. Others may be severely functionally impaired, have no fixed abode, or live in environments that exacerbate their difficulties. Residential alternatives outside hospital, such as crisis houses, are a potential resource for people in crisis who cannot appropriately be treated at home but who does not wish to go to hospital.

Residential crisis services in the community have a history spanning many decades, but have not so far been implemented nationwide in any country. This is despite strong advocacy by service user groups. Crisis houses are the most prevalent community model: these are small unlocked, stand-alone community units that are usually based in converted residential premises. An early innovative model was the Soteria house in California in the early 1970s, subsequently emulated by services in a several European countries (Bola & Mosher, 2002; Ciompi et al., 1995).

A comprehensive UK survey of alternatives to admission identified a variety of models, from services that followed a largely clinical model, with mental health professional staff and types of care similar to those on acute wards, to more radical alternatives aiming to provide treatment approaches significantly different from hospitals, often managed by third sector organisations (Johnson et al., 2009). Most of the alternatives found worked closely with CRHTTs and were well integrated into catchment area mental health systems. Family sponsor homes, where people in crisis are hosted by carefully selected and trained families, usually also with the support of the CRHTT, are another community model for avoiding admission (Aagaard et al., 2008), although few such schemes are currently available in the UK.

Ethical and practical difficulties in recruiting patients to trials at the time of a crisis, and resistance to randomisation in well-established often third sector-provided alternatives, have recently limited the conduct of RCTs of crisis houses and other residential alternatives. However, a small number of trials, generally with populations too diagnostically mixed to be within the scope of this guideline, have tended to report better patient satisfaction and otherwise similar outcomes for crisis houses compared with inpatient wards (Howard, 2010; Lloyd-Evans et al., 2009). Implementation studies of the model have suggested that service user populations are similar to hospital wards, but with most patients voluntary and already known to services and with significantly less risk of violence than hospital patients (Johnson et al., 2009). Naturalistic investigation using quantitative and qualitative methods has also indicated a marked service user preference for crisis houses rather than wards, supporting strong voluntary sector advocacy for these services (Gilburt et al., 2010; Mind, 2011; Osborn et al., 2010b). An investigation of the views of local stakeholders, including referrers and senior managers, suggested that acute residential services in the community were valued as a means of extending service user choice and available strategies for managing crises. They were also seen as taking pressure off hard-pressed hospital inpatient services by means that included diverting patients who would otherwise have been admitted, accepting early discharges and providing respite to people at potentially high risk of reaching the admission threshold without additional support (Morant et al., 2012).

A recent trend in development of crisis residential alternatives has been towards close integration between crisis teams and crisis houses - the ability of each to manage challenging patients in the community might potentially be enhanced through synergy with the other.

## **12.4.2 Crisis resolution and home treatment teams**

### *Introduction*

England is one of very few countries in which provision of acute home treatment services has been national policy, with all trusts required to introduce CRHTTs (also known in some areas as crisis assessment and treatment teams or intensive home treatment teams) under the NHS Plan (Department of Health, 2000). While provision of such services is no longer mandatory, they remain very widespread in the UK.

The primary aims of CRHTTs are to:

- assess all patients being considered for admission to acute psychiatric wards
- initiate a programme of home treatment with frequent visits (usually at least daily) for all patients for whom this appears a feasible alternative to hospital treatment
- continue home treatment until the crisis has resolved and then transfer people to other services for any further care they may need
- facilitate early discharge from acute wards by transferring inpatients to intensive home treatment.

The teams are multidisciplinary, usually containing nurses, psychiatrists and non-professional mental health staff such as support workers, with occupational therapists, psychologists, social workers and clinical psychologists less consistently represented. Guidance on model implementation suggests they should operate 24 hours a day 7 days a week, and most at least work extended hours. Gatekeeping acute beds, with no hospital admissions taking place unless the CRHTT confirms that home treatment does not appear feasible, is regarded as a key activity associated with success in reducing acute bed use (Middleton et al., 2008). Accounts of the model suggest that core team interventions should include: visiting at home (at least twice a day if needed) to provide support and monitor recovery from the crisis and risk; prescribing, dispensing and monitoring adherence to medication; helping resolve practical problems that may perpetuate the crisis; brief psychological and social interventions to alleviate symptoms and distress and reinforce coping skills and problem solving abilities; and support for carers and other key social network members (Johnson, 2013). The team's work is short term, with discharge to any services required for long-term support generally taking place within a few weeks.

### *Definition and aim of intervention/ service system*

A Cochrane review of crisis interventions for people with serious mental health problems (Murphy et al., 2012) was identified and selected by the GDG for review and further analysis.

The GDG adopted the inclusion criteria and definition of crisis resolution developed by the Cochrane review for studies of CRHTTs in the management of people with severe mental illness. Crisis intervention and the comparator treatment were defined as follows:

- crisis resolution is any type of crisis-orientated treatment of an acute psychiatric episode by staff with a specific remit to deal with such situations, in and beyond 'office hours'
- 'standard care' is the normal care given to those experiencing acute psychiatric episodes in the area concerned; this involved hospital-based treatment for all studies included.

The focus of the review was to examine the effects of CRHTT care for people with severe mental illness experiencing an acute episode, compared with the standard care they would normally receive.

### *Clinical review protocol (crisis resolution and home treatment teams)*

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 142 (the full review protocol and a complete list of review questions can be found in Appendix 6; information about the search strategy can be found in Appendix 13).

**Table 142: Clinical review protocol for the review of crisis resolution and home treatment teams**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of crisis resolution and home treatment teams compared with treatment as usual or another intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of crisis resolution and home treatment teams in the treatment of psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Crisis resolution and home treatment teams
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Service use <ul style="list-style-type: none"> <li>◦ Admission/readmission to hospital</li> <li>◦ Number of days in hospital</li> <li>◦ Number of staff/user contacts</li> </ul> </li> <li>• Satisfaction <ul style="list-style-type: none"> <li>◦ Participant satisfaction</li> <li>◦ Carer satisfaction</li> </ul> </li> <li>• Mental health act use</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	SR/RCT: 2002 to June 2013
<i>Study design</i>	RCTs
<i>Review strategy</i>	<p><i>Time-points</i></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><i>Sub-analysis</i></p> <p>Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>

### *Studies considered*<sup>53</sup>

Six RCTs (N = 851) met the eligibility criteria for this review: FENTON1979 (Fenton et al., 1979), HOULT1983 (Hoult et al., 1983), JOHNSON2005 (Johnson et al., 2005), MUIJEN1992 (Muijen et al., 1992), PASAMANICK1964 (Pasamanick et al., 1964), STEIN1975 (Stein et al., 1975). All six were published in peer-reviewed journals between 1964 and 2005, and all compared CRHTTs with standard care as defined by the study. The Cochrane review of crisis interventions (Murphy et al., 2012) was used as a source to verify that all relevant studies had been included. Further information about both included and excluded studies can be found in Appendix 15a. Table 143 provides an overview of the included trials.

**Table 143: Study information table for trials included in the meta-analysis of CRHTTs versus standard care**

	<b>CRHTTs versus standard care</b>
<i>Total no. of trials (k); participants (N)</i>	k = 6; N = 851
<i>Study ID(s)</i>	FENTON1979 HOULT1983 JOHNSON2005 MUIJEN1992 PASAMANICK1964 STEIN1975
<i>Country</i>	Australia (k = 1) Canada (k = 1) UK (k = 2) US (k = 2)
<i>Year of publication</i>	1964 to 2005
<i>Mean age of participants (range)</i>	35.76 years (30.95 to 40.08 years) <sup>1</sup>
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	74.29% (53 to 100%) <sup>2</sup>
<i>Mean gender % women (range)</i>	53.14% (41.38 to 68%)
<i>Length of follow-up (range)</i>	4 to 104 weeks
<i>Intervention type</i>	Community Living Program's home-based care (k = 1) Daily Living Program's home-based care (k = 1) Home crisis care by CRHTTs (k = 1) Home Care Group (k = 3)
<i>Comparisons</i>	Standard care: hospitalisation (k = 5) Standard care from the inpatient unit, crisis houses, and CMHTs (k = 1)
<i>Note.</i> <sup>1</sup> FENTON1979 and HOULT1983 did not provide data.	
<sup>2</sup> STEIN1975 did not provide data.	

### *Clinical evidence for crisis resolution and home treatment teams*

Evidence from each important outcome and overall quality of evidence are presented in Table 144. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

<sup>53</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

Evidence suggest that CRHTTs, when compared with standard care, reduce the likelihood of people with serious mental health problems being admitted to inpatient settings at up to 6 months (k = 3; N = 325), 12 months (k = 3; N = 400) and at 24 months' follow-up (k = 1; N = 118). However, the evidence was of either very low or low quality. Nevertheless, the size of the effects in reducing admission at each time interval was large.

However, very low quality evidence showed that CRHTTs were no more effective than standard care in reducing the likelihood of people with serious mental illness being readmitted at either 12 months' (k = 4; N = 601) or 24 months' follow-up (k = 2; N = 306). The evidence in this area is inconclusive.

**Table 144: Summary of findings tables for CRHTTs compared with standard care**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: CRHTTs					
Comparison: Standard care					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TAU	CRHTTs			
Service use (admitted to hospital) - by 3 months	Study population		RR 0.35 (0.11 to 1.18)	205 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	854 per 1000	299 per 1000 (94 to 1000)			
	833 per 1000	292 per 1000 (92 to 983)			
Service use (admitted to hospital)- by 6 months	Study population		RR 0.28 (0.09 to 0.88)	325 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	904 per 1000	253 per 1000 (81 to 795)			
	900 per 1000	252 per 1000 (81 to 792)			
Service use (admitted to hospital) - by 12 months	Study population		RR 0.4 (0.31 to 0.51)	400 (3 studies)	⊕⊕⊕⊕ Low <sup>1,4</sup>
	990 per 1000	396 per 1000 (307 to 505)			
	1000 per 1000	400 per 1000 (310 to 510)			
Service use (admitted to hospital) - by 24 months	Study population		RR 0.32 (0.22 to 0.46)	118 (1 study)	⊕⊕⊕⊕ Low <sup>5,6</sup>
	1000 per 1000	320 per 1000 (220 to 460)			
	1000 per 1000	320 per 1000 (220 to 460)			
Service use (readmitted to hospital) - by 12 months	Study population		RR 0.51 (0.21 to 1.2)	601 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	402 per 1000	205 per 1000 (84 to 482)			
	451 per 1000	230 per 1000 (95 to 541)			
Service use (readmitted to	Study population		RR 0.76 (0.36 to	306 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	391 per	297 per 1000			



<i>hospital) - by 24 months</i>	1000	(141 to 637)	1.63)		
	407 per 1000	309 per 1000 (147 to 663)			
<i>Mental Health Act admission - by 3 months</i>	Study population		RR 0.65 (0.31 to 1.35)	87 (1 study)	⊕⊕⊕⊕ Low <sup>3,5</sup>
	310 per 1000	201 per 1000 (96 to 418)			
	310 per 1000	201 per 1000 (96 to 419)			
<i>Satisfaction (patient satisfied with care - Satisfaction Scale) - by 6 months</i>	N/A	Mean satisfaction (patient satisfied with care - Satisfaction Scale - by 6 months) in the intervention groups was 0.95 standard deviations higher (0.57 to 1.34 higher)	N/A	115 (1 study)	⊕⊕⊕⊕ Low <sup>5,6</sup>
<i>Satisfaction (patient satisfied with care - Satisfaction Scale) - by 12 months</i>	N/A	Mean satisfaction (patient satisfied with care - Satisfaction Scale - by 12 months) in the intervention groups was 1.02 standard deviations higher (0.64 to 1.4 higher)	N/A	121 (1 study)	⊕⊕⊕⊕ Low <sup>5,6</sup>
<i>Satisfaction (patient satisfied with care - Satisfaction Scale) - by 20 months</i>	N/A	Mean satisfaction (patient satisfied with care - Satisfaction scale - by 20 months) in the intervention groups was 1.21 standard deviations higher (0.85 to 1.58 higher)	N/A	137 (1 study)	⊕⊕⊕⊕ Low <sup>5,6</sup>
<i>Satisfaction (patient not satisfied with care - CSQ) - by 3 months</i>	Study population		RR 1.04 (0.63 to 1.72)	87 (1 study)	⊕⊕⊕⊕ Low <sup>3,5</sup>
	405 per 1000	421 per 1000 (255 to 696)			
	286 per 1000	297 per 1000 (180 to 492)			
<i>Note.</i> CI: Confidence interval; RR: Risk ratio; TAU = treatment as usual; CSQ =					
*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).					
<sup>1</sup> Most information is from studies at moderate risk of bias.					
<sup>2</sup> Evidence of very serious heterogeneity of study effect size.					
<sup>3</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).					
<sup>4</sup> Evidence of serious heterogeneity of study effect size.					
<sup>5</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.					
<sup>6</sup> Criteria for an optimal information size not met					

Low quality evidence from a single study (N = 87) reported no difference in rate of Mental Health Act admission or in satisfaction with care between CRHTT and standard care at 3 months' follow-up. However, at 6 (k = 1; N = 115), 12 (k = 1; N = 121) and 20 months' follow-up (k = 1; N = 137) low quality evidence showed that those who received care from a CRHTT reported greater satisfaction with care compared with those who received standard care.

It was decided by the GDG not to use the data available on the duration of acute inpatient care. This was because four studies included 'index admission' in their data and were therefore deemed unrepresentative.

### *Clinical evidence summary*

For people with schizophrenia and other serious mental health problems in an acute crisis, care from a CRHTT is superior to standard hospital care in reducing hospital admissions and appears to be more acceptable at long-term follow-up. CRHTTs also appear to increase retention of service users, improve quality of life and have a marginally better effect on some clinical outcomes.

### *Health economics evidence*

The systematic literature search identified two UK-based economic studies that assessed the economic impact of CRHTTs for individuals with psychosis and schizophrenia (McCrone et al., 2009a; McCrone et al., 2009b). Details on the methods used for the systematic search of the economic literature are described in Chapter 3. References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19. Completed methodology checklists of the studies are provided in Appendix 18. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

McCrone and colleagues (2009a) conducted a cost-effectiveness analysis that compared CRHTTs with standard care. Standard care was defined as care by CMHTs, inpatient care and crisis houses. Study population comprised service users with psychosis, schizophrenia, bipolar affective disorder, unipolar depression, personality disorder, and non-psychotic disorder (<5%). The study was based on a large RCT (JOHNSON2005) (n = 260) and a public sector payer perspective was adopted. The time frame of the analysis was 6 months. The authors considered NHS costs (primary, secondary, and community care) and criminal justice sector costs incurred by prison and police cell stay. The primary outcome was the number of days not on a psychiatric ward or other inpatient setting. Costs were reported including and excluding inpatient care. Costs per person inclusive of inpatient care were lower in the CRHTTs group by £2,438 (p < 0.01) in 2003/04 prices, however if inpatient care was excluded the costs per person were higher by £768 (p < 0.01) in the CRHTT group. Days not on psychiatric ward per service user were very similar in both groups: 126.8 versus 129.9 days for CRHTTs and standard care groups, respectively. Cost-effectiveness analysis, excluding inpatient costs, showed that if society is willing to pay £100 to avoid an extra inpatient day, the probability of CRHTTs being cost effective would be 1.00. Even though the analysis has included criminal justice sector costs these costs accounted for only a very small proportion of the total costs and thus are unlikely to affect the results. Also, the authors made no attempt to estimate QALYs, however this did not affect judgement on cost effectiveness since clinical outcomes were very similar. Consequently, the analysis

was judged by the GDG to be directly applicable to this guideline review and the NICE reference case. The time horizon of the study was only 6 months, which may not be sufficiently long enough to fully capture the effects of the intervention. However, taking into account data limitations, overall the analysis was judged by the GDG to have only minor methodological limitations.

Another cost analysis by McCrone and colleagues (2009b) compared CRHTTs with standard care. Standard care included care in acute wards, crisis houses, care by CMHTs and liaison teams based in the local casualty department. The study was based on a pre- and post-observational study ( $n = 200$ ) that mainly included individuals with schizophrenia/schizoaffective disorder and bipolar affective disorder. The study adopted a public sector payer perspective and considered costs over a 6-month period. The analysis included NHS costs (inpatient, outpatient and community care) and also criminal justice sector costs incurred by arrest, solicitor, court appearance, police, probation, and police cell/prison. The authors adjusted costs for the baseline differences in participant characteristics and estimated that CRHTTs resulted in cost savings of £1,681 ( $p = ns$ ) in 2001 prices. The sensitivity analysis showed that if the unit cost of contact with the CRHTT was £40, the cost difference would increase to -£1,807 ( $p < 0.1$ ). Also, if groups were defined according to whether there was any CRHTT contact, the cost savings would increase to £2,189 ( $p < 0.1$ ). The analysis was only partially applicable to this guideline review since it included costs accruing to the criminal justice sector. Healthcare and crime costs were not reported separately; consequently it is not clear what proportion of the total costs are accounted for by contacts with the criminal justice system. The analysis was based on a pre- and post-observational study, which are prone to bias because of the inability to control for confounding factors. However, the authors used a regression approach to control for a range of confounders. As a result this study was judged by the GDG to have only minor methodological limitations.

### **12.4.3 Crisis houses**

#### ***Introduction***

Crisis houses are a residential alternative to acute care in a crisis that can be provided to support the care provided by the local CRHTT. They are designed to be a 'home away from home' based in the local community for people who are experiencing a crisis. Crisis houses are staffed 24 hours a day either by trained mental health staff and based within mental health services, or by support workers trained in crisis care and based within voluntary sector organisations. In the latter context, crisis house workers are usually supported by the local CRHTT.

The service user's treatment and medication management is sometimes the responsibility of the mental health team running the crisis house; sometimes their community-based psychiatrist and sometimes by the CRHTT. Usually, however, workers in the crisis house assist with treatment planning and offer day-to-day support for community-based treatment, employment or education, or other community-based social activities that can help the service user's social functioning

and activities of daily living. They also sometimes offer transportation to and from treatment facilities and community or outpatient appointments. The service user sleeps at the crisis house overnight with trained support workers or trained mental health staff available 24 hours a day.

### ***Definition and aim of intervention/ service system***

A crisis house is defined as a residential alternative to acute admission during a crisis. A crisis house aims to help the service user maintain autonomy and normality during a crisis within their own community but is also supported with their treatment plan and daily living, allowing an easier transition back to normal life after the crisis. Crisis houses also aims to reduce the stigma of experiencing a crisis, which sometimes may be exacerbated by admission to an inpatient facility, allowing the service user and families to move away from the idea of the service user being 'unwell' and providing the support needed for swift recovery.

### ***Clinical review protocol (crisis houses)***

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 145 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 145: Clinical review protocol for the review of crisis houses**

<b>Component</b>	<b>Description</b>
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of crisis houses compared with treatment as usual or another intervention?
<i>Objectives</i>	To evaluate the clinical effectiveness of crisis houses in the treatment of psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Crisis houses
<i>Comparison</i>	Any alternative management strategy
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Service use <ul style="list-style-type: none"> <li>○ Admission/ Readmission to hospital</li> <li>○ Number of days in hospital</li> <li>○ Number of staff/user contacts</li> </ul> </li> <li>• Satisfaction <ul style="list-style-type: none"> <li>○ Participant satisfaction</li> <li>○ Carer satisfaction</li> </ul> </li> <li>• Mental Health Act use</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	SR/RCT: Inception to June 2013
<i>Study design</i>	RCTs
<i>Review strategy</i>	<i>Time-points</i> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> </ul>

	<ul style="list-style-type: none"> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><i>Sub-analysis</i> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>
--	--

### ***Studies considered***<sup>54</sup>

One RCT (N = 185) providing relevant clinical evidence met the eligibility criteria for this review. The study was published in a peer-reviewed journal in 1998. Further information about both included and excluded studies can be found in Appendix 15a.

The one study compared crisis houses with standard care. Table 146 provides an overview of the included trial.

**Table 146: Study information table for trials included in the meta-analysis of crisis houses versus standard care**

	<b>Crisis houses versus standard care</b>
<i>Total no. of trials (k); participants (N)</i>	k = 1; N = 185
<i>Study ID</i>	FENTON1998
<i>Country</i>	USA
<i>Year of publication</i>	1998
<i>Mean age of participants</i>	37.58 years
<i>Mean percentage of participants with primary diagnosis of psychosis of schizophrenia</i>	56%
<i>Mean gender % women</i>	47.9%
<i>Length of follow-up</i>	26 weeks
<i>Intervention type</i>	Home-like acute residential facility (k = 1)
<i>Comparisons</i>	Standard care (k = 1)

### ***Clinical evidence for crisis houses***

Evidence from each important outcome and overall quality of evidence are presented in Table 147.

---

<sup>54</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

**Table 147: Summary of findings tables for crisis houses compared with standard care**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Crisis houses					
Comparison: Standard care					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TAU	Crisis houses (recovery houses)			
Service use (admitted to hospital) - by 6 months follow-up	Study population		RR 1 (0.98 to 1.02)	185 (1 study)	⊕⊕⊕⊖ Low <sup>1</sup>
	1000 per 1000	1000 per 1000 (980 to 1000)			
	1000 per 1000	1000 per 1000 (980 to 1000)			
Service use (readmitted to hospital) - by 6 months follow-up	Study population		RR 0.9 (0.76 to 1.05)	185 (1 study)	⊕⊕⊕⊖ Low <sup>2,3</sup>
	804 per 1000	724 per 1000 (611 to 845)			
	804 per 1000	724 per 1000 (611 to 844)			
Service use (days of acute inpatient care) - by 6 months follow-up	N/A	Mean service use (days of acute inpatient care - by 6 months follow-up) in the intervention groups was 0.02 standard deviations lower (0.4 lower to 0.36 higher)	N/A	108 (1 study)	⊕⊕⊕⊖ Low <sup>2,3</sup>
Service use (number of repeat admissions per participant) - by 6 months follow-up	N/A	Mean service use (number of repeat admissions per participant - by 6 months follow-up) in the intervention groups was 0.18 standard deviations lower (0.56 lower to 0.2 higher)	N/A	111 (1 study)	⊕⊕⊕⊖ Low <sup>2,3</sup>
<p>Note. CI: Confidence interval; RR: Risk ratio; TAU = treatment as usual</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Criteria for an optimal information size not met.</p> <p><sup>2</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.</p> <p><sup>3</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>					

Low quality evidence showed no additional benefit of crisis houses, when compared with standard care, on hospital admission (k = 1; N = 185), hospital readmission (k = 1; N = 185), number of days spent in acute care (k = 1; N = 108) or the number of repeat admissions per participant (k = 1; N = 111) at 6 months' follow-up. No data were available on satisfaction or Mental Health Act admissions. The data were considered by the GDG to be inconclusive.

### *Clinical evidence summary*

The data available from a single study was inconclusive.

### *Health economics evidence*

No studies assessing the cost effectiveness of crisis houses for adults with psychosis or schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

## **12.4.4 Acute day hospital care**

### *Introduction*

Given the substantial costs and high level of use of inpatient care, the possibility of day hospital treatment programmes acting as an alternative to acute admission gained credence in the early 1960s, initially in the US (Kris, 1965; Herz et al., 1971), and later in Europe (Wiersma et al., 1989) and the UK (Creed et al., 1990; Dick et al., 1985). Acute day can be provided to support the care provided by the local CRHTT.

### *Definition and aim of intervention/ service system*

A Cochrane review of acute day hospitals for people with serious mental health problems (Marshall et al., 2011) was identified and selected by the GDG for review and further analysis.

The GDG adopted the inclusion criteria and definition of acute day hospitals developed by the Cochrane review. Acute day hospitals and the comparator treatment were defined as follows:

- Acute day hospitals were defined as units that provided 'diagnostic and treatment services for acutely ill individuals who would otherwise be treated in traditional psychiatric inpatient units' (Rosie, 1987).
- Standard care was defined as admission to an inpatient unit.

Thus, trials would only be eligible for inclusion if they compared admission to an acute day hospital with admission to an inpatient unit. Participants were people with acute psychiatric disorders (all diagnoses) who would have been admitted to inpatient care had the acute day hospital not been available.

### *Clinical review protocol (acute day hospitals)*

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 148 (the full review protocol and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

**Table 148: Clinical review protocol for the review of acute day hospital treatment**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of acute day hospitals compared with standard care?
<i>Objectives</i>	To evaluate the clinical effectiveness of acute day hospitals in the treatment of psychosis and schizophrenia.
<i>Population</i>	Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	Acute day hospitals
<i>Comparison</i>	Standard care
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>• Service use <ul style="list-style-type: none"> <li>○ Hospitalisation: mean number of days per month in hospital</li> <li>○ Not remaining in contact with psychiatric services</li> <li>○ Use of services outside of mental health provision (that is, emergency services)</li> </ul> </li> <li>• Satisfaction <ul style="list-style-type: none"> <li>○ User satisfaction (validated measures only)</li> <li>○ Carer satisfaction (validated measures only)</li> </ul> </li> <li>• Mental Health Act use</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	SR/RCT: 2002 to June 2013
<i>Study design</i>	RCTs
<i>Review strategy</i>	<p><i>Time-points</i></p> <ul style="list-style-type: none"> <li>• End of treatment</li> <li>• Up to 6 months' follow-up (short-term)</li> <li>• 7-12 months' follow-up (medium-term)</li> <li>• 12 months' follow-up (long-term)</li> </ul> <p>Analyses were conducted for follow-up using data from the last follow-up point reported within the time-point groupings.</p> <p><i>Sub-analysis</i></p> <p>Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/ schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK only studies.</p>

***Studies considered<sup>55</sup>***

The GDG selected an existing Cochrane review (Marshall et al., 2011) as the basis for this section of the guideline, with a new search conducted to update it. This Cochrane review is an update of the previous Health Technology Appraisal (Marshall et al., 2001) of nine trials with the addition of a large EU multi-centre trial (Kallert-EU-2007). A search for recent RCTs did not uncover any suitable new studies to add to the Marshall review. The existing Cochrane review included ten

<sup>55</sup>Changes have not been made to the study ID format used in the Cochrane review utilised in this section.



RCTs (N = 2685) providing relevant clinical evidence meeting the eligibility criteria for the review. Studies were published in peer-reviewed journals between 1965 and 2007. Further information about included studies can be found in Appendix 15a. Further information about excluded studies can be found in (Marshall et al., 2011)

Of the ten included trials, all compared acute day hospitals with routine inpatient care. Table 149 provides an overview of the included trials.

Some difficulties were encountered in synthesising the outcome data because of the:

- Population
  - Mixed sample both within and between studies and only a quarter to a third had a diagnosis of schizophrenia in the included studies
  - Day hospital care was unsuitable for some people and a proportion of studies excluded these people prior to randomisation
  - Country
    - The setting of trials varied across studies. EU multicentre (k = 1); US (k = 4); Netherlands (k = 2); UK (k = 3).
- Intervention
  - Some interventions included additional services (for example, out-of-hours back-up, 'back-up bed') while others did not.
- Methods
  - The point of randomisation varied across studies (unsuitable patients excluded prior to randomisation or randomisation at referral).
- Outcomes
  - A number of similar outcomes were presented in slightly different formats across studies.
- Follow-up
  - Follow-up varied from 2 to 24 months between studies.

**Table 149: Study information table for trials included in the meta-analysis of acute day hospital versus standard care**

	Acute day hospital treatment teams versus standard care
<i>Total no. of trials (k); participants (N)</i>	k = 10; N = 2685
<i>Study ID(s)</i>	Creed-UK-1990 Creed-UK-1996 Dick-UK-1985 Herz-US-1971 Kallert-EU-2007 Kris-US-1965 Schene-NL-1993 Sledge-US-1996 Wiersma-NL-1989 Zwerling-US-1964
<i>Country</i>	Europe (k = 1) Netherlands (k = 2) UK (k = 3) US (k = 4)

Year of publication	1965 to 2007
Mean age of participants (range)	37.2 years (32 to 42.38 years) <sup>1</sup>
Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)	32.68% (23.5 to 39%) <sup>2</sup>
Mean percentage of women (range)	52.63% (43.01 to 67.6%)
Length of follow-up (range)	8 to 104 weeks
Intervention type	Acute day hospital treatment (k = 10)
Comparisons	Routine inpatient care (k = 10)
Note. <sup>1</sup> Dick-UK-1985, Kris-US-1965, Schene-NL-1993 did not provide data.	
<sup>2</sup> Dick-UK-1985, Kris-US-1965, Schene-NL-1993, Zwerling-US-1964 did not provide data.	

### *Clinical evidence for acute day treatment*

Evidence from each important outcome and overall quality of evidence are presented

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Acute day hospitals					
Comparison: Inpatient admission					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Inpatient admission	Acute day hospitals			
Feasibility and engagement -lost to follow-up - end of study (by 3 months) - type 1 studies	Study population 282 per 1000	274 per 1000 (226 to 330)	RR 0.97 (0.80 to 1.17)	1,117 (1 study)	⊕⊕⊕⊕ High
Feasibility and engagement - lost to follow-up - end of study (by 2-6 months) - type 1 studies	Study population 315 per 1000	262 per 1000 (183 to 375)	RR 0.83 (0.58 to 1.19)	312 (2 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
Feasibility and engagement - lost to follow-up - end of study (by 1 year) - type 1 studies	Study population 327 per 1000	307 per 1000 (268 to 353)	RR 0.94 (0.82 to 1.08)	1,704 (5 studies <sup>1</sup> )	⊕⊕⊕⊖ Moderate <sup>2</sup>
Duration of index admission (days/month) - type 1 studies	N/A	Mean duration of index admission (days/month) in the intervention groups was 27.47 higher (3.96 to 50.98 higher)	N/A	1,582 (4 studies <sup>1</sup> )	⊕⊕⊕⊖ Moderate <sup>2</sup>
Duration of all hospital care (days/month) - type 1 studies	N/A	Mean duration of all hospital care (days/month) in the intervention groups was 0.38 lower (1.32 lower to 0.55 higher)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>
Duration of stay in hospital (days/month) - type 1 studies	N/A	Mean duration of stay in hospital (days/month) in the intervention groups was 2.75 lower (3.63 to 1.87 lower)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>

<i>Duration of all day patient care (days/month) - type 1 studies</i>	N/A	Mean duration of all day patient care (days/month) in the intervention groups was 2.34 higher (1.97 to 2.70 higher)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>2,3</sup>
<i>Readmitted to day/inpatient care after discharge (days/month)- type 1 studies</i>	Study population 311 per 1000	0 per 1000 (0 to 0)	Not estimable	667 (5 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Satisfaction with services - not satisfied with care received - type 1 studies</i>	Study population 604 per 1000	278 per 1000 (163 to 477)	RR 0.46 (0.27 to 0.79)	91 (1 study)	⊕⊕⊕⊖ Moderate <sup>3,4</sup>
<i>Feasibility and engagement - lost to follow-up (at 2 years) - type 2 studies</i>	Study population 509 per 1000	351 per 1000 (244 to 504)	RR 0.69 (0.48 to 0.99)	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Duration of all hospital care (days/months, individual patient data - 'nights in' and 'nights out') - type 2 studies</i>	N/A	Mean duration of all hospital care (days/months, individual patient data - 'nights in' and 'nights out') in the intervention groups was 1.10 higher (1.58 lower to 3.78 higher)	N/A	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Readmitted to day/inpatient care after discharge (days/month) - type 2 studies</i>	Study population 439 per 1000	408 per 1000 (281 to 592)	RR 0.93 (0.64 to 1.35)	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<p>Note. CI = confidence interval; RR = risk ratio.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> One large (n = 1,117) high-quality multi-centre RCT (Kallert-EU-2007) provides data for all outcomes. This trial carries more weight than other pooled trials and this was taken into consideration when assessing overall risk of bias.</p> <p><sup>2</sup> Heterogeneity not explained by differences in populations/interventions.</p> <p><sup>3</sup> Studies included are at a moderate risk of bias.</p> <p><sup>4</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>					

### ***Clinical evidence for type 1 trials***

Low to high quality evidence from up to five trials (N = 1,714) showed that there was no difference between acute day hospitals and standard inpatient care in the number lost to follow-up at the end of the intervention (between 3 months and 1 year). Kallert-EU-2007 also did not observe a significant difference between groups in the number of participants lost to follow-up.

Moderate quality evidence from eight trials (N = 1,582) showed that participants in the day hospital care group had significantly longer index admission than those in the standard care inpatient group. This finding was mirrored by the Kallert-EU-2007

trial which found the duration of index admission was significantly longer in day hospital settings than in standard inpatient care: 78 (SD = 73) versus 46 (SD = 46) days ( $p < .001$ ).

Low quality evidence from up to three trials (N = 465) showed no difference in all hospital care between acute day hospitals and standard inpatient care. However, the day patient group spent significantly longer in day patient care and significantly less time in inpatient care than the standard care group.

Low quality evidence from up to five trials (N = 667) showed no difference between day hospital care and standard inpatient care in the number of participants readmitted to day/inpatient care after discharge.

One trial with 91 participants provided moderate quality evidence that day hospital care was significantly more satisfactory than standard inpatient care. However, the Kallert-EU-2007 trial provided no evidence of a difference between groups in satisfaction with services (using a continuous measure).

### *Clinical evidence for type 2 trials*

One study with 160 participants provided low quality evidence favouring day hospital care in the number of participants lost to follow-up. Low quality evidence from one study (N = 160) showed no difference between groups in duration of all hospital care or in the number of participants readmitted to day/inpatient care after discharge.

Trials were categorised according to the method of randomising participants. Marshall and colleagues (2011) termed trials as type 1 and type 2. Type 1 trials were those in which anyone considered ineligible for day hospital treatment was excluded before randomisation (Creed-UK-1990, Creed-UK-1996, Dick-UK-1985, Herz-US-1971, Kallert-EU-2007, Kris-US-1965, Schene-NL-1993, Sledge-US-1996.). In Type 2 trials, everyone considered for admission to the acute day hospital service was randomised, regardless of suitability; but anyone allocated to the acute day hospital but who was too unwell for day hospital care was then admitted to the inpatient ward (Wiersma-NL-1989 and Zwerling-US-1964.). Due to the methodological differences, type 1 and type 2 trials are analysed separately.

In addition, the GDG decided that the large Kallert-EU-2007 trial provides a more accurate depiction of service provision in the UK and increased confidence in the findings of the review. Therefore, the GDG decided that the findings of this trial should be assessed both as part of the meta-analysis and described individually to assess if the findings are concurrent with the overall meta-analysis. Therefore, relevant outcome findings from this trial are described narratively below.

**Table 150: Summary of findings tables for acute day hospitals compared with standard care**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Acute day hospitals					
Comparison: Inpatient admission					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Inpatient admission	Acute day hospitals			
<i>Feasibility and engagement -lost to follow-up - end of study (by 3 months) - type 1 studies</i>	Study population		RR 0.97 (0.80 to 1.17)	1,117 (1 study)	⊕⊕⊕⊕ High
	282 per 1000	274 per 1000 (226 to 330)			
<i>Feasibility and engagement - lost to follow-up - end of study (by 2-6 months) - type 1 studies</i>	Study population		RR 0.83 (0.58 to 1.19)	312 (2 studies)	⊕⊕⊕⊖ Low <sup>1,3</sup>
	315 per 1000	262 per 1000 (183 to 375)			
<i>Feasibility and engagement - lost to follow-up - end of study (by 1 year) - type 1 studies</i>	Study population		RR 0.94 (0.82 to 1.08)	1,704 (5 studies <sup>1</sup> )	⊕⊕⊕⊖ Moderate <sup>2</sup>
	327 per 1000	307 per 1000 (268 to 353)			
<i>Duration of index admission (days/month) - type 1 studies</i>	N/A	Mean duration of index admission (days/month) in the intervention groups was 27.47 higher (3.96 to 50.98 higher)	N/A	1,582 (4 studies <sup>1</sup> )	⊕⊕⊕⊖ Moderate <sup>2</sup>
<i>Duration of all hospital care (days/month) - type 1 studies</i>	N/A	Mean duration of all hospital care (days/month) in the intervention groups was 0.38 lower (1.32 lower to 0.55 higher)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Duration of stay in hospital (days/month) - type 1 studies</i>	N/A	Mean duration of stay in hospital (days/month) in the intervention groups was 2.75 lower (3.63 to 1.87 lower)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Duration of all day patient care (days/month) - type 1 studies</i>	N/A	Mean duration of all day patient care (days/month) in the intervention groups was 2.34 higher (1.97 to 2.70 higher)	N/A	465 (3 studies)	⊕⊕⊕⊖ Low <sup>2,3</sup>
<i>Readmitted to day/inpatient care after discharge (days/month)- type 1 studies</i>	Study population		Not estimable	667 (5 studies)	⊕⊕⊕⊖ Low <sup>3,4</sup>
	311 per 1000	0 per 1000 (0 to 0)			
<i>Satisfaction with services - not satisfied with care</i>	Study population		RR 0.46 (0.27 to 0.79)	91 (1 study)	⊕⊕⊕⊖ Moderate <sup>3,4</sup>
	604 per	278 per 1000			

<i>received - type 1 studies</i>	1000	(163 to 477)			
<i>Feasibility and engagement - lost to follow-up (at 2 years) - type 2 studies</i>	Study population 509 per 1000	351 per 1000 (244 to 504)	RR 0.69 (0.48 to 0.99)	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Duration of all hospital care (days/ months, individual patient data - 'nights in' and 'nights out') - type 2 studies</i>	N/A	Mean duration of all hospital care (days/ months, individual patient data - 'nights in' and 'nights out') in the intervention groups was 1.10 higher (1.58 lower to 3.78 higher)	N/A	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<i>Readmitted to day/ inpatient care after discharge (days/ month) - type 2 studies</i>	Study population 439 per 1000	408 per 1000 (281 to 592)	RR 0.93 (0.64 to 1.35)	160 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
<p><i>Note.</i> CI = confidence interval; RR = risk ratio.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> One large (n = 1,117) high-quality multi-centre RCT (Kallert-EU-2007) provides data for all outcomes. This trial carries more weight than other pooled trials and this was taken into consideration when assessing overall risk of bias.</p> <p><sup>2</sup> Heterogeneity not explained by differences in populations/interventions.</p> <p><sup>3</sup> Studies included are at a moderate risk of bias.</p> <p><sup>4</sup> CI crosses clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>					

### ***Clinical evidence for type 1 trials***

Low to high quality evidence from up to five trials (N = 1,714) showed that there was no difference between acute day hospitals and standard inpatient care in the number lost to follow-up at the end of the intervention (between 3 months and 1 year). Kallert-EU-2007 also did not observe a significant difference between groups in the number of participants lost to follow-up.

Moderate quality evidence from eight trials (N = 1,582) showed that participants in the day hospital care group had significantly longer index admission than those in the standard care inpatient group. This finding was mirrored by the Kallert-EU-2007 trial which found the duration of index admission was significantly longer in day hospital settings than in standard inpatient care: 78 (SD = 73) versus 46 (SD = 46) days (p<.001).

Low quality evidence from up to three trials (N = 465) showed no difference in all hospital care between acute day hospitals and standard inpatient care. However, the day patient group spent significantly longer in day patient care and significantly less time in inpatient care than the standard care group.

Low quality evidence from up to five trials (N = 667) showed no difference between day hospital care and standard inpatient care in the number of participants readmitted to day/inpatient care after discharge.

One trial with 91 participants provided moderate quality evidence that day hospital care was significantly more satisfactory than standard inpatient care. However, the Kallert-EU-2007 trial provided no evidence of a difference between groups in satisfaction with services (using a continuous measure).

### *Clinical evidence for type 2 trials*

One study with 160 participants provided low quality evidence favouring day hospital care in the number of participants lost to follow-up. Low quality evidence from one study (N = 160) showed no difference between groups in duration of all hospital care or in the number of participants readmitted to day/inpatient care after discharge.

### *Clinical evidence summary*

There is no evidence of a difference between day hospital care and standard inpatient care in engagement of participants. There is some evidence that the duration of index admission is longer for participants in day hospital care. Although no difference was observed between groups in the total days in hospital (day- or inpatient), while the duration of day patient care is longer, the duration of inpatient care is shorter for those in day hospital care. Although significantly more people receiving day hospital care were satisfied with services, this difference was not observed in the Kallert-EU-2007 trial.

### *Health economics evidence*

No studies assessing the cost effectiveness of acute day hospitals for adults with psychosis and schizophrenia were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

Given the large direct medical costs associated with relapse in psychosis and schizophrenia, primarily resulting from expensive inpatient treatment, it has been suggested that the lower operational cost of acute day hospitals could result in substantial savings for the health service. On the other hand, there have been fears that these savings would be achieved by shifting the cost burden to families and carers, offering no real reduction in the overall cost to society. Nevertheless, the unit cost of acute inpatient care per bed day is £330 in 2011/12 prices (Curtis, 2012). This estimate has been based on the NHS Reference Costs for 2010-2011 based on the information provided by NHS trusts and primary care trusts. The unit cost for acute day care was not available. However, Curtis (2012) provides unit costs for the day care in mental health services for different caseload sizes and grades of staff. Acute day care unit cost was conservatively approximated using day care unit cost estimate in mental health services assuming that it will be provided by qualified staff in Band 6 with a caseload of only 10 people resulting in a unit cost of £171. Based on

these crude estimates acute day care could potentially lead to a cost saving of £159 per day of acute care.

### **12.4.5 Linking evidence to recommendations**

#### ***Relative value placed on the outcomes considered***

The GDG agreed that the main aim of the review of alternatives to acute admission was to evaluate the feasibility and safety of managing a crisis outside inpatient care, taking into account service user preference and choice. The GDG also considered engagement and satisfaction with services to be critical when evaluating this evidence. Thus, the outcomes considered to be of critical importance were:

- Service use (for example, admission, re-admission)
- Mental Health Act use
- Satisfaction with services (service user and carer).

The GDG recognised that no studies adequately dealt with preference and choice. The GDG took the view that service users should have a range of alternatives to inpatient care as inpatient care is strongly associated with stigma and considerable anxiety for service users and their carers.

#### ***Trade-off between clinical benefits and harms***

#### **Crisis resolution and home treatment teams**

CRHTTs are a team-based approach to providing treatment and care for people in a crisis as an alternative to inpatient treatment. The evidence suggests that CRHTTs reduce admission when compared with standard inpatient care up to 1 year's follow-up and possibly up to 2 years' follow-up. However, there is no evidence of additional benefit in readmission rates. CRHTTs are probably preferred to inpatient treatment by service users and they may be superior to inpatient treatment at engaging service users, as well as improving service user quality of life and clinical outcomes. In terms of service user choice, the GDG regarded CRHTTs as having sufficient evidence as an alternative to recommend that these should be available and should continue to act as the single point of referral for all acute care, gatekeeping admission to inpatient units.

#### **Acute day hospitals and crisis houses**

Acute day hospitals are an alternative to home treatment for a specific service user group who have support at home in the evening and at night but not during the day; or as a form of respite for carers. The evidence reviewed here suggests that acute day hospitals are a viable and clinically effective alternative to inpatient care; and there is no reason to think that acute day hospitals could not provide evidence based therapeutic interventions recommended in this guideline. The GDG considered the



acute day hospital to be an important selective alternative to inpatient care generally preferred by service users.

Crisis houses are an alternative to inpatient admission for service users who do not have any support at home during the day or in the evenings and night time, or where carers are unable to cope and/or need respite. The evidence currently suggests that they may be equivalent to inpatient care, but the evidence reviewed here is inconclusive. There are a growing number of crisis houses around the UK. The GDG considered these as a possible alternative to inpatient care if preferred by service users and an important choice for service users to be able to avoid admission.

### *Trade-off between net health benefits and resource use*

#### **Crisis resolution and home treatment teams**

Economic evidence on CRHTTs in the UK is based on two studies. Both concluded that CRHTTs are highly likely to be cost effective when compared with standard care for people with schizophrenia and other serious mental health problems in an acute crisis. The cost savings mainly result from the reduction in costs associated with hospital admissions. The existing economic evidence supports the GDG's view that CRHTTs should be offered to all service users as an alternative to inpatient admission. Although the cost-effectiveness evidence for other alternatives is lacking, the substantial costs of inpatient treatment make it highly likely that alternatives, associated with similar or lower costs, would be cost effective.

#### **Acute day hospitals**

No economic studies were identified that assessed the cost effectiveness of acute day hospitals. Nevertheless they were found to be a viable and clinically effective alternative to inpatient care and an alternative generally preferred by service users. Moreover, very crude costing indicated that acute inpatient care is associated with substantial costs and it is highly likely that acute day care would be associated with similar or lower costs, and would be a cost-effective treatment choice for people with psychosis and schizophrenia.

### *Quality of the evidence*

#### **Crisis resolution and home treatment teams**

The quality of the evidence ranged from very low to low across outcomes. Reasons for downgrading included risk of bias in the included studies, high heterogeneity, and imprecise confidence intervals. The evidence included in the review of CRHTTs was of particular concern because of the age of the included trials. This resulted in possible poor reporting and thus high risk of bias in the included trials. Additionally, there was serious heterogeneity across the included studies, which could be explained by the differences in findings between trials from different countries as UK-only sub-analysis produced more consistent results.

#### **Acute day hospitals and crisis houses**

The quality of the evidence base for these reviews ranged from low to high. Reasons for downgrading included risk of bias, high heterogeneity or lack of precision in confidence intervals. Heterogeneity was a major concern when evaluating the evidence. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most studies. The evidence for crisis houses was low quality, which was likely to be a result of the lack of available evidence. The review of acute day hospitals was more robust due to the inclusion of the large and well-designed EU-multicentre trial. In general, the GDG acknowledged that although RCTs are an important step in evaluating the impact of complex interventions such as teams and service-level interventions, there are significant problems associated with using this type of study design in this context.

### *Other considerations*

The GDG discussed the term 'acute day hospital', a now outdated term, and felt this should be changed to 'acute day care' to increase service user choice.

The GDG judged that the evidence supports the recommendation that CRHTTs are a viable alternative to inpatient admission and should be offered as a first option to service users in a crisis. Furthermore, the GDG discussed and agreed that CRHTTs should be the single point of referral and triage for people in a crisis and thus admission to inpatient care, or any other acute care, should follow assessment by the CRHTTs. The GDG believed that acute day care, and probably crisis houses, may be considered as alternatives to inpatient care, justified at least in large part on the basis of service user preference and to expand choice. The GDG agreed that CRHTTs should be the cornerstone of acute care in the community, with other alternatives to inpatient care being determined on the basis of personal circumstances, individual need and preferences. Following extensive discussion of the acute care pathway in mental health, the GDG concluded that consideration should be given to the management of acute care as a whole system or pathway, including CRHTTs, acute day care, inpatient units and probably crisis houses for those who have no support at home or in the community. Moreover, other local alternatives such as respite for service users and for carers should be managed within this local acute care pathway. Health service managers should also give consideration to the management of the interface between acute care and non-acute care in the community.

The GDG also considered the impact upon service users of an acute episode of psychosis or schizophrenia. Service users often understand the experience very differently from health and social care professionals involved in their care. Currently, service users' notes are used predominantly as a record of care and treatment from the professionals' perspective. The GDG for the 2014 guideline agreed with the GDGs for the 2002 and 2009 guidelines that omitting service users' accounts of their experience introduces systematic bias into the case record and recommended that service users, especially those who are admitted to hospital, should add their accounts to their own notes.

## **12.4.6 Clinical practice recommendations**

- 12.4.6.1** Offer crisis resolution and home treatment teams as a first-line service to support people with psychosis or schizophrenia during an acute episode in the community if the severity of the episode, or the level of risk to self or others, exceeds the capacity of the early intervention in psychosis services or other community teams to effectively manage it. [new 2014]
- 12.4.6.2** Crisis resolution and home treatment teams should be the single point of entry to all other acute services in the community and in hospitals. [new 2014]
- 12.4.6.3** Consider acute community treatment within crisis resolution and home treatment teams before admission to an inpatient unit and as a means to enable timely discharge from inpatient units. Crisis houses or acute day facilities may be considered in addition to crisis resolution and home treatment teams depending on the person's preference and need. [new 2014]
- 12.4.6.4** If a person with psychosis or schizophrenia needs hospital care, think about the impact on the person, their carers and other family members, especially if the inpatient unit is a long way from where they live. If hospital admission is unavoidable, ensure that the setting is suitable for the person's age, gender and level of vulnerability, support their carers and follow the recommendations in [Service user experience in adult mental health](#) (NICE clinical guidance 136). [new 2014]
- 12.4.6.5** After each acute episode, encourage people with psychosis or schizophrenia to write an account of their illness in their notes. [2009]

# 13 VOCATIONAL REHABILITATION

## 13.1 INTRODUCTION

This chapter reviews the evidence for vocational rehabilitation interventions and updates the 2009 guideline. It also includes a new review assessing the efficacy of cognitive remediation in combination with vocational rehabilitation.

Types of employment vary widely and can mean different things to different people, for example, it could mean being self-employed, having paid or unpaid employment (including voluntary work), working part time or in a sheltered environment, or being in supported employment. A recent estimate of employment for people with psychosis and schizophrenia is 5 to 15%, with an average of 8% (Schizophrenia Commission, 2012), which is significantly less than the 71% of the general population currently employed. Despite much evidence that work has many benefits for people with psychosis and schizophrenia, the likelihood of employment remains extremely low. The literature suggests that up to 97.5% of service users may want some type of work role, for example volunteering or paid employment, but 53% stated they had not received any support in obtaining work (Seeböhm & Secker, 2005).

There are many benefits to having a role in society and performing that role's associated tasks (Ross, 2008). Making a contribution to society and promoting citizenship as a result of a work role can improve recovery (Repper & Perkins, 2003). It is important to note that without a work role an individual will have limited income, routines and choices and experience social isolation, which are all recognised as stressors. Evidence of increased mental distress (reduced self-esteem and increased psychosomatic symptoms) in the unemployed general population is widely recorded (Paul & Moser, 2009). The rise in suicide rates with increased unemployment (Stuckler et al., 2011) reinforces the view that employment can be better for mental health. Therefore, the right work or vocational role with the right support can be of great benefit to people with psychosis and schizophrenia in terms of health, social functioning and financial reward (The Work Foundation, 2013).

However, while recent publications reaffirm the health benefits of open employment for people with psychosis and schizophrenia (Schizophrenia Commission, 2012; The Work Foundation, 2013), there is a lack of progress in increasing the numbers in employment. Many factors contribute to this. Within mental health services, the negative attitudes of mental health professionals towards people with mental disorders may lead to pessimism and thus reduce aspirations and the subsequent provision of services (Hansson et al., 2013). Societal stigma and discrimination, the diagnostic label, fear of loss of or changes to benefits, and lack of skills in exploring and putting in place employment support within mainstream services are other factors that contribute to the problem (Marwaha & Johnson, 2004; The Work Foundation, 2013).

Guidance to support people with mental illness at work and to manage long-term sickness absence can be found in public health guidance published by NICE (NICE, 2009b; 2009c).

It is a reasonable assumption that back to work and in work support should be regarded as an essential element of interventions for people with psychosis and schizophrenia in recovery (The Work Foundation, 2013), not least because the longer the period of non-engagement with a role the greater the limitations of such roles later in life (Bell & Blanchflower, 2011).

Assessment and interventions relating to vocational rehabilitation may be offered by occupational therapists and specialist employment advisors. To aid speed of access and a link to other clinical interventions, the person providing employment interventions is based in the clinical multidisciplinary team.

The predictors for gaining employment for people with psychosis and schizophrenia are a work history and the desire to work, and there is evidence that the presence of positive symptoms has a more advantageous influence on work outcomes compared with negative symptoms (Marwaha & Johnson, 2004). Upon gaining employment, it is important that people are supported to manage disclosure at work, and negotiate reasonable adjustments and funding in order to provide the appropriate support to the employer and employee.

## **13.2 CLINICAL EVIDENCE REVIEW – VOCATIONAL REHABILITATION INTERVENTIONS**

### **13.2.1 Introduction**

The vocational rehabilitation interventions reviewed in this chapter include standard and modified supported employment and prevocational training. In addition, cognitive remediation as a possible adjunct to these interventions is also reviewed. Cognitive impairment is present in a proportion of people with psychosis schizophrenia, particularly in the domains of memory (Brenner, 1986), attention (Oltmanns & Neale, 1975) and executive functions, such as organisation and planning (Weinberger et al., 1988), and is associated with reduced capacity to work (Wexler & Bell, 2005). Therefore it is plausible that an intervention designed to improve cognitive functioning, such as cognitive remediation (Wykes & Reeder, 2005), might also improve performance in employment in people with psychosis and schizophrenia. It is also possible that vocational rehabilitation programmes might help people to embed and generalise gains made through previous cognitive remediation (Wexler & Bell, 2005). The general effectiveness of cognitive remediation is reviewed in Chapter 9. The current chapter will include a review of the effectiveness of cognitive remediation when used as an adjunctive treatment to improve the effectiveness of vocational rehabilitation.

### ***Definitions and aim of interventions***

*Prevocational training* is defined as any approach to vocational rehabilitation in which participants are expected to undergo a period of preparation before being encouraged to seek competitive employment. This preparation phase could involve either work in a sheltered environment (such as a workshop or work unit), or some form of pre-employment training or transitional employment. This included both traditional (sheltered workshop) and 'clubhouse' approaches.

*Supported employment*, referred to as individual placement and support (IPS) is any approach to vocational rehabilitation that attempts to place service users in competitive employment immediately. It was acceptable for supported employment to begin with a short period of preparation, but this had to be of less than 1 month's duration and not involve work placement in a sheltered setting, training or transitional employment.

*Modifications of vocational rehabilitation programmes* are defined as either prevocational training or supported employment that has been enhanced by some technique to increase participants' motivation. Typical techniques consist of payment for participation in the programme or some form of psychological intervention.

*Control* is defined as the usual psychiatric care for participants in the trial without any specific vocational component. In all trials where an intervention was compared with standard care, unless otherwise stated, participants would have received the intervention in addition to standard care. Thus, for example, in a trial comparing prevocational training and standard community care, participants in the former group would also have been in receipt of standard community services, such as outpatient appointments.

*Cognitive remediation* is defined as:

- an identified procedure that is specifically focused on basic cognitive processes, such as attention, working memory or executive functioning, and
- having the specific intention of bringing about an improvement in the level of performance on that specified cognitive function or other functions, including daily living, social or vocational skills.

### **13.2.2 Clinical review protocol - vocational rehabilitation interventions**

The review protocol summary, including the review question(s), information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 151 (the full review protocols and a complete list of review questions can be found in Appendix 6; further information about the search strategy can be found in Appendix 13).

The review strategy was to evaluate the clinical effectiveness of the interventions using meta-analysis. However, in the absence of adequate data, the available evidence was synthesised using narrative methods.

**Table 151: Clinical review protocol for the review of vocational rehabilitation interventions**

Component	Description
<i>Review question</i>	For adults with psychosis and schizophrenia, what are the benefits and/or potential harms of vocational rehabilitation interventions compared with treatment as usual or another interventions?
<i>Sub-questions</i>	a. Supported employment b. Prevocational training (including individual placement support, volunteering, training) c. Modifications of above (paid work or additional psychological therapy) d. Cognitive remediation with vocational rehabilitation
<i>Objectives</i>	To evaluate the effectiveness of vocational rehabilitation interventions for people with psychosis and schizophrenia.
<i>Population</i>	<b>Included</b> Adults (18+) with schizophrenia (including schizophrenia-related disorders such as schizoaffective disorder and delusional disorder) or psychosis.
<i>Intervention(s)</i>	<ul style="list-style-type: none"> <li>Supported employment</li> <li>Prevocational training (including individual placement support, volunteering, training)</li> <li>Modifications of above (paid work or additional psychological therapy)</li> <li>Cognitive remediation with vocational rehabilitation</li> </ul>
<i>Comparison</i>	<ul style="list-style-type: none"> <li>Vocational rehabilitation versus any alternative management strategy</li> <li>Cognitive remediation and vocational rehabilitation versus vocational rehabilitation alone</li> </ul>
<i>Critical outcomes</i>	<ul style="list-style-type: none"> <li>Employment and education <ul style="list-style-type: none"> <li>Competitive employment</li> <li>Occupation (any non-competitive – for example, volunteer or unpaid work)</li> <li>Attendance at school/college</li> </ul> </li> <li>Quality of life</li> <li>Functional disability</li> </ul>
<i>Electronic databases</i>	CORE: CDSR, CENTRAL, DARE, Embase, HTA, MEDLINE, MEDLINE In-Process Topic specific: CINAHL, PsycINFO
<i>Date searched</i>	<p>Sub questions a, b, c: SR/RCT: 2002 to June 2013 Sub question d: SR: 1995 to June 2013 RCT: database inception to June 2013</p> <p>NB: Vocational rehabilitation with cognitive rehabilitation was not reviewed in the 2009 guideline. Therefore, an additional search for SRs/RCTs was run from an earlier date.</p>
<i>Review strategy</i>	<p><b>Time-points</b></p> <ul style="list-style-type: none"> <li>End of treatment</li> <li>Up to 6 months' follow-up (short-term)</li> <li>7-12 months' follow-up (medium-term)</li> <li>12 months' follow-up (long-term)</li> </ul>

	<p>Where more than one follow-up point within the same period were available, the latest one was reported.</p> <p><i>Sub-analysis</i> Where data were available, sub-analyses were conducted of studies with &gt;75% of the sample described as having a primary diagnosis of schizophrenia/schizoaffective disorder or psychosis.</p> <p>Where data were available, sub-analyses were conducted for UK/Europe studies.</p>
--	---

### 13.2.3 Studies considered<sup>56</sup>

The 2009 guideline reviewed vocational rehabilitation interventions alone (without cognitive remediation), utilising and updating an existing Cochrane review (Crowther et al., 2001) of 18 RCTs. The Cochrane review was assessed as being up-to-date by the authors in December 2010. Since then, a number of new trials have been published and therefore for the 2014 guideline, a new review was conducted.

For the purposes of the guideline, vocational rehabilitation interventions were categorised as:

- standard supported employment
- modified supported employment (with additional payment or psychological intervention)
- standard prevocational training
- modified prevocational training (with additional payment or psychological intervention).

On the basis of the available evidence the reviews conducted involved the following comparisons:

- supported employment (standard or modified) versus prevocational training (standard or modified)
- supported employment (standard or modified) versus control (non-vocational)
- prevocational training (standard or modified) versus control (non-vocational)
- standard prevocational training versus modified prevocational training
- modified prevocational training (paid and psychological intervention) versus modified prevocational training (paid) supported employment (standard or modified) plus prevocational training (standard or modified) versus supported employment alone
- supported employment (standard or modified) plus prevocational training (standard or modified) versus prevocational training alone

---

<sup>56</sup>Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).



- cognitive remediation with vocational rehabilitation versus vocational rehabilitation alone.

### *Vocational rehabilitation alone*

Thirty-eight RCTs (N = 8,832) met the eligibility criteria for this review of vocational rehabilitation interventions: BEARD1963 (Beard et al., 1963), BECKER1967 (Becker, 1967), BELL1993 (Bell et al., 1993), BELL2003 (Bell et al., 2003), BIO2011 (Bio & Gattaz, 2011) BLANKERTZ1996 (Blankertz & Robinson, 1996), BOND1986 (Bond & Dincin, 1986), BOND1995 (Bond et al., 1995), BOND2007 (Bond et al., 2007), BURNS2007 (Burns et al., 2007a), CHANDLER1996 (Chandler et al., 1996), COOK2005 (Cook et al., 2005), DINCIN1982 (Dincin & Witheridge, 1982), DRAKE1994 (Drake et al., 1994), DRAKE1999 (Drake et al., 1999), FREY2011 (Frey et al., 2011), GERVEY1994 (Gervey & Bedell, 1994), GOLD2006 (Gold et al., 2006), GRIFFITHS1974 (Griffiths, 1974), HOFFMAN2012 (Hoffmann et al., 2012), HOWARD2010 (Howard et al., 2010), KILLACKEY2008 (Killackey et al., 2008), KLINE1981 (Kline & Hoisington, 1981), KOPELOWICZ2006 (Kopelowicz et al., 2006), KULDAU1977 (Kuldau & Dirks, 1977), LATIMER2006 (Latimer et al., 2006), LEHMAN2002 (Lehman et al., 2002), LYSAKER2005 (Lysaker et al., 2005), LYSAKER2009 (Lysaker et al., 2009), MCFARLANE2000 (McFarlane et al., 2000), MUESER2002<sup>57</sup>(Mueser et al., 2002a), MUESER2005 (Mueser et al., 2005), OKPAKU1997 (Okpaku & Anderson, 1997), TSANG2009 (Tsang et al., 2009), TWAMLEY2012 (Twamley et al., 2012), WALKER1969 (Walker et al., 1969), WOLKON1971 (Wolkon et al., 1971), WONG2008 (Wong et al., 2008). All 38 studies were published in peer-reviewed journals between 1963 and 2012. Further information about both included and excluded studies can be found in Appendix 15a. See Table 152, Table 153 and Table 154 for an overview of the trials included in each category.

Of the eligible trials, 18 included a large proportion (>75%) of participants with a primary diagnosis of psychosis or schizophrenia. Four of the included trials were based in the UK/Europe.

---

<sup>57</sup> In the previous guideline MUESER2002 (Mueser et al., 2002) was the conference paper referenced. Since then, the study data has been published in MUESER2004 (Mueser KT, Clark RE, Haines M, Drake RE, McHugo GJ, Bond GR, et al. The Hartford study of supported employment for persons with severe mental illness. *Journal of Consulting and Clinical Psychology*. 2004;72:479-90.). For the purpose of this guideline and to avoid confusion the previous study ID of MUESER2002 will be used in this guideline.

**Table 152: Study information table for trials comparing vocational rehabilitation interventions with any alternative management strategy**

	<b>Supported employment versus TAU</b>	<b>Prevocational training versus TAU</b>	<b>Supported employment versus prevocational training</b>
<i>Total no. of trials (k); participants (N)</i>	k = 4; N = 2,687	k = 11; N = 1,598	k = 19; N = 4,192
<i>Study ID</i>	CHANDLER1996 FREY2011 KILLACKEY2008 OKPAKU1997	BEARD1963 BECKER1967 BIO2011 BLANKERTZ1996 DINCIN1982 GRIFFITHS1974 KLINE1981 KOPELOWICZ2006 KULDAU1977 WALKER1969 WOLKON1971	BOND1986 BOND1995 BOND2007 BURNS2007 COOK2005 DRAKE1994 DRAKE1999 GERVEY1994 GOLD2006 HOFFMAN2012 HOWARD2010 LATIMER2006 LEHMAN2002 MCFARLANE2000 MUESER2002 MUESER2005 TSANG2009 TWAMLEY2012 WONG2008
<i>Country</i>	Australia (k = 1) USA (k = 3)	Brazil (k = 1) UK (k = 1) USA (k = 9)	Canada (k = 1) China (k = 2) Europe (k = 1) Switzerland (k = 1) UK (k = 1) USA (k = 13)
<i>Year of publication</i>	1996 to 2011	1963 to 2011	1986 to 2012
<i>Mean age of participants (range)</i>	35.19 years (21.36 to 47.4 years) <sup>1</sup>	34.85 years (25.4 to 46 years) <sup>2</sup>	36.39 years (19 to 51 years) <sup>5</sup>

<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	51.99% (23 to 100%)	75.03% (27.47 to 100%) <sup>3</sup>	67.71% (38 to 100%) <sup>6</sup>
<i>Mean percentage of women (range)</i>	39.02% (19.5 to 52.7%)	31.32% (0 to 65%) <sup>4</sup>	42.25% (20 to 63.79%)
<i>Length of treatment</i>	26 to 156 weeks	2 to 78 weeks	8 to 104 weeks
<i>Length of follow-up</i>	<p><i>End of treatment only</i> CHANDLER1996 FREY2011 KILLACKEY2008</p> <p><i>&gt;12 months</i> OKPAKU1997 <sup>7</sup></p>	<p><i>End of treatment only</i> BECKER1967 BIO2011 BLANKERTZ1996 DINCIN1982 KULDAU1977 WALKER1969</p> <p><i>Up to 6 months</i> BEARD1963 KLINE1981 KOPELOWICZ2006</p> <p><i>6- 12 months</i> BEARD1963</p> <p><i>&gt;12 months</i> BEARD1963 GRIFFITHS1974 WOLKON1971</p>	<p><i>End of treatment only</i> BOND1986 BOND1995 BOND2007 BURNS2007 COOK2005 DRAKE1999 GERVEY1994 GOLD2006 HOFFMAN2012 LATIMER2006 LEHMAN2002 MCFARLANE2000 MUESER2002 TSANG2009 TWAMLEY2012 WONG2008</p> <p><i>6- 12 months</i> HOWARD2010</p> <p><i>&gt;12 months</i> DRAKE1994 MUESER2005</p>
<i>Intervention type</i>	<p>Employment-oriented case management (k = 1)</p> <p>Integrated service agency (k = 1)</p>	<p>Community-based hospital industrial rehabilitation placement (k = 1)</p> <p>Rehabilitation programme (k = 5)</p> <p>Rehabilitation unit (k = 1)</p>	<p>Accelerated vocational rehabilitation (k = 1)</p> <p>Accelerated approach to supported employment (k = 1)</p> <p>IPS (k = 11)</p> <p>'Supported employment interventions' (k = 1)</p>

	IPS (k = 1) IPS + TAU (k = 1)	Thresholds' rehabilitation services (k = 1) Work experience and discussion group (k = 1) Work-focused programme (k = 1) Work tasks (k = 1)	Supported employment using job coaches (k = 2) Supported employment using natural supports in the workplace (k = 1) ACT with IPS (k = 1) Family-aided ACT (k = 1) Supported employment (k = 1) Integrated supported employment (IPS + work-related, social skills training) (k = 1)
<i>Comparisons</i>	Case management services from a community mental health centre (k = 1) Usual services (k = 3)	Other community service referral (k = 1) Usual services (k = 6) Continued treatment programme (k = 1) Usual 'Horizon House Incorporated' services (k = 1) Control ward programme (k = 1) Occupational therapy group (k = 1)	Conventional vocational rehabilitation (k = 3) Diversified placement approach (k = 1) Enhanced vocational rehabilitation (k = 1) Gradual approach to supported employment (k = 1) Gradual vocational rehabilitation Group skills training (k = 1) Prevocational training (k = 1) Psychosocial rehabilitation and day care programmes including prevocational training (k = 1) Psychosocial rehabilitation programme (k = 1) Sheltered-employment training (k=1) Standard vocational services (k = 4) Supported employment + 'Workplace Fundamentals' programme (k = 1) Supported employment program (k = 1) Traditional vocational rehabilitation programmes (k = 2)
<p><i>Note.</i> TAU = treatment as usual; IPS = individual placement and support; ACT = assertive community treatment.</p> <p><sup>1</sup> CHANDLER1996 did not provide data.</p> <p><sup>2</sup> BEARD1963, GRIFFITHS1974 and WALKER1969 did not provide data.</p> <p><sup>3</sup> GRIFFITHS1974 did not provide data.</p> <p><sup>4</sup> BECKER1967, GRIFFITHS1974 and KLINE1981 did not provide data.</p> <p><sup>5</sup> GOLD2006 did not provide data.</p> <p><sup>6</sup> GERVEY1994 did not provide data.</p> <p><sup>7</sup> OKPAKU1997 study had a variable follow-up period. All participants received 4 months of intervention and one 3-month follow-up interview; some were followed up for as long as 24 months.</p>			

**Table 153: Study information table for trials comparing vocational rehabilitation interventions with any alternative management strategy**

	<b>Modified prevocational training versus standard prevocational training</b>	<b>Modified prevocational training (paid + psychological intervention) versus modified prevocational training (paid)</b>
<i>Total no. of trials (k); participants (N)</i>	k = 2 (N = 354)	k = 3 (N = 213)
<i>Study ID</i>	BELL1993 MUESER2002	BELL2003 LYSAKER2005 LYSAKER2009
<i>Country</i>	USA (k = 2)	USA (k = 3)
<i>Year of publication</i>	1993 to 2002	2003 to 2009
<i>Mean age of participants (range)</i>	42.24 years (41.23 to 43.25 years)	46.2 years (43.98 to 48.1 years)
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	87.26% (74.51 to 100%)	100% (100 to 100%)
<i>Mean gender (% women)</i>	20.92% (3.62 to 38.21%)	5% (0 to 15%)
<i>Length of treatment</i>	26 to 104 weeks	26 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> BELL1993 MUESER2002	<i>End of treatment only</i> BELL2003 LYSAKER2005 LYSAKER2009
<i>Intervention type</i>	Prevocational training - pay condition (k = 1) Standard vocational services for clients with severe mental illness (k = 1)	Paid work programme + behavioural intervention (k = 1) Standard support (job placement) + 'Indianapolis Vocational Intervention Program' (k = 2)
<i>Comparisons</i>	Prevocational training - no pay condition (k = 1) Psychosocial rehabilitation programme (k = 1)	Paid work programme alone (k = 1) Standard support (job placement) (k = 2)

**Table 154: Study information table for trials comparing vocational rehabilitation interventions with any alternative management strategy**

	<b>Supported employment + prevocational training versus supported employment</b>	<b>Supported employment + prevocational training versus prevocational training</b>
<i>Total no. of trials (k); participants (N)</i>	k = 1; N = 163	k = 1; N = 163
<i>Study ID</i>	TSANG2009	TSANG2009
<i>Country</i>	China (k = 1)	China (k = 1)
<i>Year of publication</i>	2009	2009
<i>Mean age of participants (range)</i>	34.56 years	34.56 years
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	75.46%	75.46%
<i>Mean gender (% women)</i>	50.31%	50.31%
<i>Length of treatment</i>	65 weeks	65 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> TSANG2009	<i>End of treatment only</i> TSANG2009
<i>Intervention type</i>	Integrated supported employment (IPS + work-related, social skills training) (k = 1)	Integrated supported employment (IPS + work-related, social skills training) (k = 1)
<i>Comparisons</i>	IPS (k = 1)	Traditional vocational rehabilitation (k = 1)
<i>Note.</i> IPS = individual placement and support.		

### *Cognitive remediation with vocational rehabilitation*

Six RCTs (N = 533) met the eligibility criteria for the review of cognitive remediation with vocational rehabilitation: BELL2005 (Bell et al., 2005), BELL2008 (Bell et al., 2008), LINDENMAYER2008 (Lindenmayer et al., 2008), MCGURK2005 (McGurk et al., 2005), MCGURK2009 (McGurk et al., 2009) VAUTH2005 (Vauth et al., 2005). All six studies were published in peer-reviewed journals between 2005 and 2009. In addition, five studies were excluded from the analysis. Further information about both included and excluded studies can be found in Appendix 15a.

Of the eligible trials, five included a large proportion (>75%) of participants with a primary diagnosis of psychosis or schizophrenia. None of the included trials were based in the UK/Europe. Table 155 provides an overview of the trials included in this review.

**Table 155: Study information table for trials comparing cognitive remediation and vocational rehabilitation interventions with vocational rehabilitation alone**

	<b>Cognitive remediation with vocational rehabilitation versus vocational rehabilitation alone</b>
<i>Total no. of trials (k); participants (N)</i>	k = 6; N = 533
<i>Study ID</i>	BELL2005 BELL2008 LINDENMAYER2008 MCGURK2005 MCGURK2009 VAUTH2005
<i>Country</i>	Germany (k = 1) USA (k = 5)
<i>Year of publication</i>	2005 to 2009
<i>Mean age of participants (range)</i>	39.07 years (28.8 to 44.06 years)
<i>Mean percentage of participants with primary diagnosis of psychosis or schizophrenia (range)</i>	87.09% (61.76 to 100%)
<i>Mean percentage of women (range)</i>	36.68% (10.58 to 45.62%)
<i>Length of treatment</i>	12 to 104 weeks
<i>Length of follow-up</i>	<i>End of treatment only</i> BELL2008 MCGURK2009  <i>Up to 6 months</i> BELL2005  <i>6- 12 months</i> LINDENMAYER2008 VAUTH2005  <i>&gt;12 months</i> MCGURK2005
<i>Intervention type</i>	Cognitive remediation programme plus vocational services programme (k = 1) Cognitive training ('Thinking Skills for Work' programme) plus

	supported employment (k = 1) Computer-assisted cognitive strategy training (plus vocational rehabilitation (k = 1) Neurocognitive enhancement therapy plus vocational rehabilitation (k = 2) Work programme with cognitive remediation programme (k = 1)
<i>Comparisons</i>	Supported employment alone (k = 1) Vocational rehabilitation alone (k = 2) Vocational services programme alone (k = 1) Work programme with computerised control condition (k = 1) Work therapy alone (k = 1)

### 13.2.4 Clinical evidence for vocational rehabilitation interventions

#### *Supported employment (standard or modified) versus prevocational training (standard or modified)*

High to moderate quality evidence from up to 18 studies with 3,476 participants showed that supported employment was more effective than prevocational training for the outcomes of gaining competitive employment, hours/weeks worked, length of time in longest job, time to first competitive job, and length of time worked. There was less conclusive evidence for any benefits regarding duration of employment and number of jobs held. However, these benefits were found at the end of the intervention and the longer-term benefits of supported employment over prevocational training are unclear.

Low to very low quality evidence from up to six studies with 985 participants suggests that supported employment is more effective than prevocational training in increasing the chances of placement in any occupation (paid/unpaid/competitive/uncompetitive), time to obtain any occupation, number of weeks worked and earnings at the end of the intervention. However, the evidence for effects on the chances of obtaining a placement in volunteer employment, the number of hours worked and longest time in one job is inconclusive. None of the included trials reported follow-up term data and thus the long-term benefits are unclear.

Moderate quality evidence from up to four trials with 699 participants was inconclusive regarding any benefits on functional disability of either intervention at the end of the intervention and at medium-term follow-up.

High quality evidence from four studies with 683 participants did not show any benefit of one intervention over the other in improving quality of life at the end of the intervention. Longer-term evidence was unavailable.

Evidence from each important outcome and overall quality of evidence are presented in Table 156. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.



**Table 156: Summary of findings table for trials of supported employment (standard or modified) compared with prevocational training (standard or modified)**

Patient or population: Adults with psychosis or schizophrenia Intervention: Supported employment (standard or modified) Comparison: Pre-vocational training (standard or modified)					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Pre-vocational training (standard or modified)	Supported employment (standard or modified)			
<i>Employment (competitive) - NOT in competitive employment, end of treatment</i>	Study population		RR 0.63 (0.56 to 0.72)	3,627 (18 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
	798 per 1000	503 per 1000 (447 to 575)			
<i>Employment (competitive) - earnings, end of treatment</i>	N/A	Mean employment, competitive – earnings, end of treatment) in the intervention groups was 0.74 standard deviations higher (0.38 to 1.10 higher)	N/A	2,475 (12 studies)	⊕⊕⊕⊖ Very low <sup>2,3</sup>
<i>Employment (competitive) - duration, end of treatment</i>	N/A	Mean employment (competitive-duration, end of treatment) in the intervention groups was 0.17 standard deviations higher (0.26 lower to 0.60 higher)	N/A	406 (2 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Employment (competitive) - longest job worked, end of treatment</i>	N/A	Mean employment (competitive - longest job worked, end of treatment) in the intervention groups was 0.45 standard deviations higher (0.07 to 0.83 higher)	N/A	661 (5 studies)	⊕⊕⊕⊖ Low <sup>1,4</sup>
<i>Employment (competitive) - time to first job, end of treatment</i>	N/A	Mean employment (competitive - time to first job, end of treatment) in the intervention groups was 0.48 standard deviations lower (0.65 to 0.31 lower)	N/A	727 (7 studies)	⊕⊕⊕⊕ High
<i>Employment (competitive) - number of jobs, end of treatment</i>	N/A	Mean employment (competitive-number of jobs, end of treatment) in the intervention groups was 0.54 standard deviations higher (0.25 to 0.84 higher)	N/A	221 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Employment (competitive) - hours worked, end of treatment</i>	N/A	Mean employment (competitive – hours worked, end of treatment) in the intervention	N/A	2,404 (9 studies)	⊕⊕⊕⊖ Very low <sup>2,3</sup>

		groups was 0.67 standard deviations higher (0.35 to 0.98 higher)			
<i>Employment (competitive) - days/weeks worked, end of treatment</i>	N/ A	Mean employment (competitive - days/ weeks worked, end of treatment) in the intervention groups was 0.72 standard deviations higher (0.46 to 0.87 higher)	N/ A	994 (7 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>
<i>Employment (competitive) - NOT in competitive employment, up to 12 months' follow-up</i>	Study population 900 per 1000	828 per 1000 (738 to 918)	RR 0.92 (0.82 to 1.02)	219 (1 study)	⊕⊕⊕⊕ Low <sup>4,5</sup>
<i>Employment (competitive) - hours worked, &gt;12 months' follow-up</i>	N/ A	Mean employment (competitive - hours worked, >12 months' follow-up) in the intervention groups was 0.42 standard deviations higher (0.06 lower to 0.91 higher)	N/ A	175 (2 studies)	⊕⊕⊕⊕ Moderate <sup>6</sup>
<i>Employment (competitive) - earning, &gt;12 months' follow-up</i>	N/ A	Mean employment (competitive - earning, >12 months' follow-up) in the intervention groups was 0.37 standard deviations higher (0.09 lower to 0.84 higher)	N/ A	175 (2 studies)	⊕⊕⊕⊕ Very low <sup>2,3,4</sup>
<i>Employment (competitive) - number of jobs, &gt;12 months' follow-up</i>	N/ A	Mean employment (competitive - number of jobs, >12 months' follow-up) in the intervention groups was 0.07 standard deviations higher (0.59 lower to 0.73 higher)	N/ A	35 (1 study)	⊕⊕⊕⊕ Moderate <sup>4</sup>
<i>Employment (competitive) - days/ weeks worked &gt;12 months' follow-up</i>	N/ A	Mean employment (competitive) - days/ weeks worked, >12 months' follow-up) in the intervention groups was 0.22 standard deviations higher (0.44 lower to 0.88 higher)	N/ A	35 (1 study)	⊕⊕⊕⊕ Moderate <sup>4</sup>
<i>Occupation (any) - NOT in any occupation (paid/unpaid/ competitive/ uncompetitive), end of treatment</i>	Study population 530 per 1000 531 per 1000	371 per 1000 (297 to 461) 372 per 1000 (297 to 462)	RR 0.70 (0.56 to 0.87)	1,043 (7 studies)	⊕⊕⊕⊕ Very low <sup>1,2,4</sup>
<i>Occupation (any) - NOT in volunteer employment, end of treatment</i>	Study population 929 per 1000 870 per 1000	966 per 1000 (780 to 1000) 905 per 1000 (731 to 1000)	RR 1.04 (0.84 to 1.28)	256 (2 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>
<i>Occupation (any) - time to first job, end of treatment</i>	N/ A	The mean occupation (any - time to first job, end of treatment) in the intervention groups was	N/ A	494 (4 studies)	⊕⊕⊕⊕ Very low <sup>1,2,4</sup>

		0.23 standard deviations lower (0.42 to 0.05 lower)			
<i>Occupation (any) - weeks worked, end of treatment</i>	N/A	Mean occupation (any - weeks worked, end of treatment) in the intervention groups was 0.32 standard deviations higher (0.17 to 0.46 higher)	N/A	731 (5 studies)	⊕⊕⊕⊕ Very low <sup>1,2,4</sup>
<i>Occupation (any) - hours worked, end of treatment</i>	N/A	Mean occupation (any - hours worked, end of treatment) in the intervention groups was 0.24 standard deviations higher (0.08 to 0.40 higher)	N/A	683 (4 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>
<i>Occupation (any) - longest job worked, end of treatment</i>	N/A	Mean occupation (any - longest job worked, end of treatment) in the intervention groups was 0.23 standard deviations higher (0.08 to 0.39 higher)	N/A	638 (4 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>
<i>Occupation (any) - number of jobs, end of treatment</i>	N/A	Mean occupation (any - number of jobs, end of treatment) in the intervention groups was 0.06 standard deviations higher (0.23 lower to 0.34 higher)	N/A	186 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - earnings, end of treatment</i>	N/A	Mean occupation (any - earnings, end of treatment) in the intervention groups was 0.37 standard deviations higher (0.2 to 0.54 higher)	N/A	552 (4 studies)	⊕⊕⊕⊕ Low <sup>1,4</sup>
<i>Global state (functional disability) - end of treatment</i>	N/A	Mean global state (functional disability - end of treatment) in the intervention groups was 0.02 standard deviations higher (0.13 lower to 0.17 higher)	N/A	699 (4 studies)	⊕⊕⊕⊕ Moderate <sup>2</sup>
<i>Global state (functional disability) - up to 12 months' follow-up</i>	N/A	Mean global state (functional disability - up to 12 months' follow-up) in the intervention groups was 0.04 standard deviations higher (0.25 lower to 0.33 higher)	N/A	188 (1 study)	⊕⊕⊕⊕ Moderate <sup>2</sup>
<i>Quality of life - end of treatment</i>	N/A	Mean quality of life (end of treatment) in the intervention groups was 0.00 standard deviations higher (0.15 lower to 0.15 higher)	N/A	683 (4 studies)	⊕⊕⊕⊕ High

Note. CI = confidence interval; RR = risk ratio.

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Evidence of serious heterogeneity of study effect size.

<sup>2</sup> Most information is from studies at moderate risk of bias.

<sup>3</sup> Evidence of very serious heterogeneity of study effect size.

<sup>4</sup> CI crosses the clinical decision threshold.

<sup>5</sup> Lack of follow-up data suggests likely publication bias.

<sup>6</sup> Optimal information size not met.

*Sub-analysis: psychosis and schizophrenia only*

For the critical outcomes of competitive employment, the sub-analysis findings did not differ from the main analysis. Unlike the main analysis, although supported employment was still superior to prevocational training for the number of people who obtained any occupation, there was no longer any evidence of a difference between groups for other proxy measures such as hours worked, earnings, longest jobs worked, and time to first job. The sub-analysis also did not show any benefit of either intervention in improving quality of life. No other critical outcome data were available. See Appendix 16 for the related forest plots.

*Sub-analysis: UK/Europe trials only*

Unlike the main analysis, there was no evidence in studies based in either the UK or Europe of a difference between treatment groups in obtaining competitive employment or in earnings at the end of the intervention. It must be noted that there was a marked reduction in the number of studies included in this sub-analysis. The sub-analysis did not differ from the main analysis for the outcomes of hours/weeks worked and quality of life. No other critical outcome data were available. See Appendix 16 for the related forest plots.

***Supported employment (standard or modified) versus control (non-vocational)***

Three studies with 2,277 participants presented very low quality evidence that supported employment increased the chance of obtaining competitive employment at the end of the intervention compared with non-vocational control. However, this effect was not found at long-term follow-up. One study with 41 participants provided moderate quality evidence that supported employment increased the hours worked, however, there was no evidence of a positive effect on days/weeks/months worked, earnings or time to first job. High quality evidence from one study with 2,055 participants showed that supported employment was superior to non-vocational control on quality of life and occupational employment outcomes such as obtaining occupation, days/weeks/months worked, earnings, hours worked per week, and highest hourly wage. No functional disability data were available. See Appendix 16 for the related forest plots.

Evidence from each important outcome and overall quality of evidence are presented in Table 157. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

*Sub-analysis: psychosis and schizophrenia only*

For the critical outcomes related to competitive employment, the sub-analysis findings did not differ from the main analysis. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 157: Summary of findings table for trials of supported employment (standard or modified) compared with control (non-vocational)**

Patient or population: Adults with psychosis or schizophrenia Intervention: Supported employment (standard or modified) Comparison: TAU/Control (non-vocational comparison group)					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TAU/control (non-vocational comparison group)	Supported employment (standard or modified)			
<i>Employment (competitive) - NOT in competitive employment, end of treatment</i>	Study population		RR 0.46 (0.25 to 0.85)	2,277 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	687 per 1000	316 per 1000 (172 to 584)			
	849 per 1000	391 per 1000 (212 to 722)			
<i>Employment (competitive) - days/ weeks/ months worked, end of treatment</i>	N/ A	Mean employment (competitive - days/ weeks/ months worked, end of treatment) in the intervention groups was 0.49 standard deviations higher (1.11 lower to 0.13 higher)	N/ A	41 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
<i>Employment (competitive) - hours worked, end of treatment</i>	N/ A	Mean employment (competitive - hours worked, end of treatment) in the intervention groups was 0.85 standard deviations higher (0.20 to 1.49 higher)	N/ A	41 (1 study)	⊕⊕⊕⊕ Moderate <sup>4</sup>
<i>Employment (competitive) - earnings, end of treatment</i>	N/ A	Mean employment (competitive - earnings, end of treatment) in the intervention groups was 0.09 standard deviations higher (0.53 lower to 0.70 higher)	N/ A	41 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
<i>Employment (competitive) - time to first job, end of treatment</i>	N/ A	Mean employment (competitive - time to first job - end of treatment) in the intervention groups was 0.09 standard deviations lower (0.22 lower to 0.05 higher)	N/ A	873 (1 study)	⊕⊕⊕⊕ High
<i>Employment (competitive) - NOT in competitive employment, &gt; 12 months' follow-up</i>	Study population		RR 0.76 (0.57 to 1.02)	152 (1 study)	⊕⊕⊕⊕ Very low <sup>3,5,6</sup>
	646 per 1000	491 per 1000 (368 to 658)			
	646 per 1000	491 per 1000 (368 to 659)			
<i>Occupation (any) - NOT in any occupation, end of</i>	Study population		RR 0.67 (0.61 to 0.73)	2,055 (1 study)	⊕⊕⊕⊕ High
	598 per 1000	400 per 1000 (364 to 436)			

<i>treatment</i>	598 per 1000	401 per 1000 (365 to 437)			
<i>Occupation (any) - time to first job, end of treatment</i>	N/A	Mean occupation (any- time to first job, end of treatment) in the intervention groups was 0.11 standard deviations lower (0.24 lower to 0.01 higher)	N/A	1,028 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - days/weeks/months worked, end of treatment</i>	N/A	Mean occupation (any - days/weeks/months worked, end of treatment) in the intervention groups was 0.37 standard deviations higher (0.28 to 0.46 higher)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - weekly earnings, end of treatment</i>	N/A	Mean occupation (any- weekly earnings, end of treatment) in the intervention groups was 0.29 standard deviations higher (0.20 to 0.38 higher)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - past 3 months' earnings, end of treatment</i>	N/A	Mean occupation (any - past 3 months' earnings, end of treatment) in the intervention groups was 0.22 standard deviations higher (0.13 to 0.31 higher)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - hours per week, end of treatment</i>	N/A	Mean occupation (any - hours per week, end of treatment) in the intervention groups was 0.36 standard deviations higher (0.28 to 0.45 higher)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High
<i>Occupation (any) - highest hourly wage, end of treatment</i>	N/A	Mean occupation (any - highest hourly wage, end of treatment) in the intervention groups was 0.3 standard deviations higher (0.22 to 0.39 higher)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High
<i>Quality of life - end of treatment</i>	N/A	Mean quality of life (end of treatment) in the intervention groups was 0.14 standard deviations lower (0.22 to 0.05 lower)	N/A	2,055 (1 study)	⊕⊕⊕⊕ High

Note. TAU = treatment as usual; CI = confidence interval; RR = risk ratio.

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Most information is from studies at moderate risk of bias.

<sup>2</sup> Evidence of very serious heterogeneity of study effect size.

<sup>3</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>4</sup> Optimal information size not met.

<sup>5</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.

<sup>6</sup> Intervention and sample may not be representative.

### ***Prevocational training (standard or modified) versus control (non-vocational)***

There was no evidence that prevocational training was more effective than non-vocational control in obtaining competitive employment (both at the end of treatment and at follow-up) or increasing earnings. However, five studies with 641 participants presented very low quality evidence that prevocational training was effective in obtaining any occupation at the end of treatment. There was however no evidence for this effect at short- and long-term follow-up. In addition, a very small study (28 participants) also provided very low quality evidence of an increase in hours worked for the prevocational intervention compared with non-vocational control. There was no conclusive evidence of any benefits on attendance in education at the end of treatment.

Moderate quality evidence from one study (N = 91) shows that prevocational training is more effective than non-vocational control in increasing quality of life. This was found at the end of the intervention and follow-up evidence was not available. No functional disability data were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 158. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

#### *Sub-analysis: psychosis and schizophrenia only*

For the critical outcome of competitive employment and quality of life, the sub-analysis findings did not differ from the main analysis. However, there was no longer evidence of any benefit of prevocational training for occupation-related outcomes. No other critical outcome data were available. See Appendix 16 for the related forest plots.

#### *Sub-analysis: UK/Europe trials only*

As with the main analysis, there was no evidence that prevocational training was more effective than non-vocational control in obtaining competitive employment at follow-up. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 158: Summary of findings table for prevocational training (standard or modified) compared with control (non-vocational)**

Patient or population: Adults with psychosis or schizophrenia					
Intervention: Prevocational training (standard or modified)					
Comparison: TAU/active control (non-vocational comparison group)					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TAU/Active control (non-vocational comparison group)	Prevocational training (standard or modified)			
<i>Employment (competitive) - NOT in competitive employment, end of treatment</i>	Study population		RR 0.87 (0.76 to 1.01)	421 (5 studies)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	766 per 1000	667 per 1000 (582 to 774)			
	688 per 1000	599 per 1000 (523 to 695)			
<i>Employment (competitive) - earnings, end of treatment</i>	N/A	Mean employment (competitive - earnings, end of treatment) in the intervention groups was 0.26 standard deviations higher (0.16 lower to 0.68 higher)	N/A	89 (1 study)	⊕⊕⊕⊖ Moderate <sup>3</sup>
<i>Employment (competitive) - up to 12 months' follow-up</i>	Study population		RR 1.18 (0.87 to 1.61)	28 (1 study)	⊕⊕⊕⊖ Low <sup>3,4</sup>
	786 per 1000	927 per 1000 (684 to 1000)			
	786 per 1000	927 per 1000 (684 to 1000)			
<i>Occupation (any) - hours worked, end of treatment</i>		Mean occupation (any - hours worked, end of treatment) in the intervention groups was 0.8 standard deviations higher (0.03 to 1.58 lower)		28 (1 study)	⊕⊕⊕⊖ Low <sup>2,3</sup>
<i>Occupation (any) - NOT in any occupation, end of treatment</i>	Study population		RR 0.73 (0.58 to 0.93)	641 (5 studies)	⊕⊕⊕⊖ Very low <sup>1,2,5</sup>
	819 per 1000	598 per 1000 (475 to 761)			
	786 per 1000	574 per 1000 (456 to 731)			
<i>Occupation (any) - up to 6 months' follow-up</i>	Study population		RR 0.78 (0.53 to 1.14)	268 (2 studies)	⊕⊕⊕⊖ Very low <sup>1,2,4,5</sup>
	803 per 1000	626 per 1000 (425 to 915)			
	843 per 1000	658 per 1000 (447 to 961)			
<i>Occupation (any)- NOT employed, 7-12 months' follow-up</i>	Study population		RR 0.88 (0.72 to 1.06)	215 (1 study)	⊕⊕⊕⊖ Very low <sup>2,3,4</sup>
	750 per 1000	660 per 1000 (540 to 795)			
	750 per 1000	660 per 1000 (540 to 795)			
<i>Education</i>	Study population		RR 0.94	211	⊕⊕⊕⊖



(attendance) - NOT attending, end of treatment	936 per 1000	880 per 1000 (823 to 945)	(0.88 to 1.01)	(2 studies)	Moderate <sup>1</sup>
	927 per 1000	871 per 1000 (816 to 936)			
Quality of life - end of treatment		Mean quality of life (end of treatment) in the intervention groups was 0.6 standard deviations lower (1.02 to 0.18 lower)		91 (1 study)	⊕⊕⊕⊖ Moderate <sup>3</sup>

Note. TAU = treatment as usual; CI = confidence interval; RR = risk ratio;

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Most information is from studies at moderate risk of bias.

<sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>3</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.

<sup>4</sup> Suspicion of publication bias.

<sup>5</sup> Evidence of serious heterogeneity of study effect size

### ***Modified prevocational training versus standard prevocational training***

There was no evidence of any difference between standard and modified prevocational training in obtaining competitive employment earnings, hours worked, and duration of longest job worked at the end of treatment. Moderate quality evidence from one study with 136 participants showed that standard prevocational training was effective at increasing the number of weeks worked, but modified prevocational training was more effective for the outcome of time to first job at the end of the intervention.

Two studies with 286 participants presented very low to moderate quality evidence that modified prevocational training was more effective than standard prevocational training for obtaining any occupation, earnings, hours worked and time to first job at the end of the intervention. Follow-up data were not available. There was no evidence of any difference between modified and standard prevocational training in terms of weeks worked and longest job worked in any occupation. No functional disability or quality of life data were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 159. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

#### ***Sub-analysis: psychosis and schizophrenia only***

For the critical outcomes associated with competitive employment and occupation, the sub-analysis findings did not differ from the main analysis. No other critical outcome data were available. See Appendix 16 for the related forest plots.

**Table 159: Summary of findings table for trials of modified prevocational training compared with standard prevocational training**

Patient or population: Adults with psychosis and schizophrenia					
Intervention: Modified prevocational training					
Comparison: Standard prevocational training					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard prevocational training	Modified prevocational training			
<i>Employment (competitive) - NOT in competitive employment, end of treatment</i>	Study population		RR 0.88 (0.73 to 1.06)	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
	821 per 1000	722 per 1000 (599 to 870)			
	544 per 1000	479 per 1000 (397 to 577)			
<i>Employment (competitive)- earnings, end of treatment</i>	N/A	Mean employment (competitive - earnings, end of treatment) in the intervention groups was 0.25 standard deviations higher (0.08 lower to 0.58 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Employment (competitive) - weeks worked, end of treatment</i>	N/A	Mean employment (competitive - weeks worked, end of treatment) in the intervention groups was 3.37 standard deviations higher (3.04 to 3.7 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Employment (competitive) - hours worked, end of treatment</i>	N/A	Mean employment (competitive - hours worked, end of treatment) in the intervention groups was 0.24 standard deviations higher (0.09 lower to 0.57 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Employment (competitive) - longest job worked, end of treatment</i>	N/A	Mean employment (competitive - longest job worked, end of treatment) in the intervention groups was 0.17 standard deviations higher (0.16 lower to 0.5 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Employment (competitive) - time to first job, end of treatment</i>	N/A	Mean employment (competitive - time to first job, end of treatment) in the intervention groups was 0.76 standard deviations lower (1.1 to 0.42 lower)	N/A	136 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Occupation (any) - NOT in any paid (competitive or uncompetitive) employment, end of treatment</i>	Study population		RR 0.53 (0.3 to 0.94)	286 (2 studies)	⊕⊕⊕⊖ Very low <sup>1,2,3</sup>
	708 per 1000	375 per 1000 (212 to 666)			
	300 per 1000	159 per 1000 (90 to 282)			
<i>Occupation (any) -</i>	N/A	Mean occupation (any -	N/A	280	⊕⊕⊕⊖

<i>earnings, end of treatment</i>		earnings, end of treatment) in the intervention groups was 0.70 standard deviations higher (0.46 to 0.95 higher)		(2 studies)	Very low <sup>1,4</sup>
<i>Occupation (any) - weeks worked, end of treatment</i>	N/A	Mean occupation (any - weeks worked, end of treatment) in the intervention groups was 0.29 standard deviations higher (0.05 lower to 0.63 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Occupation (any) - hours worked, end of treatment</i>	N/A	Mean occupation (any - hours worked, end of treatment) in the intervention groups was 0.90 standard deviations higher (0.58 to 1.21 lower)	N/A	280 (2 studies)	⊕⊕⊕⊖ Moderate <sup>1</sup>
<i>Occupation (any) - longest job worked, end of treatment</i>	N/A	Mean occupation (any - longest job worked, end of treatment) in the intervention groups was 0.29 standard deviations higher (0.04 lower to 0.62 higher)	N/A	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>
<i>Occupation (any) - time to first job, end of treatment</i>	N/A	Mean occupation (any - time to first job, end of treatment) in the intervention groups was 0.60 standard deviations lower (0.95 to 0.25 lower)	N/A	136 (1 study)	⊕⊕⊕⊖ Low <sup>1,2</sup>

Note. CI = confidence interval; RR = risk ratio.

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate of effect.

<sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>3</sup> Evidence of serious heterogeneity of study effect size.

<sup>4</sup> Evidence of very serious heterogeneity of study effect size.

### ***Modified prevocational training (paid and psychological intervention) versus modified prevocational training (paid)***

Low quality evidence from up to three studies with 210 participants showed that modifying prevocational training with both payment and the addition of a psychological intervention component was more effective than payment alone for the number of weeks worked and the number of hours worked in any occupation, and quality of life at the end of the intervention period. No other employment-related or quality of life outcomes were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 160. **Error! Not a valid bookmark self-reference..** The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

#### ***Sub-analysis: psychosis and schizophrenia only***

The sub-analysis findings did not differ from the main analysis. See Appendix 16 for the related forest plots.

**Table 160: Summary of findings table for modified prevocational training (paid and psychological intervention) compared with modified prevocational training (paid)**

Patient or population: Adults with psychosis or schizophrenia Intervention: Modified prevocational training (paid + psychological intervention) Comparison: Modified prevocational training (+ paid)					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Modified prevocational training (+paid)	Modified prevocational training (paid + psychological intervention)			
Occupation (any) - weeks worked, end of treatment	N/A	Mean occupation (any - weeks worked, end of treatment) in the intervention groups was 0.51 standard deviations higher (0.18 to 0.84 higher)	N/A	147 (2 studies)	⊕⊕⊕⊕ Low <sup>1,2</sup>
Occupation (any) - hours worked, end of treatment	N/A	Mean occupation (any - hours worked, end of treatment) in the intervention groups was 0.63 standard deviations higher (0.3 to 0.96 higher)	N/A	147 (2 studies)	⊕⊕⊕⊕ Low <sup>2</sup>
Functional disability - end of treatment	N/A	Mean functional disability (end of treatment) in the intervention groups was 0.61 standard deviations lower (0.89 to 0.33 lower)	N/A	210 (3 studies)	⊕⊕⊕⊕ Low <sup>3</sup>
Note. CI = confidence interval. *The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). <sup>1</sup> Most of the information is from studies at moderate risk of bias. <sup>2</sup> Optimal information size not met. <sup>3</sup> CI crosses the clinical decision threshold.					

### ***Supported employment plus prevocational training versus supported employment alone***

Moderate quality evidence from one study with 107 participants showed that a combined supported employment and prevocational training intervention was more effective than supported employment alone in obtaining competitive employment and earnings at the end of the intervention. No other critical outcome data were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 161. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

**Table 161: Summary of findings table supported employment plus prevocational training compared with supported employment alone**

Patient or population: Adults with psychosis or schizophrenia Intervention: Supported employment plus prevocational training Comparison: Supported employment					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Supported employment	Supported employment + prevocational training			
Employment (competitive) - end of treatment	Study population		RR 0.46 (0.25 to 0.83)	108 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
	464 per 1000	214 per 1000 (116 to 385)			
Employment, (competitive) - earnings, end of treatment	N/A	Mean employment, (competitive - earnings, end of treatment) in the intervention groups was 0.34 standard deviations higher (0.04 lower to 0.72 higher)	N/A	108 (1 study)	⊕⊕⊕⊖ Moderate <sup>2</sup>
<p>Note. CI = confidence interval; RR = risk ratio.</p> <p>*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p><sup>1</sup> Optimal information size not met.</p> <p><sup>2</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).</p>					

### ***Supported employment plus prevocational training versus prevocational training***

Moderate quality evidence from one study with 108 participants showed that a combined supported employment and prevocational training intervention was more effective than prevocational training alone in obtaining competitive employment at the end of the intervention. There was no evidence of any difference between groups in earnings. No other critical outcome data were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 162. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

**Table 162: Summary of findings table for supported employment plus prevocational training compared with prevocational training alone**

Patient or population: Adults with psychosis or schizophrenia Intervention: Supported employment + prevocational training Comparison: Prevocational training					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Prevocational training	Supported employment + prevocational training			
Employment (competitive) - end of treatment	Study population		RR 0.23 (0.13 to 0.39)	107 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
	927 per 1000	213 per 1000 (121 to 362)			
Employment, (competitive) - earnings, end of treatment	N/A	Mean employment, (competitive - earnings, end of treatment) in the intervention groups was 3.86 standard deviations higher (3.21 to 4.51 higher)	N/A	107 (1 study)	⊕⊕⊕⊖ Moderate <sup>1</sup>
Note. CI = confidence interval; RR = risk ratio. *The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). <sup>1</sup> Optimal information size not met					

### *Cognitive remediation with vocational rehabilitation versus vocational rehabilitation alone*

Low quality evidence from two studies with 116 participants showed that combined vocational rehabilitation and cognitive remediation was more effective than vocational rehabilitation alone for gaining competitive employment at the end of the intervention. However, there was no evidence of a benefit at short- and medium-term follow-up. There was no conclusive evidence of any added benefit on the outcomes of hours/weeks worked, number of jobs or earnings at the end of the intervention. No further follow-up data were available. Data assessing rates of obtaining any occupation at the end of treatment were unavailable.

Very low quality evidence from one study with 34 participants showed that the combined intervention was more effective than control for the outcome of weeks worked in any occupation (maintained when assessed at medium-term follow-up). However, the evidence for any benefit of cognitive remediation with vocational rehabilitation on hours worked or earnings in any occupation were inconclusive across follow-up time points. No other critical outcome data were available.

Evidence from each important outcome and overall quality of evidence are presented in Table 163. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 16, respectively.

**Table 163: Summary of findings table for cognitive remediation with trials of vocational rehabilitation (all) with cognitive rehabilitation compared with vocational rehabilitation alone**

Patient or population: Adults with psychosis or schizophrenia Intervention: Cognitive remediation + vocational rehabilitation Comparison: Vocational rehabilitation					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Vocational rehabilitation	Cognitive remediation + vocational rehabilitation			
<i>Employment (competitive) - NOT in competitive employment, end of treatment</i>	Study population		RR 0.47 (0.24 to 0.92)	116 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
	745 per 1000	350 per 1000 (179 to 686)			
<i>Employment (competitive) - hours worked, end of treatment</i>	N/A	Mean employment (competitive - hours worked, end of treatment) in the intervention groups was 0.38 standard deviations higher (0.31 lower to 1.26 higher)	N/A	150 (3 studies)	⊕⊕⊕⊕ Very low <sup>1,3</sup>
<i>Employment (competitive) - number of jobs, end of treatment</i>	N/A	Mean employment (competitive- number of jobs, end of treatment) in the intervention groups was 0.57 standard deviations higher (1.13 lower to 2.28 higher)	N/A	116 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Employment (competitive) - weeks worked, end of treatment</i>	N/A	Mean employment (competitive- weeks worked, end of treatment) in the intervention groups was 0.05 standard deviations lower (0.33 lower to 0.43 higher)	N/A	106 (2 studies)	⊕⊕⊕⊕ Low <sup>1,3</sup>
<i>Employment (competitive) - earnings, end of treatment</i>	N/A	Mean employment (competitive - earnings, end of treatment) in the intervention groups was 0.54 standard deviations higher (0.08 lower to 1.16 higher)	N/A	78 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Employment (competitive) - NOT in competitive employment, up to 6 months' follow-up</i>	Study population		RR 0.90 (0.72 to 1.12)	127 (1 study)	⊕⊕⊕⊕ Low <sup>4,5</sup>
	761 per 1000	685 per 1000 (548 to 853)			
<i>Employment (competitive) - NOT in competitive employment, up to 12 months' follow-up</i>	Study population		RR 0.61 (0.36 to 1.06)	65 (1 study)	⊕⊕⊕⊕ Low <sup>3,4</sup>
	571 per 1000	349 per 1000 (206 to 606)			
<i>Occupation (any) - hours worked, end</i>	N/A	Mean occupation (any - hours worked, end of treatment) in	N/A	233	⊕⊕⊕⊕

<i>of treatment</i>		the intervention groups was 0.02 standard deviations lower (0.59 lower to 0.55 higher)		(3 studies)	Very low <sup>1,2,3</sup>
<i>Occupation (any) – earnings, end of treatment</i>	N/A	The mean occupation (any – earnings, end of treatment) in the intervention groups was 0.23 standard deviations higher (0.70 lower to 1.16 higher)	N/A	161 (2 studies)	⊕⊕⊕⊕ Very low <sup>1,2,3</sup>
<i>Occupation (any) - weeks worked, end of treatment</i>	N/A	Mean occupation (any - weeks worked, end of treatment) in the intervention groups was 0.89 standard deviations higher (0.18 to 1.6 higher)	N/A	34 (1 study)	⊕⊕⊕⊕ Low <sup>3,4</sup>
<i>Occupation (any) - hours worked, up to 6 months' follow-up</i>	N/A	Mean occupation (any - hours worked, up to 6 months' follow-up) in the intervention groups was 0.45 higher (0.1 to 0.8 higher)	N/A	127 (1 study)	⊕⊕⊕⊕ Low <sup>3,4</sup>
<i>Occupation (any) - earnings, up to 6 months' follow-up</i>	N/A	Mean occupation (any – earnings, up to 6 months' follow-up) in the intervention groups was 0.14 standard deviations higher (0.21 lower to 0.48 higher)	N/A	127 (1 study)	⊕⊕⊕⊕ Low <sup>3,4</sup>
<i>Occupation (any) - did not obtain work, up to 12 months' follow-up</i>	Study population		RR 0.75 (0.49 to 1.15)	68 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
	645 per 1000	484 per 1000 (316 to 742)			
<i>Occupation (any) - hours worked, up to 12 months' follow-up</i>	N/A	Mean occupation (any - hours worked, up to 12 months' follow-up) in the intervention groups was 0.43 standard deviations higher (0.06 lower to 0.91 higher)	N/A	68 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
<i>Occupation (any) - weeks worked, up to 12 months' follow-up</i>	N/A	Mean occupation (any - weeks worked, up to 12 months' follow-up) in the intervention groups was 0.49 standard deviations higher (0.00 lower to 0.97 higher)	N/A	68 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>
<i>Occupation (any) – earnings, up to 12 months' follow-up</i>	N/A	Mean occupation (any – earnings, up to 12 months' follow-up) in the intervention groups was 0.39 standard deviations higher (0.09 lower to 0.87 higher)	N/A	68 (1 study)	⊕⊕⊕⊕ Moderate <sup>3</sup>

Note. CI = confidence interval; RR = risk ratio.

\*The basis for the assumed risk (for example, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>1</sup> Most information is from studies at moderate risk of bias.

<sup>2</sup> Evidence of serious heterogeneity of study effect size.

<sup>3</sup> CI crosses the clinical decision threshold (SMD of 0.2 or -0.2; RR of 0.75 or 1.75).

<sup>4</sup> Crucial limitation for one criterion or some limitations for multiple criteria sufficient to lower confidence in the estimate. of effect

<sup>5</sup> Optimal information size not met.



### 13.2.5 Clinical evidence summary

Overall, the clinical evidence suggests that supported employment is the most effective vocational rehabilitation method for obtaining competitive employment and for obtaining any occupation (paid/unpaid or voluntary). Furthermore, there is consistent evidence across a number of outcome measures that supported employment is more effective than prevocational training in increasing competitive employment. Evidence regarding earnings and being able to sustain employment or any occupation is less conclusive. Additionally, the long-term benefits of supported employment are not known. This was also found to be the case for sub-analyses using the studies with a high proportion of participants with psychosis and schizophrenia. However, this finding was no longer apparent for UK/Europe-based studies although caution must be exercised when interpreting the results due to the smaller number of studies eligible for these sub-analyses. Evidence regarding functional disability and quality of life was less conclusive and no firm conclusions could be drawn from the available evidence. Findings from a single study showed that a combination of supported employment with prevocational training was more effective than either prevocational training or supported employment alone in gaining competitive employment at the end of treatment but long-term efficacy is unknown.

Although prevocational training was not found to increase the chances of obtaining competitive employment, it was beneficial for obtaining any occupation. However, again, there was no evidence of any benefit beyond the conclusion of the intervention and this finding was no longer apparent in sub-analyses including only psychosis and schizophrenia samples. The UK/Europe sub-analysis did not differ from the main findings. Prevocational training was however found to improve quality of life but this was on the basis of a single small study.

Modifications to prevocational training via payment or the addition of a psychological intervention was not additionally beneficial for obtaining competitive employment. It was however beneficial for obtaining any occupation, speed of gaining occupation, increasing earnings and job retention although long-term benefits are not known. The combined modification of a psychological intervention and payment with prevocational training was found to be more beneficial than payment alone for the number of hours/weeks worked in any occupation. This was also the case in the psychosis and schizophrenia diagnosis sub-analysis. However findings are based on only two studies and the effects in the long-term are unknown.

Lastly, the combined intervention of vocational rehabilitation (any type) with cognitive remediation was found to be effective for obtaining employment at the end of the intervention period. However, this outcome was based on a single study and no further longer-term benefits were found. There was no benefit of the combined intervention on other proxy vocational outcome measures such as earnings, hours/weeks worked and number of jobs. In addition, the evidence for obtaining any occupation was inconclusive showing benefit for the combined intervention at

some follow-up points but not others. The same was found in the psychosis and schizophrenia sub-analysis.

## **13.3 HEALTH ECONOMICS EVIDENCE**

### **13.3.1 Systematic literature review**

The systematic literature search identified one eligible UK study (Heslin et al., 2011; Howard et al., 2010), one international study reporting outcomes for the UK (Knapp et al., 2013) and one US study (Dixon et al., 2002). Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

References to included studies and evidence tables for all economic studies included in the guideline systematic literature review are presented in Appendix 19.

Completed methodology checklists of the studies are provided in Appendix 18.

Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

The UK study was based on an RCT (HOWARD2010) (n = 219) and evaluated the cost effectiveness of supported employment compared with standard care that consisted of existing psychosocial rehabilitation, day care programmes and prevocational training. Howard and colleagues (2010) reported outcomes at 1-year follow-up and Heslin and colleagues (2011) at 2-year follow-up. The analysis included intervention costs and the costs of primary, secondary and community care. The intervention was provided by a not-for-profit, non-governmental supported employment agency with the support provided by CMHTs. The mean cost of intervention per person over 2 years was estimated to be approximately £300 in 2006/07 prices. Supported employment resulted in cost savings at 1- and 2-year follow-up of £2,176 (p < 0.05) and £2,361 (p = ns), respectively. Also, supported employment resulted in better vocational outcomes at years 1 and 2 (risk ratio of 1.35 [95%CI: 0.95; 1.93] and 1.91 [95%CI: 0.98; 3.74], respectively). However, these differences were statistically non-significant. Only when authors controlled for all sociodemographic factors and clinical measures at baseline did results reach statistical significance at year 1. Nevertheless, the authors concluded that even though supported employment was a dominant strategy based on point estimates, the overall benefits were modest and additional interventions may need to be provided to promote social inclusion for the majority of individuals with severe mental illness. The above cost-effectiveness analysis was judged to be directly applicable to this guideline review and the NICE reference case. However, the analysis was based on a single RCT conducted in south London which may limit the generalisability of the findings. Also, the components of the intervention and standard care were not well reported. Moreover, the intervention cost of £339 (in 2011/12 prices) associated with the provision of a supported employment programme seems to be very low when compared with the unit cost ranging from as high as £7,188 to £1,902 (depending on the caseload and the provider of the intervention) as reported by Curtis (2012). According to the authors, the supported

employment intervention was not optimally provided in the RCT and other authors have expressed concerns about the fidelity of the IPS service delivered (Latimer, 2010). According to Latimer (2010) vocational workers had far fewer contacts with clients and employers than normal and it's hardly surprising that an intervention of such low intensity had little or no effects. Based on the above considerations the analysis was judged by the GDG to have potentially serious methodological limitations.

Knapp and colleagues (Knapp et al., 2013) conducted a cost-effectiveness analysis comparing IPS with standard care over 18 months. This economic evaluation was based on an international trial (BURNS2007) ( $n = 312$ ). The sample was drawn from six European cities: Groningen (Netherlands), London (UK), Rimini (Italy), Sofia (Bulgaria), Ulm-Günzburg (Germany) and Zurich (Switzerland). Standard care varied across sites and consisted of the best typical vocational rehabilitation services in each city, followed the train-and-place approach and consisted of day treatment in all cities except for residential care in Ulm-Günzburg. The study population comprised individuals with severe mental illness including schizophrenia and schizophrenia-like disorders, bipolar disorder, or depression with psychotic features. The analysis was conducted from the perspective of health and social care and included costs associated with intervention provision, accommodation, inpatient and outpatient services, community-based services, community-based professions and medication. The outcome measures were the number of days worked in competitive settings and the percentage of sample members who worked at least 1 day. The analysis reported pooled results and results for individual sites. In the RCT it was found that at 18 months 55% of individuals assigned to IPS worked at least 1 day during the 18-month follow-up period compared with 28% individuals assigned to vocational services. Moreover, in the UK total 18-month costs per person were £7,414 and £10,985 in the IPS and vocational services groups respectively (in 2003 prices), resulting in savings of £3,769 ( $p < 0.05$ ). The authors did not report the number of days worked in competitive settings. Nevertheless, it was found that IPS was dominant when compared with vocational services using both outcomes in all sites except at Groningen, where IPS resulted in an additional cost of £30 per person for an additional 1% of individuals working at least 1 day in a competitive setting and an additional £10 per person for an additional day of work. Cost-effectiveness acceptability curves (CEACs) indicated that at a willingness to pay of £0-£1,000 for an additional 1% of clients working for at least 1 day over the 18-month period, or for an additional day of work, the probability of IPS being cost effective when compared with vocational services was nearly equal to 1.00. The authors have further attempted a partial cost-benefit analysis where intervention costs and the monetary value of employment were considered. According to the analysis, IPS was associated with a net benefit of £17,005. The authors concluded that IPS represents a more efficient use of resources than standard care. Overall this study was judged to be directly applicable to this guideline review and the NICE reference case, since it reported a sub-analysis for the UK (London). In the RCT only a small proportion of the sample was based in the UK ( $n = 50$ ). Nevertheless, the pattern of the main findings was consistent across all sites except Groningen, where according to the

authors IPS was implemented in the least effective way. The use of the percentage of sample members who worked at least one day as an outcome may have potentially biased results towards IPS. However, IPS was found to be dominant using the number of days worked in competitive settings as an outcome and also IPS was associated with the net benefit of £17,005. Although the analysis did not include QALYs it was not a problem since the intervention was found to be dominant in the UK. The time frame of the analysis was under 2 years, which may not be sufficiently long enough to capture the full effects of the intervention. Nevertheless, overall this was a well-conducted analysis and was judged by the GDG as having only minor methodological limitations.

Finally, Dixon and colleagues (2002) assessed the cost effectiveness of supported employment compared with standard care in service users with schizophrenia, schizoaffective disorder, bipolar disorder, recurrent major depression or borderline personality disorder. Standard care was defined as an enhanced vocational rehabilitation programme. The analysis was based on an RCT (n = 152) (DRAKE1999) conducted in the US from the public sector perspective. The time horizon of the analysis was 18 months. The authors found that supported employment led to a cost increase of \$3,968 and resulted in significantly greater number of hours/weeks of competitive work; however standard care was associated with greater combined earnings. Consequently, supported employment was associated with additional costs of \$13 and \$283 per extra hour and week of competitive work, respectively, and was dominated by standard care when combined earnings were used as an outcome. As a result, the authors were unable to reach any firm conclusions pertaining to the cost effectiveness of supported employment. The above cost analysis was judged to be only partially applicable to this guideline review and the NICE reference case. The time horizon of the analysis was under 2 years, which may not be sufficiently long enough to capture the outcomes associated with the intervention. Overall the analysis was well conducted and was judged by the GDG to have only minor methodological limitations.

### **13.3.2 Economic modelling**

#### *Introduction - objective of economic modelling*

Provision of supported employment programmes in adults with psychosis and schizophrenia is an area with potentially major resource implications. The UK study by Howard and colleagues (2010) had potentially serious methodological limitations due to sub-optimal provision of IPS and the study by Knapp and colleagues (2013) was a multi-centre RCT with only 50 participants from the UK site. Consequently, an economic model was developed to assess the potential cost effectiveness of these programmes for this population. Supported employment programmes may be delivered by a range of different providers including health, social care and third sector organisations. The economic analysis considered IPS and used resource use estimates from the perspective of the NHS and personal social services (PSS), as reported in Curtis (2012). UK clinical evidence on supported employment programmes was very limited, consequently clinical data for the economic analysis

are derived from international RCTs including CHANDLER1996, FREY2011 and KILLACKEY2008, which compared a supported employment programme with treatment as usual (TAU) and reported the number of participants who found paid employment in each group following the supported employment programme.

### *Economic modelling methods*

#### **Interventions assessed**

The model was developed to assess the cost effectiveness of a supported employment programme compared with TAU. The service content of supported employment and the definition of TAU varied across the studies. In CHANDLER1996 the supported employment programme was provided by multidisciplinary teams. The programme was part of integrated services comprising ACT. TAU was described as local mental health services comprising limited case management and other rehabilitative services. In FREY2011 the supported employment programme was part of integrated services that comprised access to supported employment and systematic medication management services. The programme focused on consumer choice, integrated services, competitive employment in regular work settings, rapid job search, personalised follow-on support, person-centred services and benefits counselling. TAU included a comprehensive range of services available in the local community that were sought out by the service user and may have included employment. In KILLACKEY2008 the supported employment programme was provided in combination with TAU. The vocational intervention was provided by an employment consultant enlisted for the project. TAU consisted of care from an Early Psychosis Prevention and Intervention Centre (EPPIC) that included individual case management, medical review and referral to external vocational agencies, as well as involvement with the group programme at EPPIC, which may involve participation in the vocationally-orientated groups within the programme. TAU was delivered primarily by EPPIC case managers.

As is clear from the descriptions above, TAU comprised a wide range of interventions, which were difficult to combine in terms of relevant resource use for the purposes of economic modelling. Also, the reported information on the resource utilisation in the studies was not adequate to allow costing. Consequently for the purposes of the economic model, TAU was defined as day services, which is reported as an alternative to supported employment in the UK in Curtis (2012).

#### **Model structure**

A simple decision-tree followed by a two-state Markov model was constructed using Microsoft Excel XP in order to assess the costs and outcomes associated with provision of supported employment and TAU in adults with psychosis and schizophrenia actively seeking employment. The economic model is an adaptation of the economic model that assessed supported employment versus standard care (day services) in people with autism that was developed for the NICE clinical guideline on autism in adults (NICE, 2012a).

According to the decision-tree model, which was based on the data reported in CHANDLER1996, FREY2011 and KILLACKEY2008, interventions were provided over a mean of 22 months. Over this period the mean length of time spent in employment was estimated to be 10.75 months in the intervention group versus 10.37 months in the TAU groups. Subsequently, a simple Markov model was developed to estimate the number of adults remaining in employment every year from endpoint of the decision-tree (that is, from the end of provision of the intervention) and up to 10 years, using an estimated 10-year job retention rate in those who found employment following the intervention. The Markov model consisted of the states of 'employed' and 'unemployed' and was run in yearly cycles. People in the 'employed' state could remain in this state or move to the 'unemployed' state. Similarly, people in the 'unemployed' state could remain in this state or move to the 'employed' state. In both arms of the Markov model, people who were in the 'unemployed' state were assumed to receive TAU consisting of day services for the duration of time they remained unemployed. It must be noted that people in the 'employed' state were assumed to spend only a proportion of each year in employment. A schematic diagram of the economic model is presented in Figure 10.

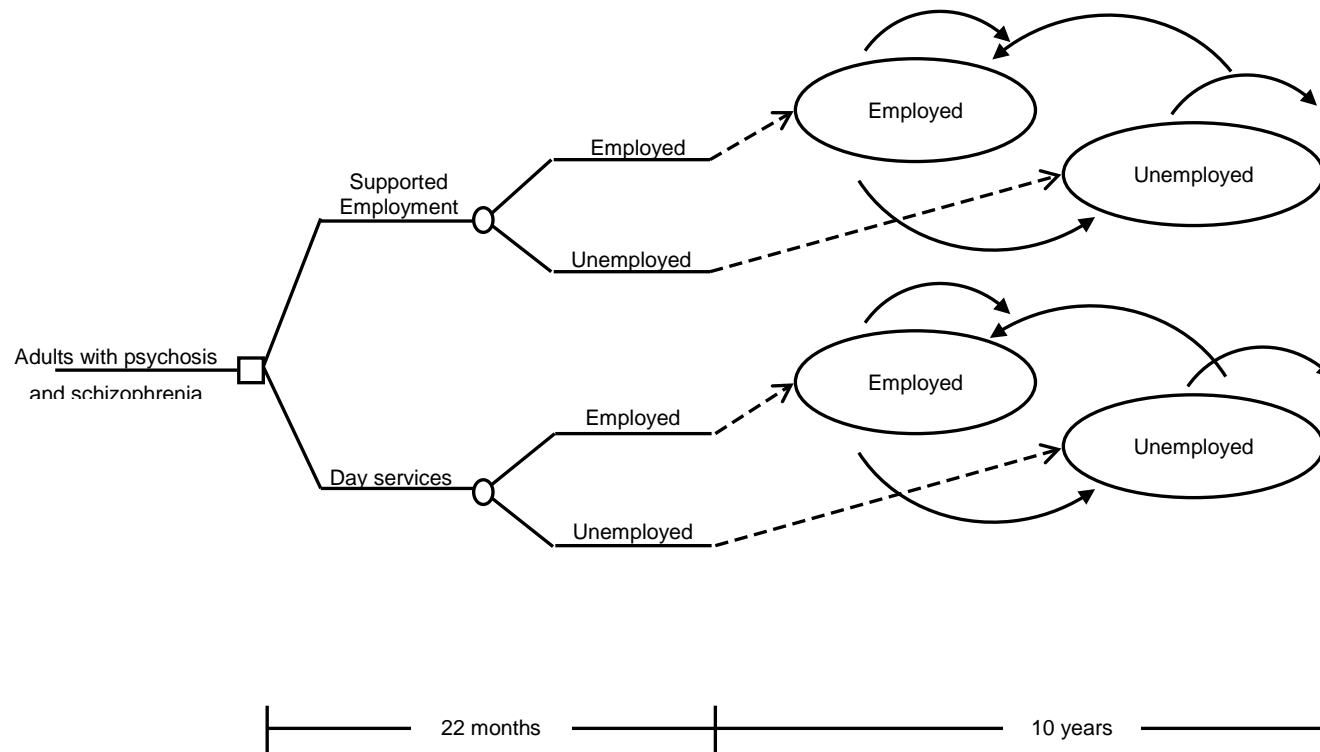
### 13.3.3 Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and PSS, as recommended by NICE (2012c). The analysis considered intervention and TAU costs and other NHS and PSS costs (including mental health, primary and secondary care). The measure of outcome was the quality-adjusted life year (QALY). Clinical input parameters of the economic model, including data on employment rates following TAU and the relative effect of supported employment programmes versus TAU at the end of the intervention period, were taken from the guideline systematic review and meta-analysis that included three RCTs (CHANDLER1996, FREY2011, KILLACKEY2008). Most of the published studies on supported employment report outcomes at the end of the intervention, consequently less is known about vocational outcomes over the long term.

Becker and colleagues (2007) conducted an exploratory study looking at 8 to 12-year employment trajectories among adults with serious mental illness who participated in the supported employment programme in a small urban mental health centre in New England, USA. This was a follow-up study to two supported employment research studies that were conducted at the same mental health centre in the early to mid-1990s with 48 and 30 participants, respectively. No significant differences in terms of patient characteristics were found between the two studies, therefore for the long-term follow-up analysis participants from both studies were combined. The authors could not contact 40 participants from the original two studies, therefore it was assumed that all had lost their jobs. In total 38 participants were interviewed 8 to 12 years later and it was found that at the follow-up interview seven participants worked 1 to 25% of time, four participants worked 26 to 50% of time, 14 participants worked 51 to 75% and 13 participants worked 76 to 100% of time. Conservatively,

only those who worked for more than 50% of the follow-up time were considered when estimating the probability of employment at 10 years' follow-up. Based on the above, the probability of employment at 10 years' follow-up was estimated to be 0.35. Although the follow-up ranged from 8 to 12 years, the unemployment rate was assumed to correspond to a mid-point of 10 years in order to estimate annual probability of unemployment.

**Figure 10: Schematic diagram of the structure of the economic model evaluating supported employment versus treatment as usual (day services) for adults with psychosis and schizophrenia**





Consequently, the annual transition probability of moving from the 'employed' to the 'unemployed' health state over long-term follow-up in the model was estimated to be 0.10. This rate was applied to both intervention and TAU groups, although it is anticipated that people attending a supported employment programme are more likely to retain their jobs after the end of the intervention compared with those under TAU. If this is the case, then the economic analysis has underestimated the long-term relative effect (in terms of remaining in paid employment) of supported employment programmes versus TAU. The annual transition probability of moving from the 'unemployed' to the 'employed' health state over 10 years was estimated using data from the studies included in the guideline systematic review (TAU arm). The same rate was applied to both intervention and TAU groups. The mean time in employment for every service user who remained in the 'employed' state of the Markov model each year following completion of the intervention was derived from the studies in the guideline systematic review – the average duration of employment was 49% in the intervention group and 47% in the TAU group for every year of employment. Clinical input parameters of the economic analysis are provided in Table 164.

### 13.3.4 Utility data and estimation of QALYs

In order to express outcomes in the form of QALYs, the health states of the economic model needed to be linked to appropriate utility scores. Utility scores represent the health-related quality of life (HRQoL) associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic search of the literature identified no studies reporting utility scores for people with psychosis and schizophrenia. To estimate QALYs for adults with psychosis and schizophrenia being in the two health states of 'employed' and 'unemployed', data reported in Squires and colleagues (2012), who conducted an economic analysis to support the NICE public health guidance on managing long-term sickness absence and incapacity for work (NICE, 2009b), were used. That economic analysis (Squires et al., 2012) used utility scores for the health states of 'being at work' and 'being on long-term sick leave' estimated based on the findings of a study aiming to predict the HRQoL of people who had been or were on long-term sick leave (Peasgood et al., 2006), which utilised data from the British Household Panel Survey (Taylor, 2003). This is a longitudinal annual survey designed to capture information on a nationally representative sample of around 10,000 to 15,000 of the non-immigrant population of Great Britain that began in 1991. Utility scores were estimated from Short Form Health Survey – 36-items (SF-36) data, using the SF-6D algorithm (Brazier et al., 2002). In the economic analysis (Squires et al., 2012), the utility scores associated with being at work or being on long-term sick leave were assumed to be the same for all individuals in each state, independent of their health status; in other words, it was assumed that the quality of life of the individual is more greatly affected by being at work or on sick leave than by the illness itself. In addition, the utility scores for people at work and those on

sick leave were assumed to capture wage and benefit payments, respectively. Utility scores were reported separately for four age categories (under 35 years; 35 to 45 years; 45 to 55 years; and over 55 years).

The economic analysis undertaken for this guideline used the utility scores reported in Squires and colleagues (2012) for adults aged below 35 years, since the mean age of participants in the studies included in the guideline systematic review ranged from 21 to 47 years. Also, the difference in utility between the states of 'being at work' and 'being on sick leave' was smaller in this age group (0.17) compared with the 35 to 45 age group (0.21), thus providing a more conservative estimate and potentially underestimating the benefit and the cost effectiveness of a supported employment programme. It must be noted that the utility of the 'unemployed' state is likely to be lower than the utility of 'being on sick leave', and therefore the analysis is likely to have further underestimated the scope for benefit of a supported employment programme. In addition, the utility scores used in the analysis refer to the general population and are not specific to adults with psychosis and schizophrenia. It is possible that adults with psychosis and schizophrenia get greater utility from finding employment compared with the general population because employment may bring them further benefits. Becker and colleagues (2007) reported that there is evidence that increased employment has enduring benefits in terms of better self-reported quality of life, self-esteem and relationships with other people. Utility data used in the economic analysis are reported in Table 164.

### **13.3.5 Cost data**

#### ***Cost data - intervention costs***

Intervention costs for supported employment programmes and day care services were based on Curtis (2012), who provided unit costs for IPS for four different grades of staff: two with professional qualifications (for example, psychology or occupational therapy) and two with no particular qualifications, ranging from Band 3 to Band 6, and for different caseloads, ranging from 10 to 25. Estimation of unit costs for IPS took into account the following cost components: wages, salary on-costs, superannuation, direct and indirect overheads, capital, team leaders who would supervise no more than ten staff and would be available to provide practical support, and a marketing budget. For this analysis, it was assumed that a supported employment programme was provided by specialists in Band 6 with a caseload of 20 people. The average annual cost per person under these conditions was £3,594.

Curtis (2012) also provides unit costs for the equivalent of IPS in day care. In the economic analysis, day care was conservatively assumed to be provided by unqualified staff in Band 3, also with a caseload of 20 people. Curtis (2012) reported that the number of day care sessions ranged from 34 to 131 annually. The lower number of sessions (34) was selected for the economic analysis, resulting in an annual cost of £1,938. All cost data input parameters are provided in Table 164.

**Table 164: Input parameters utilised in the economic model of supported employment versus treatment as usual (day care services) for adults with psychosis and schizophrenia**

Input parameter	Deterministic value	Probabilistic distribution	Source of data - comments
<b>Clinical input parameters</b>			
Probability of unemployment at 22 months – TAU	0.69	<b>Beta distribution</b> $\alpha = 796, \beta = 362$	Guideline meta-analysis
Risk ratio of unemployment at 22 months– supported employment programme versus TAU	0.46	<b>Log-normal distribution</b> 95% CI, 0.25 to 0.85	Guideline meta-analysis
Probability of employment at 10 years' follow-up	0.35	<b>Beta distribution</b> $\alpha = 27, \beta = 51$	Becker et al. (2007); data on supported employment utilised in both supported employment and treatment as usual arms
Annual transition probability from 'employed' to 'unemployed'	0.10	Distribution dependant on above distribution	-
Proportion of time employed with 'employed state' – standard care	0.47	<b>Beta distribution</b> $\alpha = 9.43, \beta = 10.57$	Studies in the guideline meta-analysis
Proportion of time employed with 'employed state' – supported employment	0.49	<b>Beta distribution</b> $\alpha = 9.77, \beta = 10.23$	Studies in the guideline meta-analysis
<b>Utility scores</b> Employed Unemployed	0.83 0.66	<b>Beta distribution</b> $\alpha = 83, \beta = 17$ $\alpha = 66, \beta = 34$	Squires et al. (2012); utility scores for general population being in work and on sick leave; distribution parameters based on assumption
<b>Cost data (2011/2012 prices)</b>			
<b>Annual intervention cost</b> Supported employment programme TAU (day care services)	£3,594 £1,938	<b>Gamma distribution</b> $\alpha = 11.11, \beta = 323.46$ $\alpha = 11.11, \beta = 174.42$	Curtis (2012); standard error assumed to be 30% of its mean estimate because of lack of relevant data
<b>Weekly health and social service cost</b> Unemployed Employed	£47 £36	<b>Gamma distribution</b> $\alpha = 24.72, \beta = 1.92$ $\alpha = 6.15, \beta = 5.85$	Schneider et al. (2009); costs were up-rated to 2011/2012 prices using the pay and prices inflation index
<b>Discount rate</b>	0.035	N/A	NICE (2012c)

It should be noted that the economic model utilised a 22-month cost for both interventions for the initial period of provision. However, after entering the Markov model, people in the 'unemployed' state were assumed to incur the annual cost of day care services in every model cycle in which they remained unemployed, and this applied to both arms of the model.

### ***Cost data - NHS and PSS costs***

Schneider and colleagues (2009) estimated the changes in costs to mental health, primary and secondary care, local authority and voluntary day care services incurred by people with mental health problems (mainly schizophrenia, bipolar disorder, anxiety disorders or depression) associated with gaining employment following registration with supported employment programmes.

The study reported baseline and 12-month follow-up data for people remaining unemployed throughout the study ( $n = 77$ ), people who found employment during the 12 months between baseline and follow-up ( $n = 32$ ), and people who were already in employment at baseline and remained in employment at follow-up ( $n = 32$ ). Cost data for people who found employment between baseline and follow-up were utilised in the economic analysis; cost data at baseline were used for the state of 'unemployed'; and cost data at follow-up were used for the state of 'employed' in both the decision-tree and the Markov part of the model. Service costs included mental health services (contacts with psychiatrist, psychologist, community psychiatric nurse, attendance at a day centre, counselling or therapeutic group work, and inpatient mental healthcare), primary care (contacts with GP, district nurse, community physiotherapist, dentist or optician), local authority services (day centres run by social services, home care and social work inputs), other secondary NHS care (hospital outpatient appointments and inpatient care for needs other than mental health) and a negligible amount of voluntary day care run by not-for-profit agencies that are independent of the public sector (about 0.3 to 0.5% of the total cost).

Chandler and colleagues (1996) found greater decline in the number of service users living in institutional settings over the 3-year period following registration with supported employment programmes when compared with service users receiving usual care. However, potential changes in accommodation type and related changes in costs have not been considered in the economic analysis since such costs may have already been included in local authority service costs reported by Schneider and colleagues (2009) and there was a risk of double counting services. All costs were expressed in 2012 prices, uplifted, where necessary, using the Hospital and Community Health Services Pay and Prices Index (Curtis, 2012). Discounting of costs and outcomes was undertaken at an annual rate of 3.5%, as recommended by NICE (2012c).

### **13.3.6 Data analysis and presentation of the results**

In order to take into account the uncertainty characterising the model input parameters, a probabilistic analysis was undertaken, in which input parameters were

assigned probability distributions, rather than being expressed as point estimates (Briggs et al., 2006b). Subsequently, 1000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Mean costs and QALYs for each intervention were then calculated by averaging across 1000 iterations. The incremental cost-effectiveness ratio (ICER) was then estimated expressing the additional cost per extra QALY gained associated with provision of supported employment instead of TAU. The probability of employment for TAU and the probability of employment at 10 years were given a beta distribution. Beta distributions were also assigned to utility values and the proportion of time employed within the 'employed' state. The risk ratio of supported employment programmes versus TAU was assigned a log-normal distribution. Costs were assigned a gamma distribution. The estimation of distribution ranges was based on available data in the published sources of evidence, and further assumptions where relevant data were not available. Table 164 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range. Results of probabilistic analysis are also presented in the form of CEACs, which demonstrate the probability of supported employment programmes being cost effective relative to TAU at different levels of willingness-to-pay per QALY, that is, at different cost-effectiveness thresholds the decision-maker may set (Fenwick et al., 2001). One-way sensitivity analyses (run with the point estimates rather than the distributions of the input parameters) explored the impact of the uncertainty characterising the model input parameters on the model's results: the intervention cost for supported employment programmes and TAU was changed by  $\pm 50\%$  to investigate whether the conclusions of the analysis would change. In addition, a threshold analysis explored the minimum relative effect of the supported employment programme that is required in order for the intervention to be cost effective using the NICE cost-effectiveness threshold.

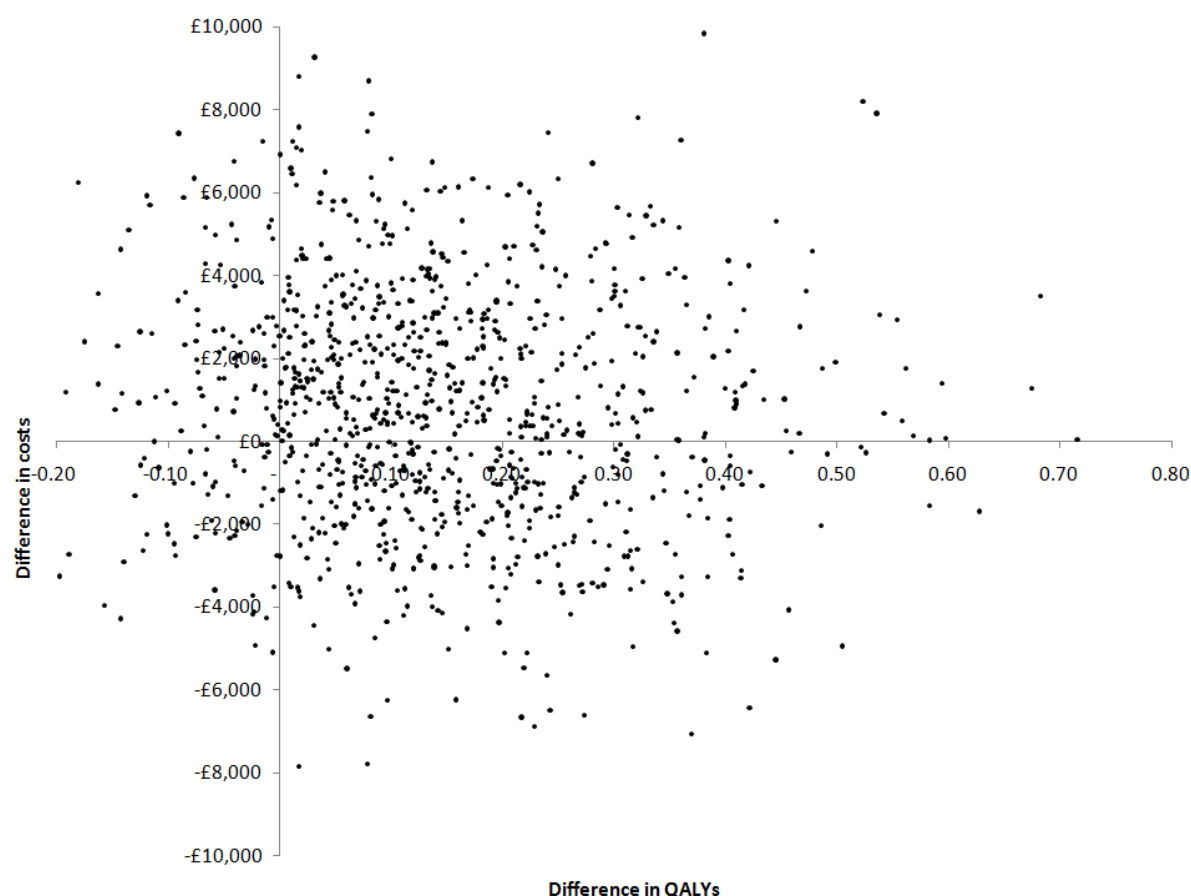
## **Results**

The results are presented in Table 165. Supported employment programmes are associated with a higher cost but also produce a higher number of QALYs compared with TAU. The ICER of supported employment programmes versus TAU is £5,723 per QALY gained, which is well below the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY, indicating that supported employment programmes may be a cost-effective option when compared with TAU. The cost effectiveness plane showing the incremental costs and QALYs of supported employment programmes versus TAU resulting from 1000 iterations of the model is shown in Figure 11. According to the CEAC the probability of supported employment programme being cost effective at the NICE lower cost-effectiveness threshold of £20,000/QALY is 0.66, while at the NICE upper cost-effectiveness threshold of £30,000/QALY it is 0.71.

**Table 165: Results of economic analysis – mean total cost and QALYs of each intervention at 10 years’ follow-up assessed per adult with psychosis and schizophrenia seeking employment**

Intervention	Supported employment programmes	Treatment as usual	Difference
Total cost	£34,239	£33,441	£798
Total QALYs	7.25	7.11	0.14
ICER		£5,723/QALY	

**Figure 11: Cost effectiveness plane showing incremental costs and QALYs of supported employment programme versus TAU (day care services) per adult with psychosis or schizophrenia seeking employment. Results based on 1000 iterations.**



One-way sensitivity analysis showed that as the risk ratio is varied across its range the cost effectiveness of supported employment ranges from being dominant to £48,307 per QALY gained. Also, threshold analysis revealed that the minimum risk ratio of supported employment programmes versus TAU required in order for the intervention to be considered cost effective according to NICE criteria was 0.69 using the lower £20,000/QALY threshold and 0.77 using the upper £30,000/QALY threshold. Moreover, as the intervention cost of supported employment programme was changed by  $\pm 50\%$ , the ICER ranged from £23,201/QALY to supported employment being dominant and if the cost of TAU was changed by  $\pm 50\%$ , then the ICER ranged from a supported employment programme being dominant to £23,903 per QALY gained.

### **13.3.7 Discussion of findings – limitations of the analysis**

The results of the economic analysis indicate that a supported employment programme is likely to be a cost-effective intervention compared with TAU. Supported employment programmes are associated with a higher cost but also produce a higher number of QALYs compared with TAU. The ICER of supported employment programmes versus TAU is £5,723 per QALY gained, which is well below the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY. The probability of supported employment programmes being cost effective at the NICE lower cost-effectiveness threshold of £20,000/QALY was 0.66, while at the NICE upper cost-effectiveness threshold it was 0.71.

In terms of clinical data, the economic analysis was based on three non-UK studies comparing a supported employment programme with TAU. Frey and colleagues (2011) conducted a large RCT (FREY2011) ( $n = 2,238$ ) in service users with schizophrenia spectrum or mood disorders across multiple locations in the USA. Killackey and colleagues (2008) conducted a small RCT (KILLACKEY2008) ( $n = 41$ ) in service users with schizophrenia in Australia. Chandler and colleagues (1996) undertook a medium-sized RCT (CHANDLER1996) ( $n = 256$ ) in service users with unspecified serious mental illness in the USA. It is not clear to what extent clinical effectiveness can be generalised to the UK, given many structural differences in the economy, the labour market, and health and social care systems between the USA, Australia and the UK. Nevertheless, a recent review by Bond and colleagues (2012) compared the results of nine RCTs of IPS in the USA with six RCTs outside the USA. The authors examined competitive employment outcomes, including employment rate, days to first job, weeks worked during follow-up, and hours worked. They also considered non-competitive employment, programme retention and non-vocational outcomes. It was found that the overall competitive employment rate for IPS clients in US studies was significantly higher than in non-US studies (62% versus 47%). However it was concluded that the consistently positive competitive employment outcomes strongly favouring IPS over a range of comparison programmes in a group of international studies suggest that IPS is an evidence-based practice that may transport well into new settings as long as programmes achieve high fidelity to the IPS model. In all studies included in the guideline meta-analysis the risk ratio of a

supported employment programme versus TAU in terms of vocational outcomes was significant. The uncertainty in the clinical effectiveness estimate was assessed using deterministic sensitivity analysis. It showed that as the risk ratio is varied across its range the cost effectiveness of supported employment ranges from being dominant to £48,307 per QALY gained, reflecting high uncertainty around the risk ratio estimate. The threshold analysis revealed that the minimum risk ratio of supported employment programmes versus TAU required in order for the intervention to be considered cost effective according to NICE criteria was 0.69 using the lower £20,000/QALY threshold and 0.77 using the upper £30,000/QALY threshold.

In the studies used to assess the clinical effectiveness of supported employment programmes in the guideline meta-analysis, TAU was defined as local mental health services that included individual case management, medical review and other rehabilitative services. A wide range of services provided under TAU and inadequate information reported in the studies made it impossible to model TAU according to these studies. According to the GDG, in the UK the current best alternative to a supported employment programme would be a prevocational training programme. However, given the lack of data pertaining to resource utilisation associated with providing a prevocational training programme it was not possible to cost it. Nevertheless, a prevocational programme is likely to be more resource intensive than a supported employment programme as it is likely to involve work crews, training, practising skills, job support, sheltered workshops, and so on. Also, a greater mix of specialists is likely to be involved in providing a prevocational programme including, but not limited to, mental health providers, vocational counsellors, case managers, employment specialists, vocational staff, and so on; usually prevocational programmes last longer because of the prolonged preparation time. In the guideline systematic review it was found that more participants gain competitive employment following a supported employment programme compared with a prevocational programme (RR 0.63 [95% CI: 0.56; 0.72]). As a result, a supported employment programme is likely to be dominant when compared with a prevocational training programme, that is, a supported employment programme results in better clinical outcomes and lower costs.

Where data were not available or further estimates needed to be made, the economic analysis always adopted conservative estimates that were likely to underestimate the cost effectiveness of supported employment programmes. The intervention cost of supported employment programme was estimated to be high because it was assumed that the intervention was provided by specialists in Band 6. Given the lack of data, in the economic analysis day care was defined as an alternative to a supported employment programme. It was conservatively assumed to be provided by unqualified staff in Band 3 and that the lower estimate of 34 annual sessions was selected. The uncertainty associated with the definition of TAU and its associated costs was assessed using deterministic sensitivity analysis. It was found that if the cost of TAU was changed by as much as 50% the ICER ranged from a supported



employment programme being dominant to £23,903 per QALY gained, which is still below the upper NICE cost-effectiveness threshold of £30,000 per QALY.

Also, most published RCT studies on supported employment report outcomes 12 to 24 months after first joining the programme. This is mainly because of the costs and complexity of following up people for much longer periods of time, particularly those who are no longer in receipt of services (Sainsbury Centre for Mental Health, 2009). Consequently, employment retention rates following a supported employment programme were taken from an exploratory study looking at 8 to 12-year employment trajectories among adults with serious mental illness who participated in a supported employment programme. Becker and colleagues (2007) interviewed 38 of 78 participants (49% with severe mental illness) 8 to 12 years after they enrolled in supported employment studies in a small urban mental health centre in New England, USA. This study reported that 35% of participants who participated in supported employment programme were in employment during the long-term follow-up which was used to estimate the annual probability of employment. The same rate was applied to both intervention and TAU groups, although service users attending a supported employment programme are more likely to retain their jobs after the end of the intervention. If this was the case, then the economic analysis has underestimated the long-term relative effects (in terms of remaining in paid employment) of supported employment programme versus TAU. Moreover, the rates were taken from a small USA-based study and it is questionable how transferable the results are to the UK, given many structural differences in the economy, labour market and health and welfare systems between the USA and other countries (Sainsbury Centre for Mental Health, 2009). Regardless of the uncertainty in the estimated employment retention rate the deterministic sensitivity analysis indicated that even if it is assumed that as few as 5% of participants retained their jobs at 10-year follow-up, the cost effectiveness of supported employment would be £16,617 per QALY gained, which is still below the lower NICE cost-effectiveness threshold of £20,000/QALY.

Moreover, the analysis considered extra NHS and PSS costs associated with employment status. Cost data were taken from a small study (n = 77) by Schneider and colleagues (2009), which measured costs incurred by people with mental health problems including schizophrenia, bipolar disorder, anxiety disorders or depression attending employment support programmes. The study reported that study participants entering work showed a substantial decrease in mental health services costs, which outweighed a slight increase in other secondary care costs, making an overall reduction in health and social care costs statistically significant. The authors' estimate was that the reduction in mental health service use was possibly an effect of getting a job, although they did not rule out the possibility that a third variable, such as cognitive impairment, might be driving both employment outcomes and reduction in service use. The reported service costs within the analysis include those that would typically fall on the NHS and PSS perspective, although some local authority costs were also included such as day centres run by social services, home care and other social work inputs. The local authority costs accounted for

approximately 10% of service costs; the deterministic sensitivity analysis indicated that reducing service costs by 10% resulted in a cost per QALY of £6,794, which is still well below the lower NICE cost-effectiveness threshold of £20,000/QALY. Also, according to the GDG, some of the aforementioned services could be provided by a range of providers including the NHS and PSS. Some trusts (but not all) provide social care/social work input on behalf of the local authorities, consequently some of the local authority costs may be relevant from the NHS and PSS perspective.

Utility scores, which are required for the estimation of QALYs, were not available for adults with psychosis and schizophrenia. Instead, utility scores obtained from the general population for the states 'being at work' and 'being on sick leave' were used in the analysis, based on data reported in Squires and colleagues (2012). It is acknowledged that these scores are not directly relevant to adults with psychosis and schizophrenia in employed or unemployed status. Moreover, the utility of the 'unemployed' state is potentially lower than the utility of 'being on sick leave'. Nevertheless, the utility scores used in the economic analysis are likely to capture, if somewhat conservatively, the HRQoL of adults with psychosis and schizophrenia with regard to their employment status. Also it is possible that adults with severe mental illness may get greater utility from finding employment compared with the general population, as employment may bring further psychological and social benefits, including enhancements to self-esteem, relationships and illness management (Becker et al., 2007).

The analysis adopted the NHS and PSS perspective. Other costs, such as lost productivity or wages earned and the tax gains to the exchequer, and reduction in welfare benefits, were not taken into account because they were beyond the perspective of the analysis. Also such programmes have a positive effect on the HRQoL of families, partners and carers of adults with psychosis and schizophrenia, which was not possible to capture in the economic analysis.

### **13.3.8 Validation of the economic model**

The economic model (including the conceptual model and the Excel spread sheet) was developed by the guideline health economist and checked by a second modeller not working on the guideline. The model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The results were discussed with the GDG for their plausibility.

### **13.3.9 Overall conclusions from economic modelling**

Overall, although based on limited evidence, the findings of the economic analysis indicate that a supported employment programme is potentially a cost-effective intervention for adults with psychosis and schizophrenia because it can increase the rate of employment in this population group, improve the person's wellbeing, and potentially reduce the economic burden to health and social services and the wider society.

## 13.4 LINKING EVIDENCE TO RECOMMENDATIONS

### *Relative value placed on the outcomes considered:*

The GDG agreed that the main aim of a vocational rehabilitation intervention is to get people into employment and to improve functioning and quality of life. For cognitive remediation with vocational rehabilitation, the aim of the review was to evaluate if the addition of a cognitive remediation intervention to vocational rehabilitation improved vocational outcomes and not if they improved cognitive outcomes (the efficacy of cognitive remediation alone is evaluated in Chapter 9). Therefore, the GDG judged that employment and education, quality of life and functional disability were critical outcomes. Important, but not critical, outcomes were considered to be adverse effects, effects on symptom-focused outcomes and service use, as well as satisfaction with services and acceptability. Although these outcomes were not considered critical in informing recommendations for the benefits of vocational rehabilitation on the outcomes pertinent to the intervention (vocational and functioning), they informed the GDG about the feasibility of the intervention.

### *Trade-off between clinical benefits and harms:*

For adults with psychosis and schizophrenia, the GDG considered there to be reasonable evidence that the benefits of a supported employment intervention outweigh the possible risk of harm (for example, relapse due to the negative effects of being employed). The evidence suggests that vocational rehabilitation (all formats) is more effective than a non-vocational intervention/control for gaining employment (competitive or otherwise) and although any additional benefit on functioning or quality of life is uncertain and varied across interventions, it also does not adversely affect psychological health or exacerbate psychotic symptoms. Furthermore, supported employment was more effective than prevocational training for vocational outcomes and equal to prevocational training for functioning and quality of life outcomes, and did not have a harmful effect on psychological health (for example, hospital admissions and psychological distress).

The GDG felt there was a paucity of follow-up data evaluating the long-term efficacy of vocational rehabilitation interventions. However, the group believed that the potential negative consequences of not being offered any vocational support outweighed the lack of confidence in the long-term benefits.

### *Trade-off between net health benefits and resource use*

For adults with psychosis and schizophrenia the health economic evidence for supported employment versus prevocational training is limited to one UK-based study. The GDG felt that prevocational training is likely to be more resource intensive and is expected to be more expensive than supported employment intervention. The international evidence is mixed. One study undertaken across six European sites found IPS dominant when compared with standard care in all but one site. However, the study undertaken in the USA could not reach firm

conclusions pertaining to the cost effectiveness of IPS. According to the guideline economic analysis, for adults with psychosis and schizophrenia a supported employment intervention appears to be cost effective when compared with a non-vocational intervention or control. Despite limitations in the economic analysis (for instance, weak and mainly USA-based evidence for the clinical effectiveness, lack of long-term follow-up data, lack of data pertaining to treatment as usual, utility values specific for this population not being available), the findings were robust to underlying assumptions. In general, the health economic evidence supports the GDG's view that a vocational rehabilitation intervention should be provided.

### *Quality of the evidence*

For supported employment versus prevocational training, the evidence ranged from very low to high. Reasons for downgrading concerned risk of bias, high heterogeneity or lack of precision in confidence intervals. Heterogeneity was a major concern when evaluating the evidence. The interventions and controls varied between studies. However, although variance was observed in the effect size across studies, the direction of effect was consistent across most studies.

### *Other considerations*

The evidence suggested that any vocational rehabilitation intervention was beneficial on quality of life and functioning outcomes compared with a non-vocational control group. The GDG felt that this finding supported their recommendation that a vocational rehabilitation intervention should be provided. The evidence also suggested that supported employment is more effective than prevocational training for gaining competitive employment. The GDG judged that this would only be appropriate for those who desired competitive employment. For those who need a more gradual introduction into work and would like support before entering into competitive employment, there is some evidence of efficacy for prevocational training. The GDG believed that there should be an element of choice for the service user, with those seeking immediate competitive employment to have the option of supported employment, and those unable to return to work immediately being provided with support and training before attempting to gain competitive employment. The GDG discussed collaboration between various local stakeholders to ensure the service user is supported in education, and obtaining and retaining occupation and employment. It was decided that this should include local stakeholders for black, Asian and minority ethnic groups. The GDG also discussed that vocational employment, education, or any daytime activities should be monitored and a part of the care plan.

The majority of the evidence base was from the USA and sub-analyses revealed that the benefit of vocational rehabilitation interventions was not as compelling in studies based in only the UK or Europe, although the same trends were observed. Although the GDG felt this was of some concern, it highlights the need for more trials evaluating services provided in the UK.

The evidence base for the combined intervention of cognitive remediation and vocational rehabilitation was found to be too limited to make a recommendation and the GDG identified this as potential topic for a research recommendation for more UK-based studies.

## **13.5 RECOMMENDATIONS**

- 13.5.1.1** For people who are unable to attend mainstream education, training or work, facilitate alternative educational or occupational activities according to their individual needs and capacity to engage with such activities, with an ultimate goal of returning to mainstream education, training or employment. [new 2014]
- 13.5.1.2** Offer supported employment programmes to people with psychosis or schizophrenia who wish to find or return to work. Consider other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment. [new 2014]
- 13.5.1.3** Mental health services should work in partnership with local stakeholders, including those representing black, Asian and minority ethnic groups, to enable people with mental health problems, including psychosis or schizophrenia, to stay in work or education and to access new employment (including self-employment), volunteering and educational opportunities. [2009; amended 2014]
- 13.5.1.4** Routinely record the daytime activities of people with psychosis or schizophrenia in their care plans, including occupational outcomes. [2009]

# 14 SUMMARY OF RECOMMENDATIONS

## 14.1 CARE ACROSS ALL PHASES

### 14.1.1 Service user experience

**14.1.1.1** Use this guideline in conjunction with [Service user experience in adult mental health](#) (NICE clinical guidance 136) to improve the experience of care for people with psychosis or schizophrenia using mental health services, and:

- work in partnership with people with schizophrenia and their carers
- offer help, treatment and care in an atmosphere of hope and optimism
- take time to build supportive and empathic relationships as an essential part of care. [2009; amended 2014]

### 14.1.2 Race, culture and ethnicity

The NICE guideline on service user experience in adult mental health (NICE clinical guidance 136) includes recommendations on communication relevant to this section.

**14.1.2.1** Healthcare professionals inexperienced in working with people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds should seek advice and supervision from healthcare professionals who are experienced in working transculturally. [2009]

**14.1.2.2** Healthcare professionals working with people with psychosis or schizophrenia should ensure they are competent in:

- assessment skills for people from diverse ethnic and cultural backgrounds
- using explanatory models of illness for people from diverse ethnic and cultural backgrounds
- explaining the causes of psychosis or schizophrenia and treatment options
- addressing cultural and ethnic differences in treatment expectations and adherence
- addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the causes of abnormal mental states
- negotiating skills for working with families of people with psychosis or schizophrenia
- conflict management and conflict resolution. [2009]

**14.1.2.3** Mental health services should work with local voluntary black, Asian and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to people from diverse ethnic and cultural backgrounds. [2009]

### **14.1.3 Physical health**

**14.1.3.1** People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider. [new 2014]

**14.1.3.2** If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see Obesity [NICE clinical guideline 43], Lipid modification [NICE clinical guideline 67] and Preventing type 2 diabetes [NICE public health guidance 38]). [new 2014]

**14.1.3.3** Offer people with psychosis or schizophrenia who smoke help to stop smoking, even if previous attempts have been unsuccessful. Be aware of the potential significant impact of reducing cigarette smoking on the metabolism of other drugs, particularly clozapine and olanzapine. [new 2014]

**14.1.3.4** Consider one of the following to help people stop smoking:

- nicotine replacement therapy (usually a combination of transdermal patches with a short-acting product such as an inhalator, gum, lozenges or spray) for people with psychosis or schizophrenia **or**
- bupropion<sup>58</sup> for people with a diagnosis of schizophrenia **or**
- varenicline for people with psychosis or schizophrenia.

Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first 2–3 weeks. [new 2014]

**14.1.3.5** For people in inpatient settings who do not want to stop smoking, offer nicotine replacement therapy to help them to reduce or temporarily stop smoking. [new 2014]

**14.1.3.6** Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia. These should be audited in the annual team report. [new 2014]

**14.1.3.7** Trusts should ensure compliance with quality standards on the monitoring and treatment of cardiovascular and metabolic disease in people with psychosis or schizophrenia through board-level performance indicators. [new 2014]

---

<sup>58</sup> At the time of publication (February 2014), bupropion was contraindicated in people with bipolar disorder. Therefore, it is not recommended for people with psychosis unless they have a diagnosis of schizophrenia.

## **14.1.4 Comprehensive services provision**

**14.1.4.1** All teams providing services for people with psychosis or schizophrenia should offer a comprehensive range of interventions consistent with this guideline. [2009]

## **14.1.5 Support for carers**

**14.1.5.1** Offer carers of people with psychosis or schizophrenia an assessment (provided by mental health services) of their own needs and discuss with them their strengths and views. Develop a care plan to address any identified needs, give a copy to the carer and their GP and ensure it is reviewed annually. [new 2014]

**14.1.5.2** Advise carers about their statutory right to a formal carer's assessment provided by social care services and explain how to access this. [new 2014]

**14.1.5.3** Give carers written and verbal information in an accessible format about:

- diagnosis and management of psychosis and schizophrenia
- positive outcomes and recovery
- types of support for carers
- role of teams and services
- getting help in a crisis.

When providing information, offer the carer support if necessary. [new 2014]

**14.1.5.4** As early as possible negotiate with service users and carers about how information about the service user will be shared. When discussing rights to confidentiality, emphasise the importance of sharing information about risks and the need for carers to understand the service user's perspective. Foster a collaborative approach that supports both service users and carers, and respects their individual needs and interdependence. [new 2014]

**14.1.5.5** Review regularly how information is shared, especially if there are communication and collaboration difficulties between the service user and carer. [new 2014]

**14.1.5.6** Include carers in decision-making if the service user agrees. [new 2014]

**14.1.5.7** Offer a carer-focused education and support programme, which may be part of a family intervention for psychosis and schizophrenia, as early as possible to all carers. The intervention should:

- be available as needed
- have a positive message about recovery. [new 2014]



### **14.1.6 Peer support and self-management**

**14.1.6.1** Consider peer support for people with psychosis or schizophrenia to help improve service user experience and quality of life. Peer support should be delivered by a trained peer support worker who has recovered from psychosis or schizophrenia and remains stable. Peer support workers should receive support from their whole team, and support and mentorship from experienced peer workers. [new 2014]

**14.1.6.2** Consider a manualised self-management programme delivered face-to-face with service users, as part of the treatment and management of psychosis or schizophrenia. [new 2014]

**14.1.6.3** Peer support and self-management programmes should include information and advice about:

- psychosis and schizophrenia
- effective use of medication
- identifying and managing symptoms
- accessing mental health and other support services
- coping with stress and other problems
- what to do in a crisis
- building a social support network
- preventing relapse and setting personal recovery goals. [new 2014]

## **14.2 PREVENTING PSYCHOSIS**

### **14.2.1 Referral from primary care**

**14.2.1.1** If a person is distressed, has a decline in social functioning and has:

- transient or attenuated psychotic symptoms **or**
- other experiences or behaviour suggestive of possible psychosis **or**
- a first-degree relative with psychosis or schizophrenia

refer them for assessment without delay to a specialist mental health service or an early intervention in psychosis service because they may be at increased risk of developing psychosis. [new 2014]

### **14.2.2 Specialist assessment**

**14.2.2.1** A consultant psychiatrist or a trained specialist with experience in at-risk mental states should carry out the assessment. [new 2014]

### **14.2.3 Treatment options to prevent psychosis**

**14.2.3.1** If a person is considered to be at increased risk of developing psychosis (as described in recommendation 14.2.1.1):

- offer individual cognitive behavioural therapy (CBT) with or without family intervention (delivered as described in recommendations 14.3.7.1 and 14.3.7.2) **and**

- offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. [new 2014]

#### **14.2.3.2 Do not offer antipsychotic medication:**

- to people considered to be at increased risk of developing psychosis (as described in recommendation 14.2.1.1) **or**
- with the aim of decreasing the risk of or preventing psychosis. [new 2014]

### **14.2.4 Monitoring and follow-up**

**14.2.4.1** If, after treatment (as described in recommendation 14.2.3.1), the person continues to have symptoms, impaired functioning or is distressed, but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using a structured and validated assessment tool. Determine the frequency and duration of monitoring by the:

- severity and frequency of symptoms
- level of impairment and/or distress and
- degree of family disruption or concern. [new 2014]

**14.2.4.2** If a person asks to be discharged from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's GP to continue monitoring changes in their mental state. [new 2014]

## **14.3 FIRST EPISODE PSYCHOSIS**

### **14.3.1 Early intervention in psychosis services**

**14.3.1.1** Early intervention in psychosis services should be accessible to all people with a first episode or first presentation of psychosis, irrespective of the person's age or the duration of untreated psychosis. [new 2014]

**14.3.1.2** People presenting to early intervention in psychosis services should be assessed without delay. If the service cannot provide urgent intervention for people in a crisis, refer the person to a crisis resolution and home treatment team (with support from early intervention in psychosis services). Referral may be from primary or secondary care (including other community services) or a self- or carer-referral. [new 2014]

**14.3.1.3** Early intervention in psychosis services should aim to provide a full range of pharmacological, psychological, social, occupational and educational interventions for people with psychosis, consistent with this guideline. [2014]

**14.3.1.4** Consider extending the availability of early intervention in psychosis services beyond 3 years if the person has not made a stable recovery from psychosis or schizophrenia. [new 2014]

## **14.3.2 Primary care**

**14.3.2.1** Do not start antipsychotic medication for a first presentation of sustained psychotic symptoms in primary care unless it is done in consultation with a consultant psychiatrist. [2009; amended 2014]

## **14.3.3 Assessment and care planning**

**14.3.3.1** Carry out a comprehensive multidisciplinary assessment of people with psychotic symptoms in secondary care. This should include assessment by a psychiatrist, a psychologist or a professional with expertise in the psychological treatment of people with psychosis or schizophrenia. The assessment should address the following domains:

- psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- physical health and wellbeing (including weight, smoking, nutrition, physical activity and sexual health)
- psychological and psychosocial, including social networks, relationships and history of trauma
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- social (accommodation, culture and ethnicity, leisure activities and recreation, and responsibilities for children or as a carer)
- occupational and educational (attendance at college, educational attainment, employment and activities of daily living)
- quality of life
- economic status. [2009; amended 2014]

**14.3.3.2** Assess for post-traumatic stress disorder and other reactions to trauma because people with psychosis or schizophrenia are likely to have experienced previous adverse events or trauma associated with the development of the psychosis or as a result of the psychosis itself. For people who show signs of post-traumatic stress, follow the recommendations in [Post-traumatic stress disorder](#) (NICE clinical guideline 26). [new 2014]

**14.3.3.3** Routinely monitor for other coexisting conditions, including depression, anxiety and substance misuse particularly in the early phases of treatment. [2009; amended 2014]

**14.3.3.4** Write a care plan in collaboration with the service user as soon as possible following assessment, based on a psychiatric and psychological formulation, and a full assessment of their physical health. Send a copy of the care plan to the primary healthcare professional who made the referral and the service user. [2009; amended 2014]

**14.3.3.5** For people who are unable to attend mainstream education, training or work, facilitate alternative educational or occupational activities according to their individual needs and capacity to engage with such activities, with an ultimate goal of returning to mainstream education, training or employment. [new 2014]

## **14.3.4 Treatment options**

**14.3.4.1** For people with first episode psychosis offer:

- oral antipsychotic medication (see sections 14.3.5. and 14.3.6) in conjunction with
- psychological interventions (family intervention and individual CBT, delivered as described in recommendations 14.3.7.1 and 14.3.7.2). [new 2014]

**14.3.4.2** Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try psychological interventions alone:

- offer family intervention and CBT
- agree a time (1 month or less) to review treatment options, including introducing antipsychotic medication
- continue to monitor symptoms, distress, impairment and level of functioning (including education, training and employment) regularly. [new 2014]

**14.3.4.3** If the person's symptoms and behaviour suggest an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in [Bipolar disorder](#) (NICE clinical guideline 38) or [Depression](#) (NICE clinical guideline 90). [new 2014]

## **14.3.5 Choice of antipsychotic medication**

**14.3.5.1** The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences). [2009; amended 2014]

## **14.3.6 How to use antipsychotic medication**

**14.3.6.1** Before starting antipsychotic medication, undertake and record the following baseline investigations:

- weight (plotted on a chart)
- waist circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity. [new 2014]

**14.3.6.2** Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if:

- specified in the summary of product characteristics (SPC)
- a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
- there is a personal history of cardiovascular disease **or**
- the service user is being admitted as an inpatient. [2009]

**14.3.6.3** Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following:

- Discuss and record the side effects that the person is most willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the British national formulary (BNF) or SPC.
- Justify and record reasons for dosages outside the range given in the BNF or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks. [2009; amended 2014]

**14.3.6.4** Monitor and record the following regularly and systematically throughout treatment, but especially during titration:

- response to treatment, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks, at 1 year and then annually (plotted on a chart)
- waist circumference annually (plotted on a chart)

- pulse and blood pressure at 12 weeks, at 1 year and then annually
- fasting blood glucose, HbA1c and blood lipid levels at 12 weeks, at 1 year and then annually
- adherence
- overall physical health. [new 2014]

**14.3.6.5** The secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. [new 2014]

**14.3.6.6** Discuss any non-prescribed therapies the service user wishes to use (including complementary therapies) with the service user, and carer if appropriate. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009]

**14.3.6.7** Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments. [2009]

**14.3.6.8** 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 14.3.6.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC. [2009]

**14.3.6.9** Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation'). [2009]

**14.3.6.10** Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). [2009]

**14.3.6.11** If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary. [2009]

### **14.3.7 How to deliver psychological interventions**

**14.3.7.1** CBT should be delivered on a one-to-one basis over at least 16 planned session and:

- Follow a treatment manual<sup>59</sup> so that:
  - people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning
  - the re-evaluation of people's perceptions, beliefs or reasoning relates to the target symptoms

---

<sup>59</sup> Treatment manuals that have evidence for their efficacy from clinical trials are preferred.

- also include at least one of the following components:
- people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms
- promoting alternative ways of coping with the target symptom
- reducing distress
- improving functioning. [2009]

#### **14.3.7.2 Family intervention should:**

- include the person with psychosis or schizophrenia if practical
- be carried out for between 3 months and 1 year
- include at least 10 planned sessions
- take account of the whole family's preference for either single-family intervention or multi-family group intervention
- take account of the relationship between the main carer and the person with psychosis or schizophrenia
- have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work. [2009]

### **14.3.8 Monitoring and reviewing psychological interventions**

**14.3.8.1** When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including service user satisfaction and, if appropriate, carer satisfaction. [2009]

**14.3.8.2** Healthcare teams working with people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review:

- access to and engagement with psychological interventions
- decisions to offer psychological interventions and equality of access across different ethnic groups. [2009]

### **14.3.9 Competencies for delivering psychological interventions**

**14.3.9.1** Healthcare professionals providing psychological interventions should:

- have an appropriate level of competence in delivering the intervention to people with psychosis or schizophrenia
- be regularly supervised during psychological therapy by a competent therapist and supervisor. [2009]

**14.3.9.2** Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological therapy interventions recommended in this guideline. [2009]

## **14.4 SUBSEQUENT ACUTE EPISODES OF PSYCHOSIS OR SCHIZOPHRENIA AND REFERRAL IN CRISIS**

### **14.4.1 Service-level interventions**

- 14.4.1.1** Offer crisis resolution and home treatment teams as a first-line service to support people with psychosis or schizophrenia during an acute episode in the community if the severity of the episode, or the level of risk to self or others, exceeds the capacity of the early intervention in psychosis services or other community teams to effectively manage it. [new 2014]
- 14.4.1.2** Crisis resolution and home treatment teams should be the single point of entry to all other acute services in the community and in hospitals. [new 2014]
- 14.4.1.3** Consider acute community treatment within crisis resolution and home treatment teams before admission to an inpatient unit and as a means to enable timely discharge from inpatient units. Crisis houses or acute day facilities may be considered in addition to crisis resolution and home treatment teams depending on the person's preference and need. [new 2014]
- 14.4.1.4** If a person with psychosis or schizophrenia needs hospital care, think about the impact on the person, their carers and other family members, especially if the inpatient unit is a long way from where they live. If hospital admission is unavoidable, ensure that the setting is suitable for the person's age, gender and level of vulnerability, support their carers and follow the recommendations in [Service user experience in adult mental health](#) (NICE clinical guidance 136). [new 2014]

### **14.4.2 Treatment options**

- 14.4.2.1** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer:
- oral antipsychotic medication in conjunction (see sections 14.3.5. and 14.3.6 with
  - psychological interventions (family intervention and individual CBT, delivered as described in recommendations 14.3.7.1 and 14.3.7.2). [new 2014]

### **14.4.3 Pharmacological interventions**

- 14.4.3.1** For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 14.3.5. and 14.3.6). Take into account the clinical response and side effects of the service user's current and previous medication. [2009; amended 2014]



#### **14.4.4 Psychological and psychosocial interventions**

**14.4.4.1** Offer CBT to all people with psychosis or schizophrenia (delivered as described in recommendation 14.3.7.1). This can be started either during the acute phase or later, including in inpatient settings. [2009]

**14.4.4.2** Offer family intervention to all families of people with psychosis or schizophrenia who live with or are in close contact with the service user (delivered as described in recommendation 14.3.7.2). This can be started either during the acute phase or later, including in inpatient settings. [2009]

**14.4.4.3** Consider offering arts therapies to all people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings. [2009]

**14.4.4.4** Arts therapies should be provided by a Health and Care Professions Council registered arts therapist with previous experience of working with people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the service user. Aims of arts therapies should include:

- enabling people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others
- helping people to express themselves and to organise their experience into a satisfying aesthetic form
- helping people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to the person. [2009]

**14.4.4.5** When psychological treatments, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption. [2009]

**14.4.4.6** Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to people with psychosis or schizophrenia. However, take service user preferences into account, especially if other more efficacious psychological treatments, such as CBT, family intervention and arts therapies, are not available locally. [2009]

**14.4.4.7** Do not offer adherence therapy (as a specific intervention) to people with psychosis or schizophrenia. [2009]

**14.4.4.8** Do not routinely offer social skills training (as a specific intervention) to people with psychosis or schizophrenia. [2009]

### **14.4.5 Behaviour that challenges**

- 14.4.5.1** Occasionally people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. The management of immediate risk should follow the relevant NICE guidelines (see recommendations 14.4.5.2 and 14.4.5.5). [2009]
- 14.4.5.2** Follow the recommendations in [Violence](#) (NICE clinical guideline 25) when facing imminent violence or when considering rapid tranquillisation. [2009]
- 14.4.5.3** After rapid tranquillisation, offer the person with psychosis or schizophrenia the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes. [2009]
- 14.4.5.4** Ensure that the person with psychosis or schizophrenia has the opportunity to write an account of their experience of rapid tranquillisation in their notes. [2009]
- 14.4.5.5** Follow the recommendations in [Self-harm](#) (NICE clinical guideline 16) when managing acts of self-harm in people with psychosis or schizophrenia. [2009]

### **14.4.6 Early post-acute period**

- 14.4.6.1** After each acute episode, encourage people with psychosis or schizophrenia to write an account of their illness in their notes. [2009]
- 14.4.6.2** Healthcare professionals may consider using psychoanalytic and psychodynamic principles to help them understand the experiences of people with psychosis or schizophrenia and their interpersonal relationships. [2009]
- 14.4.6.3** Inform the service user that there is a high risk of relapse if they stop medication in the next 1–2 years. [2009]
- 14.4.6.4** If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. [2009]
- 14.4.6.5** After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years. [2009]

## **14.5 PROMOTING RECOVERY AND POSSIBLE FUTURE CARE**

### **14.5.1 General principles**

- 14.5.1.1** Continue treatment and care in early intervention in psychosis services or refer the person to a specialist integrated community-based team. This team should:
  - offer the full range of psychological, pharmacological, social and occupational interventions recommended in this guideline

- be competent to provide all interventions offered
- place emphasis on engagement rather than risk management
- provide treatment and care in the least restrictive and stigmatising environment possible and in an atmosphere of hope and optimism in line with Service user experience in adult mental health (NICE clinical guidance 136). [new 2014]

**14.5.1.2** Consider intensive case management for people with psychosis or schizophrenia who are likely to disengage from treatment or services. [new 2014]

**14.5.1.3** Review antipsychotic medication annually, including observed benefits and any side effects. [new 2014].

## **14.5.2 Return to primary care**

**14.5.2.1** Offer people with psychosis or schizophrenia whose symptoms have responded effectively to treatment and remain stable the option to return to primary care for further management. If a service user wishes to do this, record this in their notes and coordinate transfer of responsibilities through the care programme approach. [2009]

## **14.5.3 Primary care**

### *Monitoring physical health in primary care*

**14.5.3.1** Develop and use practice case registers to monitor the physical and mental health of people with psychosis or schizophrenia in primary care. [2009]

**14.5.3.2** GPs and other primary healthcare professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, focusing on physical health problems that are common in people with psychosis and schizophrenia. Include all the checks recommended in 14.3.6.1 and refer to relevant NICE guidance on monitoring for cardiovascular disease, diabetes, obesity and respiratory disease. A copy of the results should be sent to the care coordinator and psychiatrist, and put in the secondary care notes. [new 2014]

**14.5.3.3** Identify people with psychosis or schizophrenia who have high blood pressure, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity following relevant NICE guidance (see Lipid modification [NICE clinical guideline 67], Preventing type 2 diabetes [NICE public health guidance 38], Obesity [NICE clinical guideline 43], Hypertension [NICE clinical guideline 127], Prevention of cardiovascular disease [NICE public health guidance 25] and Physical activity [NICE public health guidance 44]). [new 2014]

**14.5.3.4** Treat people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance (for example, see Lipid modification [NICE clinical guideline 67], Type 1 diabetes [NICE clinical guideline 15], Type 2 diabetes [NICE clinical guideline 66], Type 2 diabetes – newer agents [NICE clinical guideline 87]). [2009]

**14.5.3.5** Healthcare professionals in secondary care should ensure, as part of the care programme approach, that people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 14.5.3.1–14.5.3.4. [2009]

#### *Relapse and re-referral to secondary care*

**14.5.3.6** When a person with an established diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances), primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan. [2009]

**14.5.3.7** For a person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is:

- poor response to treatment
- non-adherence to medication
- intolerable side effects from medication
- comorbid substance misuse
- risk to self or others. [2009]

**14.5.3.8** When re-referring people with psychosis or schizophrenia to mental health services, take account of service user and carer requests, especially for:

- review of the side effects of existing treatments
- psychological treatments or other interventions. [2009]

#### *Transfer*

**14.5.3.9** When a person with psychosis or schizophrenia is planning to move to the catchment area of a different NHS trust, a meeting should be arranged between the services involved and the service user to agree a transition plan before transfer. The person's current care plan should be sent to the new secondary care and primary care providers. [2009]

### **14.5.4 Psychological interventions**

**14.5.4.1** Offer CBT to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission. Deliver CBT as described in recommendation 14.3.7.1. [2009]

**14.5.4.2** Offer family intervention to families of people with psychosis or schizophrenia who live with or are in close contact with the service user. Deliver family intervention as described in recommendation 14.3.7.2. [2009]

**14.5.4.3** Family intervention may be particularly useful for families of people with psychosis or schizophrenia who have:

- recently relapsed or are at risk of relapse
- persisting symptoms. [2009]

**14.5.4.4** Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms. [2009]

### **14.5.5 Pharmacological interventions**

**14.5.5.1** The choice of drug should be influenced by the same criteria recommended for starting treatment (see sections 14.3.5 and 14.3.6). [2009]

**14.5.5.2** Do not use targeted, intermittent dosage maintenance strategies<sup>60</sup> routinely. However, consider them for people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity. [2009]

**14.5.5.3** Consider offering depot /long-acting injectable antipsychotic medication to people with psychosis or schizophrenia:

- who would prefer such treatment after an acute episode
- where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. [2009]

### **14.5.6 Using depot/long-acting injectable antipsychotic medication**

**14.5.6.1** When initiating depot/long-acting injectable antipsychotic medication:

- take into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics)
- take into account the same criteria recommended for the use of oral antipsychotic medication (see sections 14.3.5 and 14.3.6), particularly in relation to the risks and benefits of the drug regimen
- initially use a small test dose as set out in the BNF or SPC. [2009]

---

<sup>60</sup> Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.

### **14.5.7 Interventions for people whose illness has not responded adequately to treatment**

**14.5.7.1** For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment:

- Review the diagnosis.
- Establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration.
- Review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families.
- Consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. [2009]

**14.5.7.2** Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic. [2009]

**14.5.7.3** For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 14.5.7.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine. [2009]

### **14.5.8 Employment, education and occupational activities**

**14.5.8.1** Offer supported employment programmes to people with psychosis or schizophrenia who wish to find or return to work. Consider other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment. [new 2014]

**14.5.8.2** Mental health services should work in partnership with local stakeholders, including those representing black, Asian and minority ethnic groups, to enable people with mental health problems, including psychosis or schizophrenia, to stay in work or education and to access new employment (including self-employment), volunteering and educational opportunities. [2009; amended 2014]

**14.5.8.3** Routinely record the daytime activities of people with psychosis or schizophrenia in their care plans, including occupational outcomes. [2009]

## **14.6 RESEARCH RECOMMENDATIONS**

### **14.6.1 Peer support interventions**

What is the clinical and cost effectiveness of peer support interventions in people with psychosis and schizophrenia?

#### **Why this is important**

Service users have supported the development of peer support interventions, which have recently proliferated in the UK, but current evidence for these interventions in people with psychotic disorders is not strong and the studies are mainly of very low quality. Moreover the content of the programmes has varied considerably, some using structured interventions, others providing more informal support. There is therefore an urgent need for high-quality evidence in this area.

The programme of research would be in several stages. First, there should be development work to establish what specifically service users want from peer support workers, as opposed to what they want from professionals, and what the conditions are for optimal delivery of the intervention. This development work should be co-produced by exploring the views of service users, experienced peer support workers and developers of peer support interventions, and suitable outcome measures should be identified reflecting the aims of peer support. Second, the intervention, delivered as far as possible under the optimal conditions, should be tested in a high-quality trial. Further research should test structured and manualised formats versus unstructured formats (in which service user and peer decide together what to cover in the session). Benefits and adverse effects experienced by peer support workers should also be measured.

### **14.6.2 People who choose not to take antipsychotic medication**

What is the clinical and cost effectiveness of psychological intervention alone, compared with treatment as usual, in people with psychosis or schizophrenia who choose not to take antipsychotic medication?

#### **Why this is important**

The development of alternative treatment strategies is important for the high proportion of people with psychosis and schizophrenia who choose not to take antipsychotic medication, or discontinue it because of adverse effects or lack of efficacy. There is evidence that psychological interventions (CBT and family intervention) as an adjunct to antipsychotic medication are effective in the treatment of psychosis and schizophrenia and are cost saving. However, there is little evidence for family intervention or CBT alone, without antipsychotic medication.

The programme of research should compare the clinical and cost effectiveness of psychological intervention alone (CBT and/or family intervention) with treatment as usual for people with psychosis or schizophrenia who choose not to take

antipsychotic medication, using an adequately powered study with a randomised controlled design. Key outcomes should include symptoms, relapse rates, quality of life, treatment acceptability, social functioning and the cost effectiveness of the interventions.

### **14.6.3 The physical health benefits of discontinuing antipsychotic medication**

What are the short- and long-term benefits to physical health of guided medication discontinuation and/or reduction in first episode psychosis and can this be achieved without major risks?

#### **Why this is important**

There is growing concern about the long-term health risks, increased mortality and cortical grey matter loss linked to cumulative neuroleptic exposure in people with psychosis. The majority of young adults discontinue their medication in an unplanned way because of these risks. A Dutch moderately-sized open trial has reported successful discontinuation of medication in 20% of people without serious relapse; at 7-year follow-up there was continuous benefit for guided reduction in terms of side effects, functioning and employment, with no long-term risks. If replicated, this would mark a significant breakthrough in reducing the long-term physical health risks associated with antipsychotic treatment and improving outcomes.

The programme of research should use an adequately powered, multicentre, double-blind, randomised controlled design to test the physical health benefits, risks and costs of discontinuing or reducing antipsychotic medication among young adults with first episode psychosis who have achieved remission. The primary outcomes should be quality of life and metabolic disorder, including weight gain; secondary outcomes should include side effects, serious relapse, acceptability and user preference.

### **14.6.4 Maintaining the benefits of early intervention in psychosis services after discharge**

How can the benefits of early intervention in psychosis services be maintained once service users are discharged after 3 years?

#### **Why this is important**

Early intervention in psychosis services deliver evidence-based interventions in a positive, youth-friendly setting, improve outcomes, are cost effective and have high service user acceptability and engagement. Once people are transferred to primary care or community mental health services these gains are diminished. The guideline recommends that trusts consider extending these services. However, the extent to which gains would be maintained and who would benefit most is not known. The successful element of early intervention in psychosis services might be incorporated



into mainstream services for psychosis, but how this would function, and its cost effectiveness, needs to be determined.

The suggested programme of research should use an adequately powered, multi-centre randomised trial comparing extending early intervention in psychosis services (for example, for 2 years) versus providing augmented (step-down) care in community mental health services versus treatment as usual to determine whether the gains of early intervention can be maintained and which service users would benefit most under each condition. The primary outcome should be treatment/service engagement and secondary outcomes should include relapse, readmission, functioning and user preference.

### **14.6.5 Interventions for PTSD symptoms in people with psychosis and schizophrenia**

What is the benefit of a CBT-based trauma reprocessing intervention on PTSD symptoms in people with psychosis and schizophrenia?

#### **Why this is important**

PTSD symptoms have been documented in approximately one-third of people with psychosis and schizophrenia. The absence of PTSD symptoms in this context predicts better mental health outcomes, lower service use and improved life satisfaction. Two-thirds of the traumatic intrusions, observed in first episode and established psychosis, relate to symptoms of psychosis and its treatment (including detention). One study has demonstrated proof-of-principle in first episode psychosis for trauma reprocessing, focusing on psychosis-related intrusions. Replication of the study will fill a major gap in treatment for this population and may have other benefits on psychotic symptoms and service use.

The suggested programme of research would use an adequately powered, multi-centre randomised trial to test whether a CBT-based trauma reprocessing intervention can reduce PTSD symptoms and related distress in people with psychosis and schizophrenia. The trial should be targeted at those with high levels of PTSD symptoms, particularly traumatic intrusions, following first episode psychosis. The follow-up should be up to 2 years and the intervention should include 'booster' elements, extra sessions of CBT-based trauma reprocessing interventions, and a health economic evaluation.

## 15 REFERENCES

- Aagaard J, Freiesleben M, Foldager L. Crisis homes for adult psychiatric patients. *Social Psychiatry and Psychiatric Epidemiology*. 2008;43:403-9.
- Aberg-Wistedt A, Cressell T, Lidberg Y, Liljenberg B, Osby U. Two-year outcome of team-based intensive case management for patients with schizophrenia. *Psychiatric Services*. 1995;46:1263-66.
- Achim AM, Maziade M, Raymond É, Olivier D, Mérette C, Roy M. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophrenia Bulletin*. 2011;37:811-21.
- Acil AA, Dogan S, Dogan O. The effects of physical exercises to mental state and quality of life in patients with schizophrenia. *Journal of Psychiatric and Mental Health Nursing*. 2008;15:808-15.
- Adams CE, Fenton MK, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *The British Journal of Psychiatry*. 2001;179:290-9.
- Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophrenia Research*. 2011;125:54-61.
- Addington J, Saeedi H, Addington D. Weight gain in first-episode psychosis over three years. *Schizophrenia Research*. 2006;86:335-36.
- Advisory Conciliation and Arbitration Service. ACAS- Promoting employment relations and HR excellence. 2009.[cited 29 May 12]:Available from: <http://www.acas.org.uk/index.aspx?articleid=1361>.
- Agid O, Mamo D, Ginovart N, Vitcu I, Wilson AA, Zipursky RB, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response-a double-blind PET study in schizophrenia. *Neuropsychopharmacology*. 2007;32:1209-15.
- AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Quality and Safety in Health Care*. 2003;12:18-23.
- Akbarpour F, Rezaei O, Khodaie-Ardakani MR, Sheikvatan M, Goodarzi H, Dolatshahi B. A double-blind placebo-controlled trial of bupropion for smoking

abstinence and cognition improvement in schizophrenia. *Minerva Psichiatrica*. 2010;51:263-69.

Alanen YO. *Schizophrenia: Its Origins and Need-Adapted Treatment*. London: Karnac Books; 1997.

Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *The Lancet*. 2005;366:1059-62.

Alexeyeva I, Mauskopf J, Earnshaw SR, Stauffer VL, Gibson JP, Ascher-Svanum H, et al. Comparing olanzapine and ziprasidone in the treatment of schizophrenia: a case study in modeling. *Journal of Drug Assessment*. 2001;4:275-88.

Almerie MQ, Alkhateeb H, Essali A, Matar HE, Rezk E. Cessation of medication for people with schizophrenia already stable on chlorpromazine. *Cochrane Database of Systematic Reviews*. 2007 Art. No. CD006329.

Almond S, Knapp M, Francois C, Toumi M, Brugha T. Relapse in schizophrenia: costs, clinical outcomes and quality of life. *The British Journal of Psychiatry*. 2004;184:346-51.

Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK. *Pharmacoeconomics*. 2000;17:383-89.

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica Supplementum*. 2004:21-7.

Alvarez-Jimenez M, Gonzalez-Blanch C, Crespo-Facorro B, Hetrick S, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. *CNS Drugs*. 2008;22:547-62.

Alvarez-Jiménez M, González-Blanch C, Vázquez-Barquero JL, Pérez-Iglesias R, Martínez-García O, Pérez-Pardal T, et al. Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naïve first-episode psychosis patients: a randomized controlled trial. *Journal of Clinical Psychiatry*. 2006;67:1253-60.

American Diabetes Association, American Psychiatric Association, American Association of Clinical E, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Journal of Clinical Psychiatry*. 2004;65:267-72.

Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Archives of General Psychiatry*. 2010;67:146-54.

Andrew A, Knapp M, McCrone PR, Parsonage M, Trachtenberg M. *Effective Interventions in Schizophrenia: The Economic Case*. London: Personal Social Services Research Unit, London School of Economics and Political Science; 2012.

Anzai N, Yoneda S, Kumagai N, Nakamura Y, Ikebuchi E, Liberman RP. Training persons with schizophrenia in illness self-management: a randomized controlled trial in Japan. *Psychiatric Services*. 2002;53:545-47.

Armstrong NP, Steffen JJ. The recovery promotion fidelity scale: assessing the organizational promotion of recovery. *Community Mental Health Journal*. 2009;45:163-70.

Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *The British Journal of Psychiatry*. 2004;184:110-7.

Askey R, Holmshaw J, Gamble C, Gray R. What do carers of people with psychosis need from mental health services? Exploring the views of carers, service users and professionals. *Journal of Family Therapy*. 2009;31:310-31.

Assion HJ, Reinbold H, Lemanski S, Basilowski M, Juckel G. Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to clozapine. A randomized, double-blind, placebo-controlled trial. *Pharmacopsychiatry*. 2008;41:24-8.

Attux C, Martini LC, Elkis H, Tamai S, Freirias A, Camargo MDGM, et al. A 6-month randomized controlled trial to test the efficacy of a lifestyle intervention for weight gain management in schizophrenia. *BMC Psychiatry*. 2013;13.

Audini B, Marks IM, Lawrence RE, Connolly J, Watts V. Home-based versus out-patient/in-patient care for people with serious mental illness. Phase II of a controlled study. *The British Journal of Psychiatry*. 1994;165:204-10.

Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoeconomics*. 2008;26:149-62.

Ayllon T, Azrin NH. The measurement and reinforcement of behavior of psychotics. *Journal of the Experimental Analysis of Behavior*. 1965;8:357-83.

Bagnall AM, Jones L, Ginnelly L, Lewis R, Glanville J, Gilbody S, et al. A systematic review of atypical antipsychotic drugs in schizophrenia. *Health Technology Assessment*. 2003;7:1-193.

Baker A, Richmond R, Haile M, Lewin T, Carr V, Taylor R, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *American Journal of Psychiatry*. 2006;163:1934-42.

Banerjee S, Clancy C, Crome I. Co-existing Problems of Mental Disorder and Substance Misuse ('Dual Diagnosis'): An Information Manual. London: Royal College of Psychiatrists Research Unit; 2002.

Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction*. 2010;105:1176-89.

Barbic S, Krupa T, Armstrong I. A randomized controlled trial of the effectiveness of a modified recovery workbook program: preliminary findings. *Psychiatric Services*. 2009;60:491-97.

Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. *Patient Education and Counseling*. 2002;48:177-87.

Barnable A, Gaudine A, Bennett L, Meadus R. Having a sibling with schizophrenia: a phenomenological study. *Research and Theory for Nursing Practice*. 2006;20:247-64.

Barnes TR, Curson DA. Long-term depot antipsychotics. A risk-benefit assessment. *Drug Safety*. 1994;10:464-79.

Barnes TR, Drake MJ, Paton C. Nocturnal enuresis with antipsychotic medication. *The British Journal of Psychiatry*. 2012;200:7-9.

Barnes TR, McPhillips MA. Critical analysis and comparison of the side-effect and safety profiles of the new antipsychotics. *The British Journal of Psychiatry*. 1999;34-43.

Barnes TR, Paton C, Cavanagh MR, Hancock E, Taylor DM, UK Prescribing Observatory for Mental Health. A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophrenia Bulletin*. 2007;33:1397-403.

Barnes TR, Shingleton-Smith A, Paton C. Antipsychotic long-acting injections: prescribing practice in the UK. *The British Journal of Psychiatry*. 2009;52:S37-42.

Barnes TRE, Buckley P, Schulz SC. Treatment-resistant schizophrenia. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia Second Edition*. Oxford: Blackwell Publishing; 2003.

- Barrowclough C, Haddock G, Tarrier N, Lewis SW, Moring J, O'Brien R, et al. Randomized controlled trial of motivational interviewing, cognitive behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *American Journal of Psychiatry*. 2001;158:1706-13.
- Basset T, Faulkner A, Repper J, Stamou E. Lived experience leading the way: peer support in mental health. Report. London: Together for Mental Wellbeing; 2010.
- Bauer MS, McBride L, Williford WO, Glick H, Kinosian B, Altshuler L, et al. Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. *Psychiatric Services*. 2006;57:927-36.
- Beard JH, Pitt RB, Fisher SH, Goertzel V. Evaluating the effectiveness of a psychiatric rehabilitation program. *American Journal of Orthopsychiatry*. 1963;33:701-12.
- Beard SM, Maciver F, Clouth J, Ruther E. A decision model to compare health care costs of olanzapine and risperidone treatment for schizophrenia in Germany. *The European Journal of Health Economics*. 2006;7:165-72.
- Bebbington P, Kuipers L. The predictive utility of expressed emotion in schizophrenia: an aggregate analysis. *Psychological medicine*. 1994;24:707-18.
- Bebbington PE, Bhugra D, Brugha T, Singleton N, Farrell M, Jenkins R, et al. Psychosis, victimisation and childhood disadvantage: evidence from the second British national survey of psychiatric morbidity. *The British Journal of Psychiatry*. 2004;185:220-6.
- Bechdolf A, Wagner M, Ruhrmann S, Harrigan S, Putzfeld V, Pukrop R, et al. Preventing progression to first-episode psychosis in early initial prodromal states. *The British Journal of Psychiatry*. 2012;200:22-9.
- Beck AT. *Cognitive Therapy and the Emotional Disorders*. New York: International Universities Press; 1979.
- Becker D, Whitley R, Bailey EL, Drake RE. Long-term employment trajectories among participants with severe mental illness in supported employment. *Psychiatric Services*. 2007;58:922-28.
- Becker RE. An evaluation of a rehabilitation program for chronically hospitalized psychiatric patients. *Social Psychiatry and Psychiatric Epidemiology*. 1967;2:32-38.
- Beebe LH. Effect of a motivational group intervention on exercise self-efficacy and outcome expectations for exercise in schizophrenia spectrum disorders. *Journal of the American Psychiatric Nurses Association*. 2010;16:105-13.

Bell DNF, Blanchflower DG. Young people and the Great Recession. *Oxford Review of Economic Policy*. 2011;27:241-67.

Bell M, Lysaker P, Bryson G. A behavioral intervention to improve work performance in schizophrenia: work behavior inventory feedback. *Journal of Vocational Rehabilitation*. 2003;18:43-50.

Bell M, Zito W, Greig T. Neurocognitive enhancement therapy and competitive employment in schizophrenia: Effects on clients with poor community functioning. *American Journal of Psychiatric Rehabilitation*. 2008;11:109-22.

Bell MD, Bryson GJ, Greig TC, Fiszdon JM, Wexler BE. Neurocognitive enhancement therapy with work therapy: productivity outcomes at 6- and 12-month follow-ups. *Journal of Rehabilitation Research and Development*. 2005;42:829-38.

Bell MD, Milstein RM, Lysaker PH. Pay as an incentive in work participation by patients with severe mental-illness. *Hospital and Community Psychiatry*. 1993;44:684-86.

Bellack AS. Skills training for people with severe mental illness. *Psychiatric Rehabilitation Journal*. 2004;27:375-91.

Bennett D, Freeman H, eds. Principles and prospect. In *Community Psychiatry*. Edinburgh: Churchill Livingstone; 1991.

Bentall RP. Deconstructing the concept of 'schizophrenia'. *Journal of Mental Health*. 1993;2:223-38.

Bentall RP, Jackson HF, Pilgrim D. Abandoning the concept of 'schizophrenia': some implications of validity arguments for psychological research into psychotic phenomena. *The British Journal of Clinical Psychology / The British Psychological Society*. 1988;27:303-24.

Bentall RP, Morrison AP. More harm than good: the case against using antipsychotic drugs to prevent severe mental illness. *Journal of Mental Health*. 2002;11:351-56.

Bergner E, Leiner AS, Carter T, Franz L, Thompson NJ, Compton MT. The period of untreated psychosis before treatment initiation: a qualitative study of family members' perspectives. *Comprehensive Psychiatry*. 2008;49:530-6.

Berlin JA. Does blinding of readers affect the results of meta-analyses? *The Lancet*. 2001;350:185-86.

Bertolote J, McGorry P. Early intervention and recovery for young people with psychosis: consensus statement. *British Journal of Psychiatry*. 2005;187:116-19.

Bhugra D, Harding C, Lippett R. Pathways into care and satisfaction with primary care for black patients in South London. *Journal of Mental Health*. 2004;13:171-83.

Bhui K, Bhugra D, McKenzie K. Specialist Services for Minority Ethnic Groups? Maudsley Discussion Paper no 8. 2000.

Bhui K, McKenzie K, Gill P. Delivering mental health services for a diverse society. *BMJ*. 2004;329:363-4.

Bhui K, Sashidharan SP. Should there be separate psychiatric services for ethnic minority groups? *The British Journal of Psychiatry*. 2003;182:10-12.

Bhui K, Warfa N, Edonya P, McKenzie K, Bhugra D. Cultural competence in mental health care: a review of model evaluations. *BMC health services research*. 2007;7:15.

Bhui KS, McKenzie K. Rates and risk factors by ethnic group for suicides within a year of contact with mental health services in England and Wales. *Psychiatric Services*. 2008;59:414-20.

Biggs D, Hovey N, Tyson PJ, MacDonald S. Employer and employment agency attitudes towards employing individuals with mental health needs. *Journal of Mental Health*. 2010;19:505-16.

Bindman J, Johnson S, Wright S, Szumukler G, Bebbington P, Kuipers E, et al. Integration between primary and secondary services in the care of the severely mentally ill: patients' and general practitioners' views. *The British Journal of Psychiatry*. 1997;171:169-74.

Bio DS, Gattaz WF. Vocational rehabilitation improves cognition and negative symptoms in schizophrenia. *Schizophrenia Research*. 2011;126:265-69.

Birchwood M. Pathways to emotional dysfunction in first-episode psychosis. *The British Journal of Psychiatry*. 2003;182:373-5.

Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *The British Journal of Psychiatry*. 1992;160:806-14.

Bjorkman T, Hansson L, Sandlund M. Outcome of case management based on the strengths model compared to standard care. A randomised controlled trial. *Social Psychiatry and Psychiatric Epidemiology*. 2002;37:147-52.

Blankertz L, Robinson S. Adding a vocational focus to mental health rehabilitation. *Psychiatric Services*. 1996;47:1216-22.



Bleuler E. *Dementia Praecox or the Group of Schizophrenias* (translated by J. Zinkin, 1950). New York: International Universities Press; 1911.

Bleuler M. *The schizophrenic disorders: Long-term patient and family studies*. New Haven, CT: Yale University Press; 1978.

Bloch B, Reshef A, Cohen T, Tafla A, Gathas S, Israel S, et al. Preliminary effects of bupropion and the promoter region (HTTLPR) serotonin transporter (SLC6A4) polymorphism on smoking behavior in schizophrenia. *Psychiatry research*. 2010;175:38-42.

Boardman J, Grove B, Perkins R, Shepherd G. Work and employment for people with psychiatric disabilities. *The British Journal of Psychiatry*. 2003;182:467-8.

Bola JR, Mosher LR. At issue: predicting drug-free treatment response in acute psychosis from the Soteria project. *Schizophrenia Bulletin*. 2002;28:559-75.

Bond GR, Dietzen LL, McGrew JH, Miller LD. Accelerating entry into supported employment for persons with severe psychiatric disabilities. *Rehabilitation Psychology*. 1995;40:75-94.

Bond GR, Dincin J. Accelerating entry into transitional employment in a psychosocial rehabilitation agency. *Rehabilitation Psychology*. 1986;31:143-55.

Bond GR, Drake RE, Becker DR. Generalizability of the Individual Placement and Support (IPS) model of supported employment outside the US. *World Psychiatry*. 2012;11:32-9.

Bond GR, Miller LD, Krumwied RD, Ward RS. Assertive case management in three CMHCs: a controlled study. *Hospital and Community Psychiatry*. 1988;39:411-8.

Bond GR, Salyers MP, Dincin J, Drake R, Becker DR, Fraser VV, et al. A randomized controlled trial comparing two vocational models for persons with severe mental illness. *Journal of Consulting and Clinical Psychology*. 2007;75:968-82.

Bond GR, Witheridge TF, Dincin J, Wasmer D, Webb J, De Graaf-Kaser R. Assertive community treatment for frequent users of psychiatric hospitals in a large city: a controlled study. *American Journal of Community Psychology*. 1990;18:865-91.

Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia: a randomized double-blind study. The Risperidone Study Group. *American Journal of Psychiatry*. 1998;155:499-504.

Bottlender R, Sato T, Jager M, Wegener U, Wittmann J, Strauss A, et al. The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. *Schizophrenia Research*. 2003;62:37-44.

Bounthavong M, Okamoto MP. Decision analysis model evaluating the cost-effectiveness of risperidone, olanzapine and haloperidol in the treatment of schizophrenia. *Journal of Evaluation in Clinical Practice*. 2007;13:453-60.

Bouras N, Tufnell G, Brough DI, Watson JP. Model for the integration of community psychiatry and primary care. *The Journal of the Royal College of General Practitioners*. 1986;36:62-6.

Bradstreet S, Pratt R. Developing peer support worker roles: reflecting on experiences in Scotland. *Mental Health and Social Inclusion*. 2010;14:36-41.

Brar JS, Ganguli R, Pandina G, Turkoz I, Berry S, Mahmoud R. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychiatry*. 2005;66:205-12.

Brazier J. Describing health. In: J. Brazier., J. Ratcliffe., A. Tsuchiya., Salomon. JA, eds. *In Measuring and Valuing Health Benefits for Economic Evaluation*. Oxford & New York: Oxford University Press; 2007a. p. 55-82.

Brazier J. Methods for obtaining health state values: generic preference-based measures of health and the alternatives. In: J. Brazier., J. Ratcliffe., A. Tsuchiya., Salomon. JA, eds. *Measuring and Valuing Health Benefits for Economic Evaluation*. Oxford & New York: Oxford University Press.; 2007b. p. 175-256.

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics*. 2002;21:271-92.

Brenner HD. On the importance of cognitive disorders in treatment and rehabilitation. In: J. S. Strauss, W. Boker, H. D. Brenner, eds. *In Psychosocial Treatment of Schizophrenia*. Toronto: Hans Huber; 1986.

Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, et al. Defining treatment refractoriness in schizophrenia. *Schizophrenia Bulletin*. 1990;16:551-61.

Briggs A, Sculpher M, Claxton C. Making decision models probabilistic. In *Decision Modelling for Health Economic Evaluation*. Briggs, A., Sculpher, M., Claxton, C. edn. New York: Oxford University Press; 2006a. p. 77-120.

Briggs AH, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. New York: Oxford University Press; 2006b.

British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary (BNF) 56. London: Pharmaceutical Press; 2008; Available from: <http://www.bnf.org/bnf/bnf/56/104945.htm>.

British Psychological Society. New Ways of Working for Applied Psychologists in Health and Social Care – The End of the Beginning. Leicester: British Psychological Society, Leicester; 2007.

Brown C, Goetz J, Hamera E. Weight loss intervention for people with serious mental illness: a randomized controlled trial of the RENEW program. *Psychiatric Services*. 2011;62:800-2.

Brown GW, Monck E, Carstairs G, Wing J. Influence of family life on the course of schizophrenic illness. *British Journal of Preventive & Social Medicine*. 1962;16:55-68.

Brown GW, Rutter M. The measurement of family activities and relationships: a methodological study. *Human Relations*. 1966;19:241-63.

Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychological medicine*. 1999;29:697-701.

Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *The British Journal of Psychiatry*. 2010;196:116-21.

Buckley LA, Pettit T, Adams CE. Supportive therapy for schizophrenia. *The Cochrane Library*. 2007.

Buckley P, Miller A, Olsen J, Garver D, Miller DD, Csernansky J. When symptoms persist: clozapine augmentation strategies. *Schizophrenia Bulletin*. 2001;27:615-28.

Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin*. 2009;35:383-402.

Buckley PF, Miller DD, Singer B, Arena J, Stirewalt EM. Clinicians' recognition of the metabolic adverse effects of antipsychotic medications. *Schizophrenia Research*. 2005;79:281-8.

Bunt L. *Music Therapy: An Art Beyond Words*. London: Routledge; 1994.

Burnett R, Mallett R, Bhugra D, Hutchinson G, Der G, Leff J. The first contact of patients with schizophrenia with psychiatric services: social factors and pathways to care in a multi-ethnic population. *Psychological medicine*. 1999;29:475-83.

Burns T, Catty J, Becker T, Drake RE, Fioritti A, Knapp M, et al. The effectiveness of supported employment for people with severe mental illness: a randomised controlled trial. *The Lancet*. 2007a;370:1146-52.

Burns T, Catty J, Dash M, Roberts C, Lockwood L, Marshall M. Use of intensive case management to reduce time in hospital in people with severe mental illness: systematic review and meta-regression. *BMJ*. 2007b;335:336.

Burns T, Cohen A. Item-of-service payments for general practitioner care of severely mentally ill persons: does the money matter? *British Journal of Clinical Pharmacology*. 1998;48:1415-6.

Burns T, Creed F, Fahy T, Thompson S, Tyrer P, White I. Intensive versus standard case management for severe psychotic illness: a randomised trial. UK 700 Group. *The Lancet*. 1999;353:2185-9.

Bush CT, Langford MW, Rosen P, Gott W. Operation outreach: intensive case management for severely psychiatrically disabled adults. *Hospital and Community Psychiatry*. 1990;41:647-49.

Bushe CJ, Taylor M, Haukka J. Mortality in schizophrenia: a measurable clinical endpoint. *Journal of Psychopharmacology*. 2010;24:17-25.

Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. *Archives of General Psychiatry*. 1998;55:547.

Caemmerer J, Correll CU, Maayan L. Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: a meta-analytic comparison of randomized controlled trials. *Schizophrenia Research*. 2012;140:159-68.

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331:897-900.

Campion J, Checinski K, Nurse J. Review of smoking cessation treatments for people with mental illness. Report No.: 1355-5146 2008.

Campion J, Hewitt J, Shiers D, Taylor D. Pharmacy guidance on smoking and mental health. Forum for Mental Health in Primary Care Report. London: Royal College of Psychiatrists and the Royal College of General Practitioners; 2010.

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry*. 2008;65:28.

Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *American Journal of Psychiatry*. 2005;162:12-24.

Care Quality Commission. The state of health care and adult social care in England: an overview of key themes in care 2011/12. Report. London: The Stationary Office; 2012.

Care Services Improvement Partnership. Report on early detection and intervention for young people at risk of developing psychosis. London: Care Services Improvement Partnership; 2005.

Carpenter WT. Anticipating DSM-V: should psychosis risk become a diagnostic class? *Schizophrenia Bulletin*. 2009;35:841-43.

Carpenter WT, Buchanan RW. Lessons to take home from CATIE. *Psychiatric Services*. 2008;59:523-5.

Carr VJ, Neil AL, Halpin SA, Holmes S, Lewin TJ. Costs of schizophrenia and other psychoses in urban Australia: findings from the low prevalence (psychotic) disorders study. *Australian and New Zealand Journal of Psychiatry*. 2003;37:31-40.

Carrà G, Montomoli C, Clerici M, Cazzullo CL. Family interventions for schizophrenia in Italy: randomized controlled trial. *European Archives of Psychiatry and Clinical Neuroscience*. 2007;257:23-30.

Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *American Journal of Psychiatry*. 2001;158:518-26.

Chan J, Sweeting M. Review: Combination therapy with non-clozapine atypical antipsychotic medication: a review of current evidence. *Journal of Psychopharmacology*. 2007;21:657-64.

Chan SH, Lee SW, Chan IW. TRIP: a psycho-educational programme in Hong Kong for people with schizophrenia. *Occupational Therapy International*. 2007;14:86-98.

Chandler D, Meisel J, Hu TW, McGowen M, Madison K. Client outcomes in a three-year controlled study of an integrated service agency model. *Psychiatric Services*. 1996;47:1337-43.

Chao PJ. A group randomized trial to examine the feasibility and effects of pedometer use and self-monitoring of daily walking in people with severe and persistent mental illnesses. *Dissertation Abstracts International*. 2010;72.

Chen EY, Tang JY, Hui CL, Chiu CP, Lam MM, Law CW, et al. Three-year outcome of phase-specific early intervention for first-episode psychosis: a cohort study in Hong Kong. *Early Intervention in Psychiatry*. 2011;5:315-23.

Chen HK, Lan TH, Wu BJ. A double-blind randomized clinical trial of different doses of transdermal nicotine patch for smoking reduction and cessation in long-term hospitalized schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience*. 2013;263:75-82.

Cheng LY, Chan S. Psychoeducation program for Chinese family carers of members with schizophrenia. *Western Journal of Nursing Research*. 2005;27:583-99.

Chien WT, Chan SWC. One-year follow-up of a multiple-family-group intervention for Chinese families of patients with schizophrenia. *Psychiatric Services*. 2004b;55:1276-84.

Chien WT, Norman I, Thompson DR. A randomized controlled trial of a mutual support group for family caregivers of patients with schizophrenia. *International Journal of Nursing Studies*. 2004a;41:637-49.

Chien WT, Thompson DR, Norman I. Evaluation of a peer-led mutual support group for Chinese families of people with schizophrenia. *American Journal of Community Psychology*. 2008;42:122-34.

Chien WT, Wong KF. A family psychoeducation group program for Chinese people with schizophrenia in Hong Kong. *Psychiatric Services*. 2007;58:1003-06.

Chinman M, Oberman RS, Young AS. A cluster randomized trial of adding peer specialists to intensive case management teams in the veterans health administration. *The Journal of Behavioral Health Services & Research*. 2013:1-13.

Chiu MYL, Wei GFW, Lee S. Personal tragedy or system failure: a qualitative analysis of narratives of caregivers of people with severe mental illness in Hong Kong and Taiwan. *The International Journal of Social Psychiatry*. 2006;52:413-23.

Chong SA, Mythily S, Verma S. Reducing the duration of untreated psychosis and changing help-seeking behaviour in Singapore. *Social Psychiatry and Psychiatric Epidemiology*. 2005;40:619-21.

Chong SA, Remington G. Clozapine augmentation: safety and efficacy. *Schizophrenia Bulletin*. 2000;26:421-40.

Chong SA, Tan CH, Lee HS. Hoarding and clozapine-risperidone combination. *Canadian Journal of Psychiatry*. 1996;41:315-16.

Chou KR, Liu SY, Chu H. The effects of support groups on caregivers of patients with schizophrenia. *International Journal of Nursing Studies*. 2002;39:713-22.

Chouinard G, Albright PS. Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. *Journal of Clinical Psychopharmacology*. 1997;17:298-307.

Chue PS, Heeg B, Buskens E, van Hout BA. Modelling the impact of compliance on the costs and effects of long-acting risperidone in Canada. *Pharmacoeconomics*. 2005;23 Suppl. 1:62-74.

Ciompi L, Dauwalder H-P, Maier C, Aebi E, Trütsch K, Kupper Z, et al. The pilot project 'Soteria Berne': clinical experiences and results. *Alternatives to the Hospital for Acute Psychiatric Treatment*. 1995;32:133.

Clarke GN, Herinckx HA, Kinney RF, Paulson RI, Cutler DL, Lewis K, et al. Psychiatric hospitalizations, arrests, emergency room visits, and homelessness of clients with serious and persistent mental illness: findings from a randomized trial of two ACT programs vs. usual care. *Mental health services research*. 2000;2:155-64.

Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Medical Decision Making*. 2002;22:340-49.

Clarke PM, Gray AM, Briggs A, et al. (On behalf of the UK Prospective Diabetes Study [UKPDS]). Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). *Diabetologia*. 2005;48:868-77.

Clay S, Schell S, Corrigan P, Ralph R. *On our own, together. Peer programs for people with mental illness*. Nashville, TN: Vanderbilt University Press; 2005.

Cocchi A, Mapelli V, Meneghelli A, Preti A. Cost-effectiveness of treating first-episode psychosis: five-year follow-up results from an Italian early intervention programme. *Early Intervention in Psychiatry*; Aug 2011;203-11.

Coid J. Failure in community care: psychiatry's dilemma. *BMJ*. 1994;308:805.

Cole E, Levy G, King M, Johnson-Sabine E, Hoar A. Pathways to care for patients with a first episode of psychosis. A comparison of ethnic groups. *The British Journal of Psychiatry*. 1995;167:770-6.

Cole J. The effects of an exercise program on chronically mentally ill outpatients; a study of symptom reduction, physical fitness, and stress. *Dissertation Abstracts International*. 1997:64.

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. *Nature*. 2011;475:27-30.

- Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. *Schizophrenia Bulletin*. 1997;23:663-74.
- Cook JA, Copeland ME, Jonikas JA, Hamilton MM, Razzano LA, Grey DD, et al. Results of a randomized controlled trial of mental illness self-management using wellness recovery action planning. *Schizophrenia Bulletin*. 2011;38:881-91.
- Cook JA, Leff HS, Blyler CR, Gold PB, Goldberg RW, Mueser KT, et al. Results of a multisite randomized trial of supported employment interventions for individuals with severe mental illness. *Archives of General Psychiatry*. 2005;62:505-12.
- Cook JA, Steigman P, Pickett S, Diehl S, Fox A, Shipley P, et al. Randomized controlled trial of peer-led recovery education using Building Recovery of Individual Dreams and Goals through Education and Support (BRIDGES). *Schizophrenia Research*. 2012;136:36-42.
- Cookson J, Taylor D, Katona C. *Use of Drugs in Psychiatry: The Evidence from Psychopharmacology*. London: Gaskell; 2002.
- Copeland ME, Mead S. *WRAP and Peer Support for People, Groups and Programs*. Brattleboro: Peach Press; 2004.
- Corcoran CM, First MB, Cornblatt B. The psychosis risk syndrome and its proposed inclusion in the DSM-V: a risk-benefit analysis. *Schizophrenia Research*. 2010;120:16-22.
- Cozolino LJ, Goldstein MJ, Nuechterlein KH, West KL, Snyder KS. The impact of education about schizophrenia on relatives varying in expressed emotion. *Schizophrenia Bulletin*. 1988;675-87.
- Craig T, Doherty I, Jamieson-Craig R, Boocock A, Attafua G. The consumer-employee as a member of a mental health assertive outreach team. I. Clinical and social outcomes. *Journal of Mental Health*. 2004a;13:59-69.
- Craig TK, Garety P, Power P, Rahaman N, Colbert S, Fornells-Ambrojo M, et al. The Lambeth early onset (LEO) team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ*. 2004;329:1067.
- Crammer J, Eccleston DA. Survey of the use of depot neuroleptics in a whole region. *Psychiatric Bulletin*. 1989;13:517-20.
- Crawford MJ, Patterson S. Arts therapies for people with schizophrenia: an emerging evidence base. *Evidence Based Mental Health*. 2007;10:69-70.



Creamer M, Burgess P, McFarlane AC. Post-traumatic stress disorder: findings from the Australian National Survey of Mental Health and Well-being. *Psychological medicine*. 2001;31:1237-47.

Creed F, Black D, Anthony P, Osborn M, Thomas P, Tomenson B. Randomised controlled trial of day patient versus inpatient psychiatric treatment. *BMJ*. 1990;300:1033-7.

Cresswell J, Lelliott P, eds. Accreditation for Inpatient Mental Health Services (AIMS): National Report for Working Age Acute Wards - July 2007-July 2009. London: Royal College of Psychiatrists Centre for Quality Improvement; 2009.

Crown S. Supportive psychotherapy: a contradiction in terms? *British Journal of Psychiatry*. 1988;152:266-9.

Crowther R, Marshall M, Bond G, Huxley P. Vocational rehabilitation for people with severe mental illness. *Cochrane Database of Systematic Reviews*. 2001:Art. No.:CD003080.

Cummins C, Stevens A, Kisely S, Executive N. The Use of Olanzapine as a First and Second Choice Treatment in Schizophrenia: Wessex Institute for Health Research and Development, Development & Evaluation Committee; 1998.

Curtis J, Newall HD, Samaras K. The heart of the matter: cardiometabolic care in youth with psychosis. *Early Intervention in Psychiatry*. 2012;6:347-53.

Curtis JL, Millman EJ, Struening E, D'Ercole A. Effect of case management on rehospitalization and utilization of ambulatory care services. *Hospital and Community Psychiatry*. 1992;43:895-9.

Curtis L. Unit Costs of Health and Social Care 2007. Canterbury: Personal Social Services Research Unit, University of Kent; 2007.

Curtis L. Unit Costs of Health and Social Care 2012. Canterbury: University of Kent; 2012.

Dalack GW, Meador-Woodruff JH. Acute feasibility and safety of a smoking reduction strategy for smokers with schizophrenia. *Nicotine & Tobacco Research*. 1999;1:53-7.

Darves-Bornoz J, Lemperiere T, Degiovanni A, Gaillard P. Sexual victimization in women with schizophrenia and bipolar disorder. *Social Psychiatry and Psychiatric Epidemiology*. 1995;30:78-84.

Darves-Bornoz JM, Alonso J, de Girolamo G, de Graaf R, Haro JM, Kovess-Masfety V, et al. Main traumatic events in Europe: PTSD in the European study of the

epidemiology of mental disorders survey. *Journal of Traumatic Stress*. 2008;21:455-62.

Darzi AR. High Quality Care for All: NHS Next Stage Review Final Report. London: Department of Health; 2008; Available from:

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_085825](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085825)

Daumit GL, Dickerson FB, Wang N-Y, Dalcin A, Jerome GJ, Anderson CAM, et al. A behavioral weight-loss intervention in persons with serious mental illness. *New England Journal of Medicine*. 2013;368:1594-602.

David A, Adams CE, Quraishi SN. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. (Cochrane review). 1999:Art. No.: CD001470.

David AS, Adams C. Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) meta-review; (2) patient and nurse attitudes. *Health Technology Assessment*. 2001;5:1-61.

Davidson L. Supported socialization for people with psychiatric disabilities: lessons from a randomized controlled trial. *Journal of Community Psychology*. 2004;32:453.

Davidson L, Chinman M, Kloos B, Weingarten R, Stayner D, Tebes JK. Peer support among individuals with severe mental illness: A review of the evidence. *Clinical Psychology: Science and Practice*. 1999;6:165-87.

Davies A, Langley PC, Keks NA, Catts SV, Lambert T, Schweitzer I. Risperidone versus haloperidol: II. Cost-effectiveness. *Clinical Therapeutics*. 1998;20:196-213.

Davies G, Welham J, Chant D, Torrey EF, McGrath J. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophrenia Bulletin*. 2003;29:587-93.

Davies L, Lewis S. Antipsychotic medication for people with first episode schizophrenia: an exploratory economic analysis of alternative treatment algorithms. University of York: Centre for Health Economics; 2000.

Davies LM, Barnes TR, Jones PB, Lewis S, Gaughran F, Hayhurst K, et al. A randomised controlled trial of the cost-utility of second-generation antipsychotics in people with psychosis and eligible for clozapine. *Value in Health*. 2008;11:549-62.

Davies LM, Drummond MF. Economics and schizophrenia: the real cost. *The British Journal of Psychiatry*. 1994;18-21.

Davies LM, Lewis S, Jones PB, Barnes TR, Gaughran F, Hayhurst K, et al. Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a

randomised controlled trial in schizophrenia responding poorly to previous therapy. *British Journal Psychiatry*. 2007;191:14-22.

Davis JM, Garver DL. Neuroleptics: Clinical Use in Psychiatry. In: Iversen. L, Iversen. S, Snyder. S, eds. *Handbook of Psychopharmacology*. New York: Plenum Press; 1978 p. 129-64.

Davis JM, Kane JM, Marder SR, Brauzer B, Gierl B, Schooler N, et al. Dose response of prophylactic antipsychotics. *Journal of Clinical Psychiatry*. 1993;54 Suppl:24-30.

De Graeve D, Smet A, Mehnert A, Caleo S, Miadi-Fargier H, Mosqueda GJ, et al. Long-acting risperidone compared with oral olanzapine and haloperidol depot in schizophrenia: a Belgian cost-effectiveness analysis. *Pharmacoeconomics*. 2005;23 Suppl 1:35-47.

De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness: position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *European Psychiatry*. 2009a;24:412-24.

De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: a review. *World Psychiatry*. 2009b;8:15-22.

de Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. Does clozapine decrease smoking? *Progress in Neuro-psychopharmacology and Biological Psychiatry*. 2005;29:757-62.

Deegan P. Recovery as a journey of the heart. *Psychiatric Rehabilitation Journal*. 1996;19:91-97.

Department of Health. National Service Framework for Mental Health services: Modern Standards and Service Models. London: Department of Health; 1999; Available from: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4009598](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009598)

Department of Health. The NHS Plan: a Plan for Investment, a Plan for Reform. London: Department of Health; 2000.

Department of Health. The Mental Health Policy Implementation Guide. London: Department of Health; 2001.

Department of Health. Delivering Race Equality: a Framework for Action. London: Department of Health; 2003; Available from: [www.doh.gov.uk/deliveringraceequality/77951-del\\_race\\_equality.pdf](http://www.doh.gov.uk/deliveringraceequality/77951-del_race_equality.pdf).

Department of Health. Delivering Race Equality in Mental Health Care: an Action Plan for Reform Inside and Outside Services and the Government's Response to the Independent Inquiry Into the Death Of David Bennett. London: Department of Health; 2005; Available from:

<http://www.dh.gov.uk/assetRoot/04/10/07/75/04100775.pdf>.

Department of Health. NHS Reference Costs 2006–07. London: Department of Health; 2008; Available from: [www.hesonline.nhs.uk](http://www.hesonline.nhs.uk).

Dettling M, Sachse C, Brockmoller J, Schley J, Muller-Oerlinghausen B, Pickersgill I, et al. Long-term therapeutic drug monitoring of clozapine and metabolites in psychiatric in- and outpatients. *Psychopharmacology*. 2000;152:80-6.

Diaz FJ, de Leon J, Josiassen RC, Cooper TB, Simpson GM. Plasma clozapine concentration coefficients of variation in a long-term study. *Schizophrenia Research*. 2005;72:131-5.

Dick P, Cameron L, Cohen D, Barlow M, Ince A. Day and full time psychiatric treatment: a controlled comparison. *The British Journal of Psychiatry*. 1985;147:246-9.

Dick S. Homophobic hate crime: The Gay British Crime Survey. London: Stonewall; 2008.

Dieterich M, Irving CB, Park B, Marshall M. Intensive case management for severe mental illness. *Cochrane Database of Systematic Reviews*. 2010;Art. No.:CD007906.

Dincin J, Witheridge TF. Psychiatric rehabilitation as a deterrent to recidivism. *Hospital and Community Psychiatry*. 1982;33:645-50.

Dinesh M, David A, Quraishi SN. Depot pipotiazine palmitate and undecylenate for schizophrenia. *Cochrane Database of Systematic Reviews*. 2004;Art. No.:CD001720.

Dixon L, Hoch JS, Clark R, Bebout R, Drake R, McHugo G, et al. Cost-effectiveness of two vocational rehabilitation programs for persons with severe mental illness. *Psychiatric Services*. 2002;53:1118-24.

Dixon LB, Lehman AF, Levine J. Conventional antipsychotic medications for schizophrenia. *Schizophrenia Bulletin*. 1995;21:567-77.

Dowell DA, Ciarlo JA. Overview of the community mental health centers program from an evaluation perspective. *Community Mental Health Journal*. 1983;19:95-125.

Drake RE, Becker DR, Anthony WA. A research induction group for clients entering a mental health research project. *Hospital and Community Psychiatry*. 1994;45:487-9.

Drake RE, McHugo G. Assertive community treatment for patients with co-occurring severe mental illness and substance use disorder: a clinical trial. *American Journal of Orthopsychiatry*. 1998;68.

Drake RE, McHugo GJ, Bebout RR, Becker DR, Harris M, Bond GR, et al. A randomized clinical trial of supported employment for inner-city patients with severe mental disorders. *Archives of General Psychiatry*. 1999;56:627-33.

Duffy SA, Kilbourne AM, Austin KL, Dalack GW, Woltmann EM, Waxmonsky J, et al. Risk of smoking and receipt of cessation services among veterans with mental disorders. *Psychiatric Services*. 2012;63:126-33.

Dumouchel W, Fram D, Yang XG, Mahmoud RA, Grogg AL, Engelhart L, et al. Antipsychotics, glycemic disorders, and life-threatening diabetic events: a bayesian data-mining analysis of the FDA adverse event reporting system (1968-2004). *Annals of Clinical Psychiatry*. 2008;20:21-31.

Duraiswamy G, Thirthalli J, Nagendra HR, Gangadhar BN. Yoga therapy as an add-on treatment in the management of patients with schizophrenia-a randomized controlled trial. *Acta Psychiatrica Scandinavica*. 2007;116:226-32.

Durham RC, Guthrie M, Morton RV, Reid DA, Treliving LR, Fowler D, et al. Tayside-Fife clinical trial of cognitive-behavioural therapy for medication-resistant psychotic symptoms. Results to 3-month follow-up. *The British Journal of Psychiatry*. 2003;182:303-11.

Durson SM, Deakin JF. Augmenting antipsychotic treatment with lamotrigine in patients with treatment-resistant schizophrenia: a naturalistic case-series outcome study. *Journal of Psychopharmacology*. 2001;15:297-301.

Duvivier BM, Schaper NC, Bremers MA, van Crombrugge G, Menheere PP, Kars M, et al. Minimal intensity physical activity (standing and walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable. *PLoS One*. 2013;8:e55542.

Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: methods of developing guidelines for efficient drug use in primary care. *BMJ*. 1998;316:1232-35.

Eckman TA, Wirshing WC, Marder SR, Liberman RP, Johnston CK, Zimmermann K, et al. Technique for training schizophrenic patients in illness self-management: a controlled trial. *American Journal of Psychiatry*. 1992;149:1549-55.

Edgell ET, Andersen SW, Johnstone BM, Dulisse B, Revicki D, Breier A. Olanzapine versus risperidone. A prospective comparison of clinical and economic outcomes in schizophrenia. *Pharmacoeconomics*. 2000;18:567-79.

Edmundson E, Bedell J, Archer R, Gordon R. Intergrating skill building and peer support in mental health treatment. In: Jeger A, Slotnick R., ed. *Community Mental Health and Behavioural Ecology*. NY: Springer US; 1982. p. 127-39.

Edwards NC, Locklear JC, Rupnow MF, Diamond RJ. Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. *Pharmacoeconomics*. 2005;23 Suppl 1:75-89.

Essock SM, Kontos N. Implementing assertive community treatment teams. *Psychiatric Services*. 1995;46:679-83.

Essock SM, Mueser KT, Drake RE, Covell NH, McHugo GJ, Frisman LK, et al. Comparison of ACT and standard case management for delivering integrated treatment for co-occurring disorders. *Psychiatric Services*. 2006;57:185-96.

Evans J, Repper J. Employment, social inclusion and mental health. *Journal of Psychiatric and Mental Health Nursing*. 2000;7:15-24.

Evans S, Newton R, Higgins S. Nutritional intervention to prevent weight gain in patients commenced on olanzapine: a randomized controlled trial. *Australian and New Zealand Journal of Psychiatry*. 2005;39:479-86.

Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, et al. A 12-week double-blind, placebo-controlled study of bupropion sr added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *Journal of Clinical Psychopharmacology*. 2007;27:380-6.

Evins AE, Cather C, Deckersbach T, Freudenreich O, Culhane MA, Olm-Shipman CM, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology*. 2005;25:218-25.

Evins AE, Mays VK, Rigotti NA, Tisdale T, Cather C, Goff DC. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine & Tobacco Research*. 2001;3:397-403.

Expert Group. Schizophrenia and diabetes 2003: an expert consensus meeting. Introduction. *The British Journal of Psychiatry*. 2004;47:S53-4.

Faber G, Smid HGOM, VanGool AR, Wiersma D, VanDen Bosch RJ. The effects of guided discontinuation of antipsychotics on neurorecognition in first onset psychosis. *European Psychiatry*. 2012;27:275-80.

Fadden G, Heelis R. The Meriden Family Programme: lessons learned over 10 years. *Journal of Mental Health*. 2011;20:79-88.

Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Archives of General Psychiatry*. 1992;49:538-44.

Färdig R, Lewander T, Melin L, Folke F, Fredriksson A. A randomized controlled trial of the illness management and recovery program for persons with schizophrenia. *Psychiatric Services*. 2011;62:606-12.

Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophrenia Bulletin*. 2009;35:528-48.

Fatemi SH, Stary JM, Hatsukami DK, Murphy SE. A double-blind placebo-controlled cross over trial of bupropion in smoking reduction in schizophrenia. *Schizophrenia Research*. 2005;76:353-56.

Faulkner A, Basset T. A helping hand: taking peer support into the 21st century. *Mental Health and Social Inclusion*. 2012;16:41-47.

Faulkner G, Cohn T, Remington G. Validation of a physical activity assessment tool for individuals with schizophrenia. *Schizophrenia Research*. 2006;82:225-31.

Fedorowicz VJ, Fombonne E. Metabolic side effects of atypical antipsychotics in children: a literature review. *Journal of Psychopharmacology*. 2005;19:533-50.

Fenton FR, Tessier L, Struening EL. A comparative trial of home and hospital psychiatric care. One-year follow-up. *Archives of General Psychiatry*. 1979;36:1073-79.

Fenton WS, McGlashan TH. Schizophrenia: individual psychotherapy. In *Comprehensive Textbook of Psychiatry*. H. Kaplan & B. Sadock edn. Baltimore, Maryland: Williams & Wilkins.; 1995.

Fenton WS, McGlashan TH. We can talk: Individual psychotherapy for schizophrenia. *American Journal of Psychiatry*. 1997;154:1493-95.

Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics*. 2001;10:779-87.

Fidler JA, Shahab L, West O, MJarvis MJ, McEwen A, Stapleton A, et al. 'The smoking toolkit study': a national study of smoking cessation in England. *BMC Public Health*. 2011;11:479.

Flanagan RJ. Therapeutic monitoring of antipsychotic drugs. CPD Clinical Biochemistry. 2006;3-18.

Fleischhacker WW, Hummer M. Drug treatment of schizophrenia in the 1990s. Achievements and future possibilities in optimising outcomes. Drugs. 1997;53:915-29.

Fleischhacker WW, Siu CO, Boden R, Pappadopulos E, Karayal ON, Kahn RS. Metabolic risk factors in first-episode schizophrenia: baseline prevalence and course analysed from the European first-episode schizophrenia trial. The International Journal of Neuropsychopharmacology. 2012;1:1-9.

Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Archives of General Psychiatry. 2011;68:609-16.

Ford R, Beadsmoore A, Ryan P, Repper J, Craig T, Muijen M. Providing the safety net: case management for people with a serious mental illness. Journal of Mental Health. 1995;4:91-97.

Foster K, Meltzer H, Gill B, Hinds K. OPCS Surveys of Psychiatric Morbidity in Great Britain. London: Office of Population Censuses and Surveys; 1996.

Freeman D, Garety PA. Connecting neurosis and psychosis: the direct influence of emotion on delusions and hallucinations. Behaviour Research and Therapy. 2003;41:923-47.

Freud S. New introductory lectures on psycho-analysis. In: Strachey J, ed. The Standard Edition of the Complete Psychological Works of Sigmund Freud. London: Hogarth Press; 1964.

Frey W, Drake RE, Goldman HH, Salkever D, Miller A, Bond GR. The mental health treatment study: final report to social security administration. Rockville, MD: Westat; 2011.

Friedlander AH, Marder SR. The psychopathology, medical management and dental implications of schizophrenia. Journal of the American Dental Association. 2002;133:603-10.

Frith CD. The Cognitive Neuropsychology of Schizophrenia. Hillsdale, NJ: Lawrence Erlbaum; 1992.

Fromm-Reichmann F. Principles of Intensive Psychotherapy. Chicago, IL: University of Chicago Press; 1950.



Gabbard GO. Psychodynamic Psychiatry in Clinical Practice: The DSM-IV Edition. Washington DC: American Psychiatric Press; 1994.

Gaertner I, Gaertner HJ, Vonthein RI, Dietz K. Therapeutic drug monitoring of clozapine in relapse prevention: a five-year prospective study. *Journal of Clinical Psychopharmacology*. 2001;21:305-10.

Gallagher SM, Penn PE, Schindler E, Layne W. A comparison of smoking cessation treatments for persons with schizophrenia and other serious mental illnesses. *Journal of Psychoactive Drugs*. 2007;39:487-97.

Galletly CA, Clark CR, MacFarlane AC. Treating cognitive dysfunction in patients with schizophrenia. *Journal of Psychiatry and Neuroscience*. 2000;25:117-24.

Ganguly R, Miller LS, Martin BC. Future employability, a new approach to cost-effectiveness analysis of antipsychotic therapy. *Schizophrenia Research*. 2003;63:111-9.

Garety PA, Bebbington P, Fowler D, Freeman D, Kuipers E. Implications for neurobiological research of cognitive models of psychosis: a theoretical paper. *Psychological medicine*. 2007;37:1377-91.

Garety PA, Fowler DG, Freeman D, Bebbington P, Dunn G, Kuipers E. Cognitive-behavioural therapy and family intervention for relapse prevention and symptom reduction in psychosis: randomised controlled trial. *The British Journal of Psychiatry*. 2008;192:412-23.

Garety PA, Hemsley DR. *Delusions: Investigations into the Psychology of Delusional Reasoning*. Hove, UK: Psychology Press; 1994.

Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychological medicine*. 2001;31:189-95.

Gater R, Goldberg D, Jackson G, Jennett N, Lowson K, Ratcliffe J, et al. The care of patients with chronic schizophrenia: a comparison between two services. *Psychological medicine*. 1997;27:1325-36.

Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000;321:1371-6.

Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I. Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: a cost effectiveness study. *Annals of general psychiatry*. 2008;7:16.

Gelkopf M, Noam S, Rudinski D, Lerner A, Behrbalk P, Bleich A, et al. Nonmedication smoking reduction program for inpatients with chronic schizophrenia: a randomized control design study. *The Journal of Nervous and Mental Disease*. 2012;200:142-46.

Genc Y, Taner E, Candansayar S. Comparison of clozapine-amisulpride and clozapine-quetiapine combinations for patients with schizophrenia who are partially responsive to clozapine: a single-blind randomized study. *Advances in Therapy*. 2007;24:1-13.

George TP, Vessicchio JC, Sacco KA, Weinberger AH, Dudas MM, Allen TM, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biological Psychiatry*. 2008;63:1092-6.

George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biological Psychiatry*. 2002;52:53-61.

George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *American Journal of Psychiatry*. 2000;157:1835-42.

Gervery R, Bedell JR. Psychological Assessment And Treatment Of Persons With Severe Mental Disorders. In: Bendall JR, ed. *Supported employment in vocational rehabilitation*. Washington DC: Taylor and Francis; 1994. p. 170-5.

Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Archives of General Psychiatry*. 1995;52:173-88.

Gilburt H, Slade M, Rose D, Lloyd-Evans B, Johnson S, Osborn DP. Service users' experiences of residential alternatives to standard acute wards: qualitative study of similarities and differences. *The British Journal of Psychiatry*. 2010;197:s26-s31.

Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. *BMJ*. 2008;336.

Gilmore JH. Understanding what causes schizophrenia: a developmental perspective. *American Journal of Psychiatry*. 2010;167:8-10.

Gilroy A, McNeilly G. *The Changing Shape of Art Therapy*. London: Jessica Kingsley Publishers; 2000.

Gingerich S, Tornvall K. *Illness Management and Recovery*. Hanover: Hazelden Publishing; 2005.

Glennie JL. Pharmacoeconomic Evaluation in Schizophrenia: Clozapine in Treatment-Resistant Schizophrenia and Risperidone in Chronic Schizophrenia. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment; 1997.

Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. *Health Technology Assessment*. 2005;9:1-134.

Glover G, Arts G, Babu KS. Crisis resolution/home treatment teams and psychiatric admission rates in England. *The British Journal of Psychiatry*. 2006;189:441-5.

Godleski LS, Sernyak MJ. Agranulocytosis after addition of risperidone to clozapine treatment. *American Journal of Psychiatry*. 1996;153:735-6.

Goeree R, Farahati F, Burke N, Blackhouse G, O'Reilly D, Pyne J, et al. The economic burden of schizophrenia in Canada in 2004. *Current Medical Research and Opinion*. 2005;21:2017-28.

Gold PB, Meisler N, Santos AB, Carnemolla MA, Williams OH, Keleher J. Randomized trial of supported employment integrated with assertive community treatment for rural adults with severe mental illness. *Schizophrenia Bulletin*. 2006;32:378-95.

Goldstein MJ. Psychoeducational family programs in the United States. In: Moscarelli M, Rupp A, Sartorius N, eds. *Handbook of Mental Health Economics and Health Policy*, vol 1: Schizophrenia. New York: John Wiley; 1996.

Goodwin V, Happell B. Conflicting agendas between consumers and carers: The perspectives of carers and nurses. *International Journal of Mental Health Nursing*. 2006;15:135-43.

Grawe RW, Falloon IR, Widen JH, Skogvoll E. Two years of continued early treatment for recent-onset schizophrenia: a randomised controlled study. *Acta Psychiatrica Scandinavica*. 2006;114:328-36.

Gray JA, Feldon J, Rawlins JNP, Hemsley DR, Smith AD. The neuropsychology of schizophrenia. *Behavioral and Brain Sciences*. 1991;14:1-20.

Gray R, Leese M, Bindman J, Becker T, Burti L, David A, et al. Adherence therapy for people with schizophrenia. European multicentre randomised controlled trial. *The British Journal of Psychiatry*. 2006;189:508-14.

Green BL, Wehling C, Talsky GJ. Group art-therapy as an adjunct to treatment for chronic outpatients. *Hospital and Community Psychiatry*. 1987;38:988-91.

Green MF. Neuropsychological performance in the unaffected twin. *Archives of General Psychiatry*. 1992;49:247.

Griffiths RD. Rehabilitation of chronic psychotic patients. An assessment of their psychological handicap, an evaluation of the effectiveness of rehabilitation, and observations of the factors which predict outcome. *Psychological medicine*. 1974;4:316-25.

Grubaugh AL, Zinzow HM, Paul L, Egede LE, Frueh BC. Trauma exposure and posttraumatic stress disorder in adults with severe mental illness: a critical review. *Clinical Psychology Review*. 2011;31:883-99.

Guest JF, Cookson RF. Cost of schizophrenia to UK Society. An incidence-based cost-of-illness model for the first 5 years following diagnosis. *Pharmacoeconomics*. 1999;15:597-610.

Gulbinat W, Dupont A, Jablensky A, Jensen OM, Marsella A, Nakane Y, et al. Cancer incidence of schizophrenic patients. Results of record linkage studies in three countries. *The British Journal of Psychiatry*. 1992;75-83.

Gutierrez-Maldonado J, Caqueo-Uriazar A. Effectiveness of a psycho-educational intervention for reducing burden in Latin American families of patients with schizophrenia. *Quality of Life Research*. 2007;739-47.

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011;64:383-94.

Hack S, Chow B. Pediatric psychotropic medication compliance: a literature review and research-based suggestions for improving treatment compliance. *Journal of Child and Adolescent Psychopharmacology*. 2001;11:59-67.

Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*. 2004;64:2291-314.

Halvorson A, Whitter M. Approaches to Recovery-Oriented Systems of Care at the State and Local Levels: Three Case Studies. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration; 2009.

Hamilton SH, Revicki DA, Edgell ET, Genduso LA, Tollefson G. Clinical and economic outcomes of olanzapine compared with haloperidol for schizophrenia. Results from a randomised clinical trial. *Pharmacoeconomics*. 1999;15:469-80.

Hampton B, Korr W, Bond G, Mayes J, Havis P. Integration service system approach to avert homelessness: CSP homeless prevention project for HMI adults. Chicago, IL: Illinois Department of Mental Health and Developmental Disabilities; 1992.

Hansson L, Jormfeldt H, Svedberg P, Svensson B. Mental health professionals' attitudes towards people with mental illness: do they differ from attitudes held by people with mental illness? *The International Journal of Social Psychiatry*. 2013;59:48-54.

Haro JM, Novick D, Bertsch J, Karagianis J, Dossenbach M, Jones PB. Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. *The British Journal of Psychiatry*. 2011;199:194-201.

Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D, et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *European Neuropsychopharmacology*. 2007;17:235-44.

Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? *Psychological medicine*. 2003;33:97-110.

Harrington M, Lelliott P, Paton C, Konsolaki M, Sensky T, Okocha C. Variation between services in polypharmacy and combined high dose of antipsychotic drugs prescribed for in-patients. *Psychiatric Bulletin*. 2002;26:418-20.

Harris EC, Barraclough B. Excess mortality of mental disorder. *The British Journal of Psychiatry*. 1998;173:11-53.

Harrison-Read P, Lucas B, Tyrer P, Ray J, Shipley K, Simmonds S, et al. Heavy users of acute psychiatric beds: randomized controlled trial of enhanced community management in an outer London borough. *Psychological medicine*. 2002;32:403-16.

Harrison G, Hopper K, Craig T, Laska E, Siegel C, Wanderling J, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *The British Journal of Psychiatry*. 2001;178:506-17.

Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. *Schizophrenia Bulletin*. 2005;31:723-34.

Harrow M, Jobe TH, Faull RN. Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. *Psychological Medicine*. 2012;42:2145-55.

Hartman N, Leong GB, Glynn SM, Wilkins JN, Jarvik ME. Transdermal nicotine and smoking behavior in psychiatric patients. *American Journal of Psychiatry*. 1991;148:374-5.

Hasselblad V. Meta-analysis of multitreatment studies. *Medical Decision Making*. 1998;18:37-43.

Hasson-Ohayon I, Roe D, Kravetz S. A randomized controlled trial of the effectiveness of the illness management and recovery program. *Psychiatric Services*. 2007;58:1461-66.

Hastrup LH, Kronborg C, Bertelsen M, Jeppesen P, Jorgensen P, Petersen L, et al. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *The British Journal of Psychiatry*. 2013;202:35-41.

Healey A, Knapp M, Astin J, Beecham J, Kemp R, Kirov G, et al. Cost-effectiveness evaluation of compliance therapy for people with psychosis. *The British Journal of Psychiatry*. 1998;172:420-4.

Health and Social Care Information Centre. NHS Staff Earnings Estimates June 2012 - Based on Payments to Staff in the NHS in England from January to March 2012. Leeds: Health and Social Care Information Centre; 2012.

Healthcare Commission. Count Me In 2008: Results of the 2008 National Census of Inpatients in Mental Health and Learning Disability Services in England and Wales. London: Commission for Healthcare Audit and Inspection; 2008.

Healy D. *The Creation of Psychopharmacology*. Cambridge, MA: Harvard University Press; 2002.

Hearing Voices Network. Assisting people who hear voices. 2003; Available from: <http://www.hearing-voices.org>

Heeg B, Antunes J, Figueira M, Jara J, Marques Teixeira J, Palha A, et al. Cost-effectiveness and budget impact of long-acting risperidone in Portugal: a modeling exercise. *Current Medical Research and Opinion*. 2008;24:349-58.

Heeg B, Buskens E, Knapp M, van Aalst G, Dries PJ, de Haan L, et al. Modelling the treated course of schizophrenia: development of a discrete event simulation model. *Pharmacoeconomics*. 2005;23(Suppl. 1):17-33.

Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin*. 1984;10:388-98.

Hemsley DR. A simple (or simplistic?) cognitive model for schizophrenia. *Behaviour Research and Therapy*. 1993;31:633-45.

Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *American Heart Journal*. 2005;150:1115-21.

Herek GM, Gillis JR, Cogan JC. Psychological sequelae of hate-crime victimization among lesbian, gay, and bisexual adults. *Journal of Consulting and Clinical Psychology*. 1999;67:945.

Herinckx HA, Kinney RF, Clarke GN, Paulson RI. Assertive community treatment versus usual care in engaging and retaining clients with severe mental illness. *Psychiatric Services*. 1997;48:1297-306.

Herman JL, Schatzow E. Recovery and verification of memories of childhood sexual trauma. *Psychoanalytic Psychology*. 1987;4:1.

Hersen M, Bellack AS. Social skills training for chronic psychiatric patients: rationale, research findings, and future directions. *Comprehensive Psychiatry*. 1976;17:559-80.

Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10:52-77.

Heslin M, Howard L, Leese M, McCrone P, Rice C, Jarrett M, et al. Randomized controlled trial of supported employment in England: 2 Year follow-up of the Supported Work and Needs (SWAN) study. *World Psychiatry*. 2011;10:132-37.

Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Oxford: The Cochrane Collaboration.

Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Statistics in Medicine*. 1996;15:2733-49.

Himelhoch S, Daumit G. To whom do psychiatrists offer smoking-cessation counseling? *American Journal of Psychiatry*. 2003;160:2228-30.

Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in general practice 1995-2008: analysis of the QResearch® database. Report. Leeds: The Information Centre for Health and Social Care; 2009.

Hirsch SR, Barnes TRE. The clinical treatment of schizophrenia with antipsychotic medication. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia*. Oxford: Blackwell; 1995. p. 443-68.

HMSO. Equality Act 2010. London: The Stationary Office; 2010. Available from: <http://www.legislation.gov.uk/ukpga/2010/15/contents>.

HMSO. The Mental Capacity Act 2005. London: The Stationery Office; 2005. Available at: [http://www.opsi.gov.uk/acts/acts2005/pdf/ukpga\\_20050009\\_en.pdf](http://www.opsi.gov.uk/acts/acts2005/pdf/ukpga_20050009_en.pdf).

HMSO. The Mental Health Act 2007. London: The Stationery Office; 2007. Available at: [http://www.opsi.gov.uk/acts/acts2007/pdf/ukpga\\_20070012\\_en.pdf](http://www.opsi.gov.uk/acts/acts2007/pdf/ukpga_20070012_en.pdf).

Hoffmann H, Jäckel D, Glauser S, Kupper Z. A randomised controlled trial of the efficacy of supported employment. *Acta Psychiatrica Scandinavica*. 2012;125:157-67.

Hogarty GE, Ulrich RF, Mussare F, Aristigueta N. Drug discontinuation among long term, successfully maintained schizophrenic outpatients. *Diseases of the Nervous System*. 1976;37:494-500.

Hollister LE. Clinical differences among phenothiazines in schizophrenics. Introduction: specific indications for antipsychotics: elusive end of the rainbow. *Advances in Biochemical Psychopharmacology*. 1974;9:667-73.

Holloway F, Carson J. Intensive case management for the severely mentally ill. Controlled trial. *The British Journal of Psychiatry*. 1998;172:19-22.

Holloway F, Lloyd ES. Inpatient treatment. Thornicroft G, Szmukler G, Mueser KT, Drake RE, eds. Oxford: Oxford University Press; 2011.

Holt RI, Bushe C, Citrome L. Diabetes and schizophrenia 2005: are we any closer to understanding the link? *Journal of Psychopharmacology*. 2005;19:56-65.

Homel P, Casey D, Allison DB. Changes in body mass index for individuals with and without schizophrenia, 1987-1996. *Schizophrenia Research*. 2002;55:277-84.

Honer WG, Thornton AE, Chen EY, Chan RC, Wong JO, Bergmann A, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *New England Journal of Medicine*. 2006;354:472-82.

Hong LE, Thaker GK, McMahon RP, Summerfelt A, Rachbeisel J, Fuller RL, et al. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. *Archives of General Psychiatry*. 2011;68:1195-206.

Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *Journal of Psychopharmacology*. 2010;24:81-90.



Horst WD, Klein MW, Williams D, Werder SF. Extended use of nicotine replacement therapy to maintain smoking cessation in persons with schizophrenia. *Neuropsychiatric Disease and Treatment*. 2005;1:349-55.

Hosalli P, Davis JM. Depot risperidone for schizophrenia. *Cochrane Database of Systematic Reviews*. 2003;4:Art. No. CD004161. DOI: 10.1002/14651858.CD004161.

Hoult J. Home treatment in New South Wales. In: Hall P, Brockington I, eds. *The Closure of Mental Hospitals*. London: Gaskell/Royal College of Psychiatrists; 1991.

Hoult J, Reynolds I, Charbonneau-Powis M, Weekes P, Briggs J. Psychiatric hospital versus community treatment: the results of a randomised trial. *Australian and New Zealand Journal of Psychiatry*. 1983;17:160-7.

Howard L. Effectiveness and cost-effectiveness of admissions to women's crisis houses compared with traditional psychiatric wards: pilot patient-preference randomised controlled trial. *The British Journal of Psychiatry*. 2010;197:s32.

Howard LM, Heslin M, Leese M, McCrone P, Rice C, Jarrett M, et al. Supported employment: randomised controlled trial. *The British Journal of Psychiatry*. 2010;196:404-11.

Hughes H, Meddings S, Vandrevalla T, Holmes S, Hayward M. Carers' experiences of assertive outreach services: an exploratory study. *Journal of Mental Health*. 2011;20:70-78.

Intagliata J. Improving the quality of community care for the chronically mentally disabled: the role of case management. *Schizophrenia Bulletin*. 1982;8:655-74.

International Early Psychosis Association Writing Group. International clinical practice guidelines for early psychosis. *The British Journal of Psychiatry*. 2005;187:s120-s24.

Iqbal MM, Rahman A, Husain Z, Mahmud SZ, Ryan WG, Feldman JM. Clozapine: a clinical review of adverse effects and management. *Annals of Clinical Psychiatry*. 2003;15:33-48.

Isaac M. Trends in the development of psychiatric services in India. *Psychiatric Bulletin*. 1996;20:43-45.

Jaaskelainen E, Miettunen J, Veijola J, McGrath JJ, Murray GK, Jones PB, et al. Associations between early development and outcome in schizophrenia- a 35-year follow-up of the Northern Finland 1966 Birth Cohort. *Schizophrenia Research*. 2008;99:29-37.

- Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological medicine*. 1992;20:1-97.
- Jackson C, Trower P, Reid I, Smith J, Hall M, Townend M, et al. Improving psychological adjustment following a first episode of psychosis: a randomised controlled trial of cognitive therapy to reduce post psychotic trauma symptoms. *Behaviour Research and Therapy*. 2009;47:454-62.
- Jackson H, McGorry P, Edwards J, Hulbert C, Henry L, Harrigan S, et al. A controlled trial of cognitively oriented psychotherapy for early psychosis (COPE) with four-year follow-up readmission data. *Psychological medicine*. 2005;35:1295-306.
- Jackson HJ, McGorry PD, Killackey E, Bendall S, Allott K, Dudgeon P, et al. Acute-phase and 1-year follow-up results of a randomized controlled trial of CBT versus Befriending for first-episode psychosis: the ACE project. *Psychological medicine*. 2008;38:725-35.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*. 1996;17:1-12.
- Jankovic J, Yeeles K, Katsakou C, Amos T, Morriss R, Rose D, et al. Family caregivers' experiences of involuntary psychiatric hospital admissions of their relatives-a qualitative study. *PLoS ONE*. 2011;6:e25425.
- Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, Graaf Rd, et al. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandinavica*. 2004;109:38-45.
- Jeppesen P, Petersen L, Thorup A, Abel MB, Oehlenschlaeger J, Christensen T, et al. Integrated treatment of first-episode psychosis: effect of treatment on family burden: OPUS trial. *The British Journal of Psychiatry*. 2005;48:s85-s90.
- Jerrell JM. Toward managed care for persons with severe mental illness: implications from a cost-effectiveness study. *Health Affairs*. 1995;14:197-207.
- Jerrell JM. Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications. *Schizophrenia Bulletin*. 2002;28:589-605.
- Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical co-morbidity in schizophrenia. *Schizophrenia Bulletin*. 1996;22:413-20.

Ji J, Sundquist K, Ning Y, Kendler KS, Sundquist J, Chen X. Incidence of cancer in patients with schizophrenia and their first-degree relatives: a population-based study in Sweden. *Schizophrenia Bulletin*. 2013;39:527-36.

Joa I, Johannessen JO, Auestad B, Friis S, McGlashan T, Melle I, et al. The key to reducing duration of untreated first psychosis: information campaigns. *Schizophrenia Bulletin*. 2008;34:466-72.

Jobe TH, Harrow M. Long-term outcome of patients with schizophrenia: a review. *Canadian Journal of Psychiatry*. 2005;50:892-900.

Johannessen JO, McGlashan TH, Larsen TK, Horneland M, Joa I, Mardal S, et al. Early detection strategies for untreated first-episode psychosis. *Schizophrenia Research*. 2001;51:39-46.

Johnson S. Crisis resolution and home treatment teams: an evolving model. *Advances in Psychiatric Treatment*. 2013;19:115-23.

Johnson S, Gilbert H, Lloyd-Evans B, Osborn DP, Boardman J, Leese M, et al. In-patient and residential alternatives to standard acute psychiatric wards in England. *The British Journal of Psychiatry*. 2009;194:456-63.

Johnson S, Lloyd-Evans B, Howard L, Osborn DPJ, Slade M. Where next with residential alternatives to admission? *The British Journal of Psychiatry*. 2010;197:s52-s54.

Johnson S, Needle J. Crisis resolution teams: rationale and core model. *Crisis Resolution and Home Treatment in Mental Health*. 1st edn. Cambridge: Cambridge University Press; 2008.

Johnson S, Needle J, Bindman J, Thornicroft G. *Crisis Resolution and Home Treatment in Mental Health*. Cambridge: Cambridge University Press; 2008.

Johnson S, Nolan F, Pilling S, Sandor A, Hoult J, McKenzie N, et al. Randomised controlled trial of acute mental health care by a crisis resolution team: the north Islington crisis study. *BMJ*. 2005;331:599.

Johnston S, Salkeld G, Sanderson K, Issakidis C, Teesson M, Buhrich N. Intensive case management: a cost-effectiveness analysis. *Australian and New Zealand Journal of Psychiatry*. 1998;32:551-9.

Jones B. Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. 151st Annual Meeting of the American Psychiatric Association:1998; Toronto, Ontario.

Jones C, Cormac I, Silveira da Mota Neto JI, Campbell C. Cognitive Behaviour Therapy for Schizophrenia. The Cochrane Library. 1998.

Jones F, Riazi A. Self-efficacy and self-management after stroke: a systematic review. *Disability and Rehabilitation*. 2011;33:797-810.

Jones P. *Drama as Therapy: Theatre as Living*. London: Routledge; 1996.

Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). *Archives of General Psychiatry*. 2006;63:1079-87.

Jørgensen P, Nordentoft M, Abel M, Gouliaev G, Jeppesen P, Kassow P. Early detection and assertive community treatment of young psychotics: the Opus Study Rationale and design of the trial. *Social Psychiatry and Psychiatric Epidemiology*. 2000;35:283-87.

Josiassen RC, Joseph A, Kohegyi E, Stokes S, Dadvand M, Paing WW, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry*. 2005;162:130-6.

Joy CB, Adams CE, Rice K. Crisis intervention for people with severe mental illnesses. *Cochrane Database of Systematic Reviews*. 2002;2: Art. No.:CD001087.DOI:10.1002/14651858.CD001087.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *The Lancet*. 2008;371:1085-97.

Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*. 1988;45:789-96.

Kane JM. Treatment of schizophrenia. *Schizophrenia Bulletin*. 1987;13:133-56.

Kane JM. Treatment programme and long-term outcome in chronic schizophrenia. *Acta Psychiatrica Scandinavica Supplementum*. 1990;358:151-7.

Kane JM, Marder SR. Psychopharmacologic treatment of schizophrenia. *Schizophrenia Bulletin*. 1993;19:287-302.

Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month

randomized and double-blind comparison. *Archives of General Psychiatry*. 2001;58:965-72.

Kaplan K, Salzer MS, Solomon P, Brusilovskiy E, Cousounis P. Internet peer support for individuals with psychiatric disabilities: a randomized controlled trial. *Social Science and Medicine*. 2011;72:54-62.

Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Progress in Neuro-psychopharmacology and Biological Psychiatry*. 2003;27:1081-90.

Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biological Psychiatry*. 2001;50:873-83.

Karow A, Reimer J, Konig HH, Heider D, Bock T, Huber C, et al. Cost-effectiveness of 12-month therapeutic assertive community treatment as part of integrated care versus standard care in patients with schizophrenia treated with quetiapine immediate release (ACCESS trial). *Journal of Clinical Psychiatry*. 2012;73:e402-e08.

Karunakaran K, Tungaraza TE, Harborne GC. Is clozapine-aripiprazole combination a useful regime in the management of treatment-resistant schizophrenia? *Journal of Psychopharmacology*. 2006;21:453-6.

Kasckow JW, Twamley E, Mulchahey JJ, Carroll B, Sabai M, Strakowski SM, et al. Health-related quality of well-being in chronically hospitalized patients with schizophrenia: comparison with matched outpatients. *Psychiatry research*. 2001;103:69-78.

Kasper S, Winkler D. Addressing the limitations of the CATIE study. *World Journal of Biological Psychiatry*. 2006;7:126-7.

Kavanagh S, Opit L, Knapp M, Beecham J. Schizophrenia: shifting the balance of care. *Social Psychiatry and Psychiatric Epidemiology*. 1995;30:206-12.

Kelly DL, McMahon RP, Weiner E, Boggs DL, Dickinson D, Conley RR, et al. Lack of beneficial galantamine effect for smoking behavior: a double-blind randomized trial in people with schizophrenia. *Schizophrenia Research*. 2008;103:161-68.

Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomised controlled trial. *BMJ*. 1996;312:345-9.

Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomised controlled trial of compliance therapy. 18-month follow-up. *The British Journal of Psychiatry*. 1998;172:413-9.

Kemp V. Use of 'chronic disease self-management strategies' in mental healthcare. *Current Opinion in Psychiatry*. 2011;24:144-48.

Kendall T. The rise and fall of the atypical antipsychotics. *The British Journal of Psychiatry*. 2011;199:266-68.

Kendrick T, Burns T, Freeling P, Sibbald B. Provision of care to general practice patients with disabling long-term mental illness: a survey in 16 practices. *British Journal of General Practice*. 1994;44:301-5.

Kendrick T, Sibbald B, Burns T, Freeling P. Role of general practitioners in care of long term mentally ill patients. *BMJ*. 1991;302:508-10.

Keshavan MS, Nasrallah HA, Tandon R. Schizophrenia, "Just the Facts" 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. *Schizophrenia Research*. 2011;127:3-13.

Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry*. 2007;20:359-64.

Khan I, Pillay K. Users' attitudes towards home and hospital treatment: a comparative study between South Asian and white residents of the British Isles. *Journal of Psychiatric and Mental Health Nursing*. 2003;10:137-46.

Killackey E, Jackson HJ, McGorry PD. Vocational intervention in first-episode psychosis: individual placement and support v. treatment as usual. *The British Journal of Psychiatry*. 2008;193:114-20.

Killaspy H. From the asylum to community care: learning from experience. *BMJ*. 2006;79-80:245-58.

Killaspy H, Bebbington P, Blizard R, Johnson S, Nolan F, Pilling S, et al. The REACT study: Randomised evaluation of assertive community treatment in north London. *BMJ*. 2006;332:815-18.

Killaspy H, Marston L, Omar RZ, Green N, Harrison I, Lean M, et al. Service quality and clinical outcomes: an example from mental health rehabilitation services in England. *The British Journal of Psychiatry*. 2013;202:28-34.

Kingdon DG, Kinoshita Y, Naeem F, Swelam M, Hansen L, Vincent S, et al. Schizophrenia can and should be renamed. *BMJ*. 2007;334:221-2.

Kinon BJ, Kane JM, Johns C, Perovich R, Ismi M, Koreen A, et al. Treatment of neuroleptic-resistant schizophrenia relapse. *Psychopharmacology Bulletin*. 1993;29:309-14.

Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, et al. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. *PLoS One*. 2012;7:e31660.

Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Archives of General Psychiatry*. 2006;63:250-8.

Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. *JAMA Psychiatry*. 2013;70:209-17.

Kissling W. The current unsatisfactory state of relapse prevention in schizophrenic psychoses-suggestions for improvement. *Clinical Neuropharmacology*. 1991;14(Suppl:2):S33-44.

Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. *PLoS medicine*. 2006;3:e294.

Kline MN, Hoisington V. Placing the psychiatrically disabled - a look at work values. *Rehabilitation Counseling Bulletin*. 1981;24:366-69.

Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Archives of General Psychiatry*. 2001;58:158-64.

Knapp M, Chisholm D, Leese M, Amaddeo F, Tansella M, Schene A, et al. Comparing patterns and costs of schizophrenia care in five European countries: the EPSILON study. *European psychiatric services: inputs linked to outcome domains and needs*. *Acta Psychiatrica Scandinavica*. 2002;105:42-54.

Knapp M, King D, Pugner K, Lapuerta P. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *British Journal Psychiatry*. 2004;184:509-16.

Knapp M, Patel A, Curran C, Latimer E, Catty J, Becker T, et al. Supported employment: cost-effectiveness across six European sites. *World Psychiatry*. 2013;12:60-8.

Knapp M, Windmeijer F, Brown J, Kontodimas S, Tzivelekis S, Haro JM, et al. Cost-utility analysis of treatment with olanzapine compared with other antipsychotic treatments in patients with schizophrenia in the pan-European SOHO study. *Pharmacoeconomics*. 2008;26:341-58.

Knudson B, Coyle A. Parents' experiences of caring for sons and daughters with schizophrenia: a qualitative analysis of coping. *European Journal of Psychotherapy, Counselling and Health*. 2002;5:169-83.

König HH, Roick C, Angermeyer MC. Validity of the EQ-5D in assessing and valuing health status in patients with schizophrenic, schizotypal or delusional disorders. *European Psychiatry*. 2007;22:177-87.

Kontaxakis VP, Ferentinos PP, Havaki-Kontaxaki BJ, Roukas DK. Randomized controlled augmentation trials in clozapine-resistant schizophrenic patients: a critical review. *European Psychiatry*. 2005;20:409-15.

Kontaxakis VP, Havaki-Kontaxaki BJ, Stamouli SS, Christodoulou GN. Toxic interaction between risperidone and clozapine: a case report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2002;26:407-9.

Koolaee AK, Etemadi A. The outcome of two family interventions for the mothers of schizophrenia patients in Iran. *The International Journal of Social Psychiatry*. 2009;56:634-46. E-pub 4 September 2010.

Kopelowicz A. Adapting social skills training for Latinos with schizophrenia. *International Review of Psychiatry*. 1998;10:47-50.

Kopelowicz A, Liberman RP, Wallace CJ, Aguirre F, Mintz J. Differential performance of job skills in schizophrenia: an experimental analysis. *Journal of Rehabilitation*. 2006;72:31-39.

Kopelowicz A, Wallace CJ, Zarate R. Teaching psychiatric inpatients to re-enter the community: a brief method of improving the continuity of care. *Psychiatric Services*. 1998;49:1313-6.

Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ*. 2002;325:243.

Krabbendam L, van Os J. Affective processes in the onset and persistence of psychosis. *European Archives of Psychiatry and Clinical Neuroscience*. 2005;255:185-9.

Kreyenbuhl JA, Valenstein M, McCarthy JF, Ganoczy D, Blow FC. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. *Psychiatric Services*. 2007;58:489-95.



Krstev H, Carbone S, Harrigan SM, Curry C, Elkins K, McGorry PD. Early intervention in first-episode psychosis--the impact of a community development campaign. *Social Psychiatry and Psychiatric Epidemiology*. 2004;39:711-9.

Kuipers E, Fowler D, Garety P, Chisholm D, Freeman D, Dunn G, et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis. III: follow-up and economic evaluation at 18 months. *The British Journal of Psychiatry*. 1998;173:61-68.

Kuipers E, Holloway F, Rabe HS, Tennakoon L, Croydon Outreach and Assertive Support Team. An RCT of early intervention in psychosis: Croydon Outreach and Assertive Support Team (COAST). *Social Psychiatry and Psychiatric Epidemiology*. 2004;39:358-63.

Kuipers L, Bebbington P. *Working in Partnership: Clinicians and Carers in the Management of Longstanding Mental Illness*. Oxford: Heinemann Medical Books; 1990.

Kuldau JM, Dirks SJ. Controlled evaluation of a hospital-originated community transitional system. *Archives of General Psychiatry*. 1977;34:1331-40.

Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM, Vinogradov S, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophrenia Bulletin*. 2008;34:60-71.

Kurtz MM, Mueser KT. A meta-analysis of controlled research on social skills training for schizophrenia. *Journal of Consulting and Clinical Psychology*. 2008;76:491.

Kwon JS, Choi JS, Bahk WM, Yoon KC, Hyung KC, Chul SY, et al. Weight management program for treatment-emergent weight gain in olanzapine-treated patients with schizophrenia or schizoaffective disorder: a 12-week randomized controlled clinical trial. *Journal of Clinical Psychiatry*. 2006;67:547-53.

Laird B, Smith B, Dutu G, Mellsop G. Views and experiences of family/whanau carers of psychiatric service users on diagnosis and classification. *The International Journal of Social Psychiatry*. 2010;56:270-79.

Lambert M, Naber D, Schacht A, Wagner T, Hundemer HP, Karow A, et al. Rates and predictors of remission and recovery during 3 years in 392 never-treated patients with schizophrenia. *Acta Psychiatrica Scandinavica*. 2008;118:220-9.

Lamberti JS, Herz MI. Psychotherapy, social skills training, and vocational rehabilitation in schizophrenia. In: Shrikui C, Nasrallah H, eds. *Contemporary Issues in the Treatment of Schizophrenia*. Washington DC: American Psychiatric Press; 1995.

Lang FH, Forbes JF, Murray GD, Johnstone EC. Service provision for people with schizophrenia. I. Clinical and economic perspective. *The British Journal of Psychiatry*. 1997;171:159-64.

Langan J, Mercer SW, Smith DJ. Multimorbidity and mental health: can psychiatry rise to the challenge? *The British Journal of Psychiatry*. 2013;202:391-93.

Latimer E. An effective intervention delivered at sub-therapeutic dose becomes an ineffective intervention. *The British Journal of Psychiatry*. 2010;196:341-42.

Latimer EA, Lecomte T, Becker DR, Drake RE, Duclos I, Piat M, et al. Generalisability of the individual placement and support model of supported employment: results of a Canadian randomised controlled trial. *The British Journal of Psychiatry*. 2006;189:65-73.

Launois R, Graf von der Schulenberg M, Knapp M, Toumi M. Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model. *International Journal of Psychiatry in Clinical Practice*. 1998;2:S79-S86.

Laux G, Heeg B, van Hout BA, Mehnert A. Costs and effects of long-acting risperidone compared with oral atypical and conventional depot formulations in Germany. *Pharmacoeconomics*. 2005;23 (Suppl:1):49-61.

Lawn S. Mental health peer support for hospital avoidance and early discharge: An Australian example of consumer driven and operated service. *Journal of Mental Health*. 2008;17:498-508.

Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ*. 2013;346:f2539.

Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. *Journal of Psychopharmacology*. 2010;24:61-68.

Lawrence DM, Holman CD, Jablensky AV, Hobbs MS. Death rate from ischaemic heart disease in Western Australian psychiatric patients 1980-1998. *The British Journal of Psychiatry*. 2003;182:31-6.

Lawrie SM, Martin K, McNeill G, Drife J, Chrystie P, Reid A, et al. General practitioners' attitudes to psychiatric and medical illness. *Psychological medicine*. 1998;28:1463-7.

Leavey G, Gulamhussein S, Papadopoulos C, Johnson-Sabine E, Blizzard B, King M. A randomized controlled trial of a brief intervention for families of patients with a first episode of psychosis. *Psychological medicine*. 2004;34:423-31.

Lecomte P, De Hert M, van Dijk M, Nuijten M, Nuyts G, Persson U. A 1-year cost-effectiveness model for the treatment of chronic schizophrenia with acute exacerbations in Belgium. *Value in Health*. 2000;3:1-11.

Leff J, Kuipers L, Berkowitz R, Eberlein-Vries R, Sturgeon D. A controlled trial of social intervention in the families of schizophrenic patients. *The British Journal of Psychiatry*. 1982;141:121-34.

Leff MS, Daniel Chisholm, Ray Bell, Catherine Gamble, Julian. Training community psychiatric nurses in schizophrenia family work: a study of clinical and economic outcomes for patients and relatives. *Journal of Mental Health*. 2001;10:189-97.

Lehman AF, Dixon LB, Kernan E, DeForge BR, Postrado LT. A randomized trial of assertive community treatment for homeless persons with severe mental illness. *Archives of General Psychiatry*. 1997;54:1038-43.

Lehman AF, Goldberg R, Dixon LB, McNary S, Postrado L, Hackman A, et al. Improving employment outcomes for persons with severe mental illnesses. *Archives of General Psychiatry*. 2002;59:165-72.

Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. *Schizophrenia Bulletin*. 1998;24:11-20.

Lehman AF, Steinwachs DM, PORT-Coinvestigators. Patterns of usual care for schizophrenia: initial survey results from the schizophrenia patient outcomes research team (PORT) survey. *Schizophrenia Bulletin*. 1998;24:11-20.

Lenert LA, Sturley AP, Rapaport MH, Chavez S, Mohr PE, Rupnow M. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. *Schizophrenia Research*. 2004;71:155-65.

Lester H, Birchwood M, Bryan S, England E, Rogers H, Sirvastava N. Development and implementation of early intervention services for young people with psychosis: case study. *The British Journal of Psychiatry*. 2009a;194:446-50.

Lester H, Birchwood M, Freemantle N, Michail M, Tait L. REDIRECT: cluster randomised controlled trial of GP training in first-episode psychosis. *British Journal of General Practice*. 2009b;59:e183-90.

Lester HE, Tritter JQ, Sorohan H. Providing primary care for people with serious mental illness: a focus group study. *BMJ*. 2005;1122-28.

Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatrica Scandinavica*. 2007;116:317-33.

Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*. 2013;382:951-62.

Levine IS, Ligenza LR. In their own voices: families in crisis. A focus group study families of persons with serious mental illness. *Journal of Psychiatric Practice*. 2002;8:344-53.

Levitt AJ, Mueser KT, Degenova J, Lorenzo J, Bradford-Watt D, Barbosa A, et al. Randomized controlled trial of illness management and recovery in multiple-unit supportive housing. *Psychiatric Services*. 2009;60:1629-36.

Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology*. 1993;102:133-44.

Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomised controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia Bulletin*. 2006a;32:715-23.

Lewis SW, Davies L, Jones PB, Barnes TR, Murray RM, Kerwin R, et al. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technology Assessment*. 2006b;10:1-165.

Li J, Zhang T, Wang B, Li X. An efficacy analysis of bupropion for smoking cessation in schizophrenia. *Chinese Journal of New Drugs and Clinical Remedies*. 2009;28:231-34.

Liberman RP, Cardin V, McGill CW, Falloon IRH, Evans CD. Behavioral family management of schizophrenia: clinical outcome and costs. *Psychiatric Annals*. 1987;17:610.

Liberman RP, Kopelowicz A. Training skills for illness self-management in the rehabilitation of schizophrenia. A family-assisted program for Latinos in California. *Salud Mental*. 2009;32:93.

Liberman RP, Wallace CJ, Blackwell G, Eckmaiu T, Kuehnel TG. Skills training for the seriously mentally ill: modules in the UCLA social and independent living skills

program. In: Ancill R, ed. *Schizophrenia: Exploring the Spectrum of Psychosis*. Chichester: Wiley; 1994. p. 35-47.

Lieberman RP, Wallace CJ, Blackwell G, Kopelowicz A, Vaccaro JV, Mintz J. Skills training versus psychosocial occupational therapy for persons with persistent schizophrenia. *American Journal of Psychiatry*. 1998;155:1087-91.

Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Archives of General Psychiatry*. 1993;50:369-76.

Lieberman J, Jody D, Geisler S, Vital-Herne J, Alvir JM, Walsleben J, et al. Treatment outcome of first episode schizophrenia. *Psychopharmacology Bulletin*. 1989;25:92-6.

Lieberman JA. Comparative effectiveness of antipsychotic drugs - a commentary on Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). *Archives of General Psychiatry*. 2006;63:1069-72.

Lieberman JA, Alvir JM, Woerner M, Degreef G, Bilder RM, Ashtari M, et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophrenia Bulletin*. 1992;18:351-71.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*. 2005;353:1209-23.

Lincoln TM, Arens E, Berger C, Rief W. Can antistigma campaigns be improved? A test of the impact of biogenetic vs psychosocial causal explanations on implicit and explicit attitudes to schizophrenia. *Schizophrenia Bulletin*. 2008;34:984-94.

Lindamer LA, McKibbin C, Norman GJ, Jordan L, Harrison K, Abeyesinhe S, et al. Assessment of physical activity in middle-aged and older adults with schizophrenia. *Schizophrenia Research*. 2008;104:294-301.

Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *American Journal of Psychiatry*. 2003;160:290-6.

Lindenmayer JP, Czobor P, Volavka J, Lieberman JA, Citrome L, Sheitman B, et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *Journal of Clinical Psychiatry*. 2002;63:931-35.

Lindenmayer JP, McGurk SR, Mueser KT, Khan A, Wance D, Hoffman L, et al. A randomized controlled trial of cognitive remediation among inpatients with persistent mental illness. *Psychiatric Services*. 2008;59:241-47.

Lindsley OR. Direct measurement and functional definition of vocal hallucinatory symptoms. *The Journal of Nervous and Mental Disease*. 1963;136:293-97.

Littrell KH, Hilligoss NM, Kirshner CD, Petty RG, Johnson CG. The effects of an educational intervention on antipsychotic-induced weight gain. *Journal of Nursing Scholarship*. 2003;35:237-41.

Llorca PM, Lancon C, Disdier B, Farisse J, Sapin C, Auquier P. Effectiveness of clozapine in neuroleptic-resistant schizophrenia: clinical response and plasma concentrations. *Journal of Psychiatry Neuroscience*. 2002;27:30-7.

Lloyd-Evans B, Crosby M, Stockton S, Pilling S, Hobbs L, Hinton M, et al. Initiatives to shorten duration of untreated psychosis: systematic review. *The British Journal of Psychiatry*. 2011;198:256-63.

Lloyd-Evans B, Slade M, Jagielska D, Johnson S. Residential alternatives to acute psychiatric hospital admission: systematic review. *The British Journal of Psychiatry*. 2009;195:109-17.

Lobban F, Barrowclough C. *A Casebook of Family Interventions for Psychosis*. Chichester: Wiley; 2009.

Lobban F, Glentworth D, Chapman L, Wainwright L, Postlethwaite A, Dunn G, et al. Feasibility of a supported self-management intervention for relatives of people with recent onset psychosis: REACT study. *British Journal of Psychiatry*. 2013;203:366-720.

Lobban F, Glentworth D, Haddock G, Wainwright L, Clancy A, Bentley R. The views of relatives of young people with psychosis on how to design a Relatives Education And Coping Toolkit (REACT). *Journal of Mental Health*. 2011;20:567-79.

Loebel AD, Lieberman JA, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. *American Journal of Psychiatry*. 1992;149:1183-8.

Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine*. 2004;23:3105-24.

Lu GB, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association*. 2006;101:447-59.

Lumsden V, Rajan L. Carer satisfaction with an assertive outreach service. *Clinical Psychology Forum*. 2011;11-15.

Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*. 2000;10:325-37.

Lysaker PH, Bond G, Davis LW, Bryson GJ, Bell MD. Enhanced cognitive-behavioral therapy for vocational rehabilitation in schizophrenia: effects on hope and work. *Journal of Rehabilitation Research and Development*. 2005;42:673-82.

Lysaker PH, Davis LW, Bryson GJ, Bell MD. Effects of cognitive behavioral therapy on work outcomes in vocational rehabilitation for participants with schizophrenia spectrum disorders. *Schizophrenia Research*. 2009;107:186-91.

Macias C, Kinney R, Farley OW, Jackson R, Vos B. The role of case management within a community support system: partnership with psychosocial rehabilitation. *Community Mental Health Journal*. 1994;30:323-39.

Mackin P, Bishop D, Watkinson H, Gallagher P, Ferrier IN. Metabolic disease and cardiovascular risk in people treated with antipsychotics in the community. *The British Journal of Psychiatry*. 2007a;191:23-9.

Mackin P, Bishop DR, Watkinson HM. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. *BMC Psychiatry*. 2007b;7:28.

MacMillan JF, Crow TJ, Johnson AL, Johnstone EC. Short-term outcome in trial entrants and trial eligible patients. *The British Journal of Psychiatry*. 1986;148:128-33.

Macpherson R, Shepherd G, Thyarappa P. Supported accommodation for people with severe mental illness: an update. *Advances in Psychiatric Treatment*. 2012;18:381-91.

Madigan K, Egan P, Brennan D, Hill S, Maguire B, Horgan F, et al. A randomised controlled trial of carer-focussed multi-family group psychoeducation in bipolar disorder. *European Psychiatry*. 2012;27:281-84.

Magliano L, Fadden G, Madianos M, de Almeida JM, Held T, Guarneri M, et al. Burden on the families of patients with schizophrenia: results of the BIOMED I study. *Social Psychiatry and Psychiatric Epidemiology*. 1998;33:405-12.

Magliano L, Fiorillo A, Malangone C, De Rosa C, Maj M. Patient functioning and family burden in a controlled, real-world trial of family psychoeducation for schizophrenia. *Psychiatric Services*. 2006;57:1784-91.

Malla A, Bechard-Evans L, Joobar R, King S, Abadi S. Understanding the complexities of delay in treatment of psychosis and relevance for early detection interventions. *Schizophrenia Research*. 2006;86:S40.

Malla A, Norman R, Scholten D, Manchanda R, McLean T. A community intervention for early identification of first episode psychosis: impact on duration of untreated psychosis (DUP) and patient characteristics. *Social Psychiatry and Psychiatric Epidemiology*. 2005;40:337-44.

Malmberg L, Fenton M, Rathbone J. Individual psychodynamic psychotherapy and psychoanalysis for schizophrenia and severe mental illness (Cochrane review). *Cochrane Database of Systematic Reviews*. 2001;3: Art. No. CD001360.DOI:10.1002/14651858.CD001360.

Mangalore R, Knapp M. Cost of schizophrenia in England. *Journal of Mental Health Policy and Economics*. 2007;10:23-41.

Mann T. Clinical Guidelines: Using Clinical Guidelines to Improve Patient Care Within the NHS. London: NHS Executive; 1996.

Manu P, Correll CU, van Winkel R, Wampers M, De Hert M. Prediabetes in patients treated with antipsychotic drugs. *Journal of Clinical Psychiatry*. 2012;73:460-6.

Marder SR, Glynn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *American Journal of Psychiatry*. 2003;160:1405-12.

Marder SR, Wirshing DA. Maintenance treatment. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia*, 2nd edition. Oxford: Blackwell; 2003.

Marder SR, Wirshing WC, Mintz J, McKenzie J, Johnston K, Eckman TA, et al. Two-year outcome of social skills training and group psychotherapy for outpatients with schizophrenia. *American Journal of Psychiatry*. 1996;153:1585-92.

Mari J, Streiner D. Family intervention for schizophrenia. *The Cochrane Database of Systematic Reviews*. 2000;2: Art. No. CD000088. DOI:10.1002/14651858.CD000088.pub2.

Marks IM, Connolly J, Muijen M, Audini B, McNamee G, Lawrence RE. Home-based versus hospital-based care for people with serious mental illness. *The British Journal of Psychiatry*. 1994;165:179-94.

Marrone J, Golowka E. If work makes people with mental illness sick, what do unemployment, poverty and social isolation cause? *Psychiatric Rehabilitation Journal*. 1999;23:187-93.



Marshall M. What have we learnt from 40 years of research on intensive case management? *Epidemiologia e Psichiatria Sociale* 2008;17:2.

Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiters H, et al. Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) acute day hospital versus admission; (2) vocational rehabilitation; (3) day hospital versus outpatient care. *Health Technology Assessment*. 2001;5:1-75.

Marshall M, Crowther R, Sledge WH, Rathbone J, Soares-Weiser K. Day hospital versus admission for acute psychiatric disorders. *Cochrane Database of Systematic Reviews*. 2011;12: Art. No.CD004026. DOI:1002/14651858.CD004026.pub2.

Marshall M, Gray A, Lockwood A, Green R. Case management for people with severe mental disorders. *Cochrane Database of Systematic Reviews*. 2000;12: Art. No.CD000050. DOI:1002/14651858.CD000050.pub2.

Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry*. 2005;62:975-83.

Marshall M, Lockwood A. Assertive community treatment for people with severe mental disorders – a systematic review. 2000;12: Art. No.CD001089. DOI:1002/14651858.CD001089.pub2.

Marshall M, Lockwood A. Assertive community treatment for people with severe mental disorders. *Cochrane Database of Systematic Reviews*. 2002;2: Art. No.CD001089. DOI:1002/14651858.CD001089.pub2.

Marshall M, Lockwood A, Gath D. Social services case-management for long-term mental disorders: a randomised controlled trial. *The Lancet*. 1995;345:409-12.

Marwaha S, Johnson S. Schizophrenia and employment - a review. *Social Psychiatry and Psychiatric Epidemiology*. 2004;39:337-49.

Mauri M, Simoncini M, Castrogiovanni S, Iovieno N, Cecconi D, Dell'Agnello G, et al. A psychoeducational program for weight loss in patients who have experienced weight gain during antipsychotic treatment with olanzapine. *Pharmacopsychiatry*. 2008;41:17-23.

May PRA. *Treatment of Schizophrenia: A Comparative Study of Five Treatment Methods*. New York: Science House; 1968

McAuliffe D, Andriske L, Moller E, O'Brien M, Breslin P, Hickey P. 'Who cares?' An exploratory study of carer needs in adult mental health. *Australian e-Journal for the Advancement of Mental Health*. 2009;8:1-12.

McCabe R, Priebe S. The therapeutic relationship in the treatment of severe mental illness: a review of methods and findings. *The International Journal of Social Psychiatry*. 2004;50:115-28.

McCann TV, Lubman DI, Clark E. First-time primary caregivers' experience accessing first-episode psychosis services. *Early Intervention in Psychiatry*. 2011;5:156-62.

McCann TV, Lubman DI, Clark E. Primary caregivers' satisfaction with clinicians' response to them as informal carers of young people with first-episode psychosis: a qualitative study. *Journal of Clinical Nursing*. 2012a;21:224-31.

McCann TV, Lubman DI, Cotton SM, Murphy B, Crisp K, Catania L, et al. A randomized controlled trial of bibliotherapy for carers of young people with first-episode psychosis. *Schizophrenia Bulletin*. 2012b.

McCarthy RH. Seizures following smoking cessation in a clozapine responder. *Pharmacopsychiatry*. 1994;27:210-1.

McCarthy RH, Terkelsen KG. Risperidone augmentation of clozapine. *Pharmacopsychiatry*. 1995;28:61-63.

McCrone P, Beecham J, Knapp M. Community psychiatric nurse teams: cost-effectiveness of intensive support versus generic care. *The British Journal of Psychiatry*. 1994;165:218-21.

McCrone P, Craig TK, Power P, Garety PA. Cost-effectiveness of an early intervention service for people with psychosis. *The British Journal of Psychiatry*. 2010;196:377-82.

McCrone P, Johnson S, Nolan F, Pilling S, Sandor A, Hoult J, et al. Economic evaluation of a crisis resolution service: a randomised controlled trial. *Epidemiologia e Psichiatria Sociale*. 2009a;18:54-8.

McCrone P, Johnson S, Nolan F, Pilling S, Sandor A, Hoult J, et al. Impact of a crisis resolution team on service costs in the UK. *Psychiatric Bulletin*. 2009b;33:17-19.

McCrone P, Killaspy H, Bebbington P, Johnson S, Nolan F, Pilling S, et al. The REACT study: cost-effectiveness analysis of assertive community treatment in north London. *Psychiatric Services*. 2009c;60:908-13.

McCrone P, Knapp M, Dhanasiri S. Economic impact of services for first-episode psychosis: a decision model approach. *Early Intervention in Psychiatry*. 2009d;3:266-73.

McCrone P, Singh SP, Knapp M, Smith J, Clark M, Shiers D. The economic impact of early intervention in psychosis services for children and adolescents. *Early Intervention in Psychiatry*. 2013;7:368-73.

McDonel EC, Bond GR, Salyers M, Fekete D, Chen A, McGrew JH, et al. Implementing assertive community treatment programs in rural settings. *Administration and Policy in Mental Health*. 1997;25:153- 73.

McEvoy JP, Schooler NR, Wilson WH. Predictors of therapeutic response to haloperidol in acute schizophrenia. *Psychopharmacology Bulletin*. 1991;27:97-101.

McFarlane WR, Dushay RA, Deakins SM, Stastny P, Lukens EP, Toran J, et al. Employment outcomes in family-aided assertive community treatment. *American Journal of Orthopsychiatry*. 2000;70:203-14.

McFarlane WR, Lukens E, Link B, Dushay R, Deakins SA, Newmark M, et al. Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Archives of General Psychiatry*. 1995;52:679.

McGlashan TH. The Chestnut Lodge follow-up study: II. Long-term outcome of schizophrenia and the affective disorders. *Archives of General Psychiatry*. 1984;41:586.

McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *American Journal of Psychiatry*. 2006;163:790-9.

McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, et al. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophrenia Research*. 2003;61:7-18.

McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophrenia Bulletin*. 1996;22:305-26.

McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Australian and New Zealand Journal of Psychiatry*. 2006;40:616-22.

McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*. 2002;59:921-8.

McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*. 2008;30:67-76.

McGrath JJ. Variations in the incidence of schizophrenia: data versus dogma. *Schizophrenia Bulletin*. 2006;32:195-7.

McGrew JH, Bond GR. Critical ingredients of assertive community treatment: judgments of the experts. *The Journal of Mental Health Administration*. 1995;22:113-25.

McGurk SR, Mueser KT, DeRosa TJ, Wolfe R. Work, recovery, and comorbidity in schizophrenia: a randomized controlled trial of cognitive remediation. *Schizophrenia Bulletin*. 2009;35:319-35.

McGurk SR, Mueser KT, Pascaris A. Cognitive training and supported employment for persons with severe mental illness: one-year results from a randomized controlled trial. *Schizophrenia Bulletin*. 2005;31:898-909.

McGurk SR, Twamley EW, Sitzler DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry*. 2007;164:1791-802.

McIntosh AM, Conlon L, Lawrie SM, Stanfield AC. Compliance therapy for schizophrenia (Cochrane review). *Cochrane Database of Systematic Reviews*. 2006;3: Art. No. CD003442.pub 2. DOI:10.1002/14651858.CD003442.pub2.

McKenzie K, Bhui K. Institutional racism in mental health care. *BMJ*. 2007;334:649-50.

McKibbin CL, Patterson TL, Norman G, Patrick K, Jin H, Roesch S, et al. A lifestyle intervention for older schizophrenia patients with diabetes mellitus: a randomized controlled trial. *Schizophrenia Research*. 2006;86:36-44.

Meaney AM, Smith S, Howes OD, O'Brien M, Murray RM, O'Keane V. Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *The British Journal of Psychiatry*. 2004;184:503-8.

Meli G, Ottl B, Paladini A, Cataldi L. Prenatal and perinatal risk factors of schizophrenia. *The Journal of Maternal-Fetal and Neonatal Medicine*. 2012;25:2559-63.

Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Archives of General Psychiatry*. 2004;61:143-50.

Merson S, Tyrer P, Onyett S, Lack S, Birkett P, Lynch S, et al. Early intervention in psychiatric emergencies: a controlled clinical trial. *The Lancet*. 1992;339:1311-14.

Michon HW, van Weeghel J, Kroon H, Schene AH. Person-related predictors of employment outcomes after participation in psychiatric vocational rehabilitation programmes-a systematic review. *Social Psychiatry and Psychiatric Epidemiology*. 2005;40:408-16.

Middleton H, Glover G, Onyett S, Linde K. Crisis resolution/home treatment teams, gate-keeping and the role of the consultant psychiatrist. *Psychiatric Bulletin*. 2008;32:378-79.

Mihalopoulos C, Harris M, Henry L, Harrigan S, McGorry P. Is early intervention in psychosis cost-effective over the long term? *Schizophrenia Bulletin*. 2009;35:909-18.

Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin MR, Koponen H, et al. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. *Schizophrenia Bulletin*. 2011;37:1039-47.

Miller P, Lawrie S, Hodges A, Clafferty R, Cosway R, Johnstone E. Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*. 2001;36:338-42.

Miller WR, Rollnick S. *Motivational Interviewing: Preparing People to Change Addictive Behaviour*. New York: Guilford Press; 1991.

Mind. Listening to experience: an independent report into acute and crisis mental healthcare. London: Mind; 2011; Available from: [http://www.mind.org.uk/assets/0001/5921/Listening\\_to\\_experience\\_web.pdf](http://www.mind.org.uk/assets/0001/5921/Listening_to_experience_web.pdf).

Moffat J, Sass B, McKenzie K, Bhui K. Improving pathways into mental health care for black and ethnic minority groups: a systematic review of the grey literature. *International Review of Psychiatry*. 2009;21:439-49.

Mohan R, McCrone P, Szmukler G, Micali N, Afuwape S, Thornicroft G. Ethnic differences in mental health service use among patients with psychotic disorders. *Social Psychiatry and Psychiatric Epidemiology*. 2006;41:771-76.

Möller HJ. Do effectiveness ("real world") studies on antipsychotics tell us the real truth? *European Archives of Psychiatry and Clinical Neuroscience*. 2008;258:257-70.

Möller HJ, van Zerssen D. Course and outcome of schizophrenia. In: Hirsch S, Weinberger D, eds. *Schizophrenia* Oxford: Blackwell; 1995. p. 106-27.

Moncrieff J. A critique of the dopamine hypothesis of schizophrenia and psychosis. *Harvard Review of Psychiatry*. 2009;17:214-25.

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *The Lancet*. 2007;370:319-28.

Morant N, Lloyd-Evans B, Gilbert H, Slade M, Osborn D, Johnson S. Implementing successful residential alternatives to acute in-patient psychiatric services: lessons from a multi-centre study of alternatives in England. *Epidemiologia e Psichiatria Sociale*. 2012;21:175-85.

Morgan C, Dazzan P, Morgan K, Jones P, Harrison G, Leff J, et al. First episode psychosis and ethnicity: initial findings from the AESOP study. *World Psychiatry*. 2006;5:40.

Morgan C, Kirkbride J, Leff J, Craig T, Hutchinson G, McKenzie K, et al. Parental separation, loss and psychosis in different ethnic groups: a case-control study. *Psychological medicine*. 2007;37:495-503.

Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care*. 2009;32:1037-42.

Morrison AP, Byrne R, Bentall RP. DSM-5 and the 'psychosis risk syndrome': whose best interests would it serve? *Psychosis*. 2010;2:96-99.

Morrison AP, French P, Parker S, Roberts M, Stevens H, Bentall RP, et al. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophrenia Bulletin*. 2007;33:682-7.

Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *The British Journal of Psychiatry*. 2004;185:291-97.

Morrison AP, Hutton P, Shiers D, Turkington D. Antipsychotics: is it time to introduce patient choice? *The British Journal of Psychiatry*. 2012a;201:83-84.

Morrison AP, Hutton P, Wardle M, Spencer H, Barratt S, Brabban A, et al. Cognitive therapy for people with a schizophrenia spectrum diagnosis not taking antipsychotic medication: an exploratory trial. *Psychological Medicine*. 2012b;42:1049-56.

Morse G, Calsyn R, Allen G, Tempelhoff B, Smith R. Experimental comparison of the effects of three treatment programs for homeless mentally ill people. *Hospital and Community Psychiatry*. 1992;43:1005-10.

Morse GA, Calsyn RJ, Klinkenberg WD, Helminiak TW, Wolff N, Drake RE, et al. Treating homeless clients with severe mental illness and substance use disorders: costs and outcomes. *Community Mental Health Journal*. 2006;42:377-404.

Mossaheb N, Sacher J, Wiesegeger G, Klein N, Spindelegger CJ, Asenbaum S, et al. Haloperidol in combination with clozapine in treatment-refractory patients with schizophrenia. *European Neuropsychopharmacology*. 2006;16:S416-S16.

Mueser KT, Aalto S, Becker DR, Ogden JS, Wolfe RS, Schiavo D, et al. The effectiveness of skills training for improving outcomes in supported employment. *Psychiatric Services*. 2005;56:1254-60.

Mueser KT, Clark RE, Haines M, Drake RE, Bond GR, Becker DR, et al. The Hartford study of supported employment for severe mental illness: employment and nonvocational outcomes. 155th Annual Meeting of the American Psychiatric Association:2002a; Philadelphia, PA.

Mueser KT, Clark RE, Haines M, Drake RE, McHugo GJ, Bond GR, et al. The Hartford study of supported employment for persons with severe mental illness. *Journal of Consulting and Clinical Psychology*. 2004;72:479-90.

Mueser KT, Corrigan PW, Hilton DW, Tanzman B, Schaub A, Gingerich S, et al. Illness management and recovery: a review of the research. *Psychiatric Services*. 2002b;53:1272-84.

Mueser KT, Gingerich S. Illness self-management programmes. In: Thornicroft G, Szukler G, Mueser K, Drake R, eds. *Oxford Textbook of Community Mental Health*. Oxford: Oxford University Press; 2011.

Muijen M, Marks I, Connolly J, Audini B. Home based care and standard hospital care for patients with severe mental illness: a randomised controlled trial. *BMJ*. 1992;304:749-54.

Muller-Clemm WJ. Halting the 'revolving door' of serious mental illness: evaluating an assertive case management programme (deinstitutionalization, community mental health). Victoria, Canada: University of Victoria; 1996.

Murphy S, Irving CB, Adams CE, Driver R. Crisis intervention for people with severe mental illnesses. *Cochrane Database of Systematic Reviews*. 2012;5: Art. No.CD001087.DOI:10.1002/14651858.CD00087.

Murray CJ, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: findings of the global burden of disease study 2010. *The Lancet*. 2013;381:997-1020.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *The Lancet*. 2012;380:2197-223.

Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of Clinical Epidemiology*. 2013;66:736-42.

Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *Journal of Clinical Psychiatry*. 2012;73:468-75.

Nagel T, Robinson G, Condon J, Trauer T. Approach to treatment of mental illness and substance dependence in remote Indigenous communities: results of a mixed methods study. *The Australian Journal of Rural Health*. 2009;17:174-82.

Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology*. 2003;28(Suppl:1):83-96.

Nasrallah H. Folie en masse! It's so tempting to drink the Kool-Aid (from the Editor). *Current Psychiatry*. 2011;10.

Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Molecular Psychiatry*. 2008;13:27-35.

Nasrallah HA, Meyer JM, Goff DC, McEvoy JP, Davis SM, Stroup TS, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. *Schizophrenia Research*. 2006;86:15-22.

National Institute for Mental Health in England. NIMHE Inside Outside. Improving Mental Health Services for Black and Minority Ethnic Communities. London: Department of Health; 2003; Available from: [www.nimhe.org.uk/downloads/inside\\_outside.pdf](http://www.nimhe.org.uk/downloads/inside_outside.pdf).

National Institute for Mental Health in England. NIMHE Guiding Statement on Recovery. London: National Institute for Mental Health in England; 2005.

Nayor C, Bell B. Mental health and the productivity challenge: improving quality and value for money. Report. London: The King's Fund and Centre for Mental Health; 2010.

Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. *BMJ*. 1993;307:32-4.



Nazareth ID, King MB. Controlled evaluation of management of schizophrenia in one general practice: a pilot study. *Family Practice*. 1992;9:171-2.

NCCMH. Schizophrenia: Full National Clinical Guideline on Core Interventions in Primary and Secondary Care. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists; 2003.

NCCMH. Bipolar Disorder: the Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care. Clinical guideline No. 38. Leicester & London: The British Psychological Society and Gaskell; 2006 [full guideline].

NCCMH. Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. Updated edition. Clinical guideline No. 82. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists; 2010 [full guideline].

NCCMH. Service User Experience in Adult Mental Health: Improving the Experience of Care for People Using Adult NHS Mental Health Services. Clinical guideline No. 136. London: RCPsych Publications; 2012 [full guideline].

NCCMH. Psychosis and Schizophrenia in Children and Young People: Recognition and Management. Clinical guideline No. 155. Leicester and London: The British Psychological Society and the Royal College of Psychiatrists; 2013 [full guideline].

Neelam K, Garg D, Marshall M. A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. *BMC Psychiatry*. 2011;11:139.

Nelson MT, Seal ML, Pantelis C, Phillips LJ. Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neuroscience and Biobehavioral Reviews*. 2013;37:317-27.

Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *Journal of Clinical Psychiatry*. 2007;68(Suppl:4):8-13.

Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Canadian Journal of Psychiatry*. 2006;51:480-91.

Newcomer JW, Wieden PJ, Buchanan RW. Switching antipsychotic medications to reduce adverse event burden in schizophrenia: establishing evidence-based practice. *Journal of Clinical Psychiatry*. 2013;74:1108-20.

NHS Business Services Authority, Prescription Pricing Division. Electronic Drug Tariff for England and Wales, June 2008. Compiled on behalf of the Department of Health. 2008 [updated December 2008].

NHS Employers. Pay Circular (AforC) 1/2006. Pay and Conditions for NHS Staff Covered by the Agenda for Change Agreement. London: NHS Employers; 2006.

NHS Employers. Quality and Outcomes Framework guidance for GMS contract 2011/12. London: NHS Employers; 2011.

NHS The Information Centre. Average Daily Quantity Values. London: The NHS Information Centre, Prescribing Support Unit, NHS; 2008a; Available from: [http://www.ic.nhs.uk/webfiles/Services/PSU/adqs\\_2007\\_08.pdf](http://www.ic.nhs.uk/webfiles/Services/PSU/adqs_2007_08.pdf).

NHS The Information Centre. Hospital Episode Statistics 2006–07. London: The NHS Information Centre; 2008b; Available from: <http://www.hesonline.nhs.uk>.

NHS The Information Centre. Prescription Cost Analysis England 2007. London: The NHS Information Centre, Prescribing Support Unit, NHS; 2008c; Available from: <http://www.ic.nhs.uk/pubs/prescostanalysis2007>.

NICE. Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia: Technology Appraisal. London: NICE; 2002a.

NICE. Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care. NICE clinical guideline 1. London: NICE; 2002b.

NICE. Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care. Clinical guideline no. 38. London: National Institute for Health and Clinical Excellence; 2006a. Available from: [www.nice.org.uk/CG38](http://www.nice.org.uk/CG38).

NICE. Obesity: Guidance on the Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children. NICE clinical guideline 43. London: NICE; 2006b.[cited Chapter 7]:Available from: [www.nice.org.uk/CG43](http://www.nice.org.uk/CG43).

NICE. The Guidelines Manual. London: NICE; 2007.

NICE. Guide to the Methods of Technology Appraisal. London: NICE; 2008a.

NICE. Social Value Judgements. Principles for the Development of NICE Guidance. 2nd edition. London: NICE; 2008b.

NICE. Depression in Adults: The Treatment and Management of Depression in Adults. NICE clinical guideline no. 90. London: National Institute of Health and Clinical Excellence; 2009a. Available from: [www.nice.org.uk/CG90](http://www.nice.org.uk/CG90).

NICE. Management of Long-term Sickness and Incapacity for Work. Public health guidance 19. London: NICE; 2009b.

NICE. Promoting Mental Wellbeing Through Productive and Healthy Working Conditions: Guidance for Employers. Public health guidance 22. London: NICE; 2009c.

NICE. Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care (Update). NICE clinical guideline 82. London: NICE; 2009d. Available from: [www.nice.org.uk/CG82](http://www.nice.org.uk/CG82).

NICE. Service user experience in adult mental health: improving the experience of care for people using adult mental health service. Clinical guideline CG136 2011. Available from: <http://guidance.nice.org.uk/CG136>.

NICE. Autism: Recognition, Referral, Diagnosis and Management of Adults on the Autism Spectrum. Clinical guideline no. 142. London: NICE; 2012a. Available from: [www.nice.org.uk/CG142](http://www.nice.org.uk/CG142).

NICE. The Guidelines Manual. London: NICE; 2012b; Available from: <http://publications.nice.org.uk/pmg6>.

NICE. Preventing Type 2 Diabetes: Risk Identification and Interventions for Individuals at High Risk. NICE Public health guidance 38. 2012c. Available from: <http://www.nice.org.uk/PH38>.

NICE. Psychosis and Schizophrenia in Children and Young People: Recognition and Management. NICE clinical guideline no. 155. London: NICE; 2013a. Available from: [www.nice.org.uk/CG155](http://www.nice.org.uk/CG155).

NICE. Smoking Cessation Services. NICE public health guidance no. 10. London: NICE; 2013b.

Nicholls CJ, Hale AS, Freemantle N. Cost-effectiveness of amisulpride compared with risperidone in patients with schizophrenia. *Journal of Drug Assessment*. 2003;6:79-89.

Nicholls E, Pernice R. Perceptions of the relationship between mental health professionals and family caregivers: has there been any change? *Issues in Mental Health Nursing*. 2009;30:474-81.

Nordby K, Kjongsberg K, Hummelvoll JK. Relatives of persons with recently discovered serious mental illness: In need of support to become resource persons in treatment and recovery. *Journal of Psychiatric and Mental Health Nursing*. 2010;17:304-11.

Norman R, Malla A, Verdi M, Hassall L, Fazekas C. Understanding delay in treatment for first episode psychosis. *Psychological Medicine*. 2006;34:255-66.

Nose M, Barbui C, Tansella M. How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. *Psychological medicine*. 2003;33:1149-60.

Nuechterlein KH. Vulnerability models for schizophrenia: state of the art. In *Search for the Causes of Schizophrenia*. In: Hafner H, Gattaz WF, Janzarik W, eds. Heidelberg: Springer; 1987. p. 297-316.

Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*. 2004;72:29-39.

Office for National Statistics. Population Trends 131. Deaths: Age and Sex, Numbers and Rates, 1976 Onwards (England and Wales). London: Office for National Statistics; 2008; Available from: <http://www.statistics.gov.uk/STATBASE/ssdataset.asp?vlnk=9552&More=Y>.

Office of the Deputy Prime Minister. Mental Health and Social Exclusion. Report. London: Office of the Deputy Prime Minister Publications; 2004.

Oh PI, Lanctôt KL, Mittmann N, Iskedjian M, Einarson TR. Cost-utility of risperidone compared with standard conventional antipsychotics in chronic schizophrenia. *Journal of Medical Economics*. 2001;4:137-56.

Okpaku SO, Anderson KH. The effectiveness of a multidisciplinary case management. *Psychiatric Rehabilitation Journal*. 1997;20:34.

Oltmanns TF, Neale JM. Schizophrenic performance when distractors are present: attentional deficit or differential task difficulty? *Journal of Abnormal Psychology*. 1975;84:205-9.

Oosthuizen P, Emsley RA, Turner J, Keyter N. Determining the optimal dose of haloperidol in first-episode psychosis. *Journal of Psychopharmacology*. 2001;15:251-5.

Organisation for Economic Co-operation and Development. Mental Health and Work Project: Organisation for Economic Co-operation and Development; 2011. Available from: [http://www.oecd.org/document/20/0,3746,en\\_2649\\_33933\\_38887124\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/20/0,3746,en_2649_33933_38887124_1_1_1_1,00.html).

Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the

United Kingdom's General Practice Research Database. *Archive of General Psychiatry*. 2007a;64:242-49.

Osborn DP, Nazareth I, King MB. Physical activity, dietary habits and Coronary Heart Disease risk factor knowledge amongst people with severe mental illness: a cross sectional comparative study in primary care. *Social Psychiatry and Psychiatric Epidemiology*. 2007b;42:787-93.

Osborn DP, Nazareth I, Wright CA, King MB. Impact of a nurse-led intervention to improve screening for cardiovascular risk factors in people with severe mental illnesses. Phase-two cluster randomised feasibility trial of community mental health teams. *BMC Health Services Research* 2010a;10:61.

Osborn DPJ, King MB, Nazareth I. Risk of cardiovascular disease in people with severe mental illness: a cross sectional comparative study in primary care. *The British Journal of Psychiatry*. 2006:271-77.

Osborn DPJ, Lloyd-Evans B, Johnson S, Gilbert H, Byford S, Leese M, et al. Residential alternatives to acute in-patient care in England: satisfaction, ward atmosphere and service user experiences. *The British Journal of Psychiatry*. 2010b;197:S41-S45.

Ozdemir V, Kalow W, Posner P, Collins EJ, Kennedy JL, Tang BK, et al. CYP1A2 activity as measured by a caffeine test predicts clozapine and active metabolite steady-state concentration in patients with schizophrenia. *Journal of Clinical Psychopharmacology*. 2002;21:398-407.

Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I, et al. Hippocampal plasticity in response to exercise in schizophrenia. *Archives of General Psychiatry*. 2010;67:133-43.

Palmer CS, Brunner E, Ruiz-Flores LG, Paez-Agraz F, Revicki DA. A cost-effectiveness clinical decision analysis model for treatment of schizophrenia. *Archives of Medical Research*. 2002;33:572-80.

Palmer CS, Revicki DA, Genduso LA, Hamilton SH, Brown RE. A cost-effectiveness clinical decision analysis model for schizophrenia. *American Journal of Managed Care*. 1998;4:345-55.

Pantelis C, Lambert TJ. Managing patients with 'treatment resistant' schizophrenia. *Medical Journal of Australia*. 2003;178 (Supl.):62-66.

Papadopoulos I, Tilki M, Lees S. Promoting cultural competence in healthcare through a research-based intervention in the UK. *Diversity in Health and Social Care*. 2004;1:107-16.

Pasamanick B, Scarpitti F, Lefton M, Dinitz S, Wernert JJ, McPheerers H. Home vs hospital care for schizophrenics. *Jama: Journal of the American Medical Association*. 1964;1:177-87.

Patel MX, David AS. Why aren't depot antipsychotics prescribed more often and what can be done about it? *Advances in Psychiatric Treatment*. 2005;11:203-11.

Paton C, Barnes TR, Cavanagh MR, Taylor D, Lelliott P. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. *The British Journal of Psychiatry*. 2008;192:435-9.

Paton C, Lelliott P, Harrington M, Okocha C, Sensky T, Duffett R. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. *Journal of Psychopharmacology*. 2003;17:223-9.

Paton C, Whittington C, Barnes TR. Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis. *Journal of Clinical Psychopharmacology*. 2007;27:198-204.

Patterson TL, Mausbach BT, McKibbin C, Goldman S, Bucardo J, Jeste DV. Functional adaptation skills training (FAST): a randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. *Schizophrenia Research*. 2006;86:291-99.

Patterson TL, McKibbin C, Taylor M, Goldman S, Davila FW, Bucardo J, et al. Functional adaptation skills training (FAST): a pilot psychosocial intervention study in middle-aged and older patients with chronic psychotic disorders. *American Journal of Geriatric Psychiatry*. 2003;11:17-23.

Paul KI, Moser K. Unemployment impairs mental health: Meta-analyses. *Journal of Vocational Behavior*. 2009;74:264-82.

Peasgood T, Roberts J, Tsuchiya A. Incapacity benefit: a health or labour market phenomenon? Sheffield economic research paper series number: 2006011. Sheffield: Department of Economics, University of Sheffield; 2006.

Pekkala E, Merinder L. Psychoeducation for schizophrenia. *The Cochrane Library*. 2002;2: Art. No.CD002831.DOI:1001002/14651858.CD002831.pub 2.

Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry*. 2005;162:1785-804.

Perkins R, Repper J, Rinaldi M, Brown H. Briefing. Recovery colleges: implementing recovery through organisational change. Centre for Mental Health; NHS Confederation Mental Health Network. London and Leeds;2012. Available from:

<http://www.nhsconfed.org/Documents/ImROC%20Briefing%20Recovery%20Colleges.pdf>.

Perkins R, Slade M. Recovery in England: transforming statutory services? *International Review of Psychiatry*. 2012;24:29-39.

Perlick DA, Miklowitz DJ, Lopez N, Chou J, Calvin C, Adzhishvili V, et al. Family-focused treatment for caregivers of patients with bipolar disorder. *Bipolar Disorders*. 2010;12:627-37.

Petersen L, Jeppesen P, Thorup A, Abel MB, Øhlenschlaeger J, Christensen TØ, et al. A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ*. 2005;331:602.

Phillips LJ, Nelson B, Yuen HP, Francey SM, Simmons M, Stanford C, et al. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics. *Australian and New Zealand Journal of Psychiatry*. 2009;43:818-29.

Phutane VH, Tek C, Chwastiak L, Ratliff JC, Ozyuksel B, Woods SW, et al. Cardiovascular risk in a first-episode psychosis sample: a 'critical period' for prevention? *Schizophrenia Research*. 2011;127:257-61.

Pierides M. Mental health services in Cyprus. *Psychiatric Bulletin*. 1994;18:425-27.

Pilling S, Bebbington P, Kuipers E, Garety P, Geddes J, Martindale B, et al. Psychological treatments in schizophrenia: II. Meta-analyses of randomized controlled trials of social skills training and cognitive remediation. *Psychological medicine*. 2002;32:783-91.

Pique TW. Cost-effectiveness of an African American Focus Assertive Community Treatment Program. Alameda: California School of Professional Psychology; 1999.

Pitt L, Kilbride M, Welford M, Nothard S, Morrison AP. Impact of a diagnosis of psychosis: user-led qualitative study. *Psychiatric Bulletin*. 2009;33:419-23.

Polak PR, Kirby MW, Deitchman WS. Treating acutely psychotic patients in private homes. *New Directions for Mental Health Services*. 1979;1:49-64.

Posner CM, Wilson KG, Kral MJ, Lander S, McIlwraith RD. Family psychoeducational support groups in schizophrenia. *American Journal of Orthopsychiatry*. 1992;62:206-18.

Potter WZ, Ko GN, Zhang LD, Yan WW. Clozapine in China - a review and preview of US/PRC collaboration. *Psychopharmacology*. 1989;99:S87-S91.

Power P, Iacoponi E, Reynolds N, Fisher H, Russell M, Garety P, et al. The Lambeth early onset crisis assessment team study: general practitioner education and access to an early detection team in first-episode psychosis. *The British Journal of Psychiatry*. 2007;51:s133-s39.

Priebe S, Badesconyi A, Fioritti A, Hansson L, Kilian R, Torres-Gonzales F, et al. Reinstitutionalisation in mental health care: comparison of data on service provision from six European countries. *BMJ*. 2005;330:123-6.

Priebe S, Katsakou C, Amos T, Leese M, Morriss R, Rose D, et al. Patients' views and readmissions 1 year after involuntary hospitalisation. *The British Journal of Psychiatry*. 2009;194:49-54.

Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. *The Lancet*. 2007;370:859-77.

Querido A. Community mental hygiene in the city of Amsterdam. *Mental Hygiene*. 1935;19:177-95.

Quinlivan R, Hough R, Crowell A, Beach C, Hofstetter R, Kenworthy K. Service utilization and costs of care for severely mentally ill clients in an intensive case management program. *Psychiatric Services*. 1995;46:365-71.

Rathod S, Kingdon D, Smith P, Turkington D. Insight into schizophrenia: the effects of cognitive behavioural therapy on the components of insight and association with sociodemographics – data on a previously published randomised controlled trial. *Schizophrenia Research*. 2005;74:211-19.

Read J, Agar K, Argyle N, Aderhold V. Sexual and physical abuse during childhood and adulthood as predictors of hallucinations, delusions and thought disorder. *Psychology and Psychotherapy*. 2003;76:1-22.

Read J, Bentall RP. Negative childhood experiences and mental health: theoretical, clinical and primary prevention implications. *British Journal of Psychiatry*. 2012;200:89-91.

Read J, Haslam N, Sayce L, Davies E. Prejudice and schizophrenia: a review of the 'mental illness is an illness like any other' approach. *Acta Psychiatrica Scandinavica*. 2006;114:303-18.

Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*. 2005;112:330-50.

Rector NA, Seeman MV, Segal ZV. Cognitive therapy for schizophrenia: a preliminary randomized controlled trial. *Schizophrenia Research*. 2003;63:1-11.



Reid J, Lloyd C, de Groot L. The psychoeducation needs of parents who have an adult son or daughter with a mental illness. *Australian e-Journal for the Advancement of Mental Health*. 2005;4:65-67.

Reilly S, Planner C, Hann M, Reeves D, Nazareth I, Lester H. The role of primary care in service provision for people with severe mental illness in the United Kingdom. *PLoS One*. 2012;7:e36468.

Reinares M, Vieta E, Colom F, Martínez-Arán A, Torrent C, Comes M, et al. Impact of a psychoeducational family intervention on caregivers of stabilized bipolar patients. *Psychotherapy and Psychosomatics*. 2004:312-9.

Remington G, Kapur S, Zipursky RB. Pharmacotherapy of first-episode schizophrenia. *The British Journal of Psychiatry*. 1998;172:66-70.

Renwick L, Gavin B, McGlade N, Lacey P, Goggins R, Jackson D, et al. Early intervention service for psychosis: views from primary care. *Early Intervention in Psychiatry*. 2008;2:285-90.

Repper J, Carter T. Using personal experience to support others with similar difficulties: a review of the literature on peer support in mental health services. Nottingham: Together and the University of Nottingham. 2010.

Repper J, Perkins R. *Social Inclusion and Recovery: A Model for Mental Health Practice*. Edinburgh: Balliere Tindall; 2003.

Repper J, Watson E. A year of peer support in Nottingham: lessons learned. *Journal of Mental Health Training, Education and Practice*. 2012;7:70-78.

Revicki DA, Shakespeare A, Kind P. Preferences for schizophrenia-related health states: a comparison of patients, caregivers and psychiatrists. *International Clinical Psychopharmacology*. 1996;11:101-8.

Rice CD, Howard L, Leese M, Jarrett M, Thornicroft G. Determinants of wanting to seek full versus part-time paid employment among people with severe mental illness. *Journal of Mental Health*. 2009;18:424-32.

Riley G, Gregory N, Bellinger J, Davies N, Mabbott G, Sabourin R. Carer's education groups for relatives with a first episode of psychosis: An evaluation of an eight-week education group. *Early Intervention in Psychiatry*. 2011;5:57-63.

Rinaldi M, Miller L, Perkins R. Implementing the individual placement and support (IPS) approach for people with mental health conditions in England. *International Review of Psychiatry*. 2010;22:163-72.

Rivera JJ, Sullivan AM, Valenti SS. Adding consumer-providers to intensive case management: does it improve outcome? *Psychiatric Services*. 2007;58:802-09.

Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry*. 1999;56:241-7.

Rogers ES, Teague GB, Lichenstein C, Campbell J, Lyass A, Chen R, et al. Effects of participation in consumer-operated service programs on both personal and organizationally mediated empowerment: results of multisite study. *Journal of Rehabilitation Research and Development*. 2007;44:785-800.

Rohricht F, Priebe S. Effect of body-oriented psychological therapy on negative symptoms in schizophrenia: a randomized controlled trial. *Psychological medicine*. 2006;36:669-78.

Roick C, Heider D, Bebbington PE, Angermeyer MC, Azorin J-M, Brugha TS, et al. Burden on caregivers of people with schizophrenia: comparison between Germany and Britain. *The British Journal of Psychiatry*. 2007;190:333-38.

Rooney R, Wright B, O'Neil K. Issues faced by carers of people with a mental illness from culturally and linguistically diverse backgrounds: carers' and practitioners' perceptions. *Australian e-Journal for the Advancement of Mental Health*. 2006;5:1-13.

Rosen K, Garety P. Predicting recovery from schizophrenia: a retrospective comparison of characteristics at onset of people with single and multiple episodes. *Schizophrenia Bulletin*. 2005;31:735-50.

Rosenfarb IS, Bellack AS, Aziz N. A sociocultural stress, appraisal, and coping model of subjective burden and family attitudes toward patients with schizophrenia. *Journal of Abnormal Psychology*. 2006;115:157-65.

Rosenheck R, Neale M, Gallup P. Community-oriented mental health care: assessing diversity in clinical practice. *Psychosocial Rehabilitation Journal*. 1993;16:39-50.

Rosenheck R, Perlick D, Bingham S, Liu-Mares W, Collins J, Warren S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. *JAMA: The Journal of the American Medical Association*. 2003;290:2693-702.

Rosenheck RA, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al. A comparison of clozapine and haloperidol in hospitalised patients with refractory schizophrenia. *The New England Journal of Medicine*. 1997;337:809-15.

Rosenheck RA, Leslie DL, Sindelar J, Miller EA, Lin H, Stroup TS, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *American Journal of Psychiatry*. 2006;163:2080-9.

Rosie JS. Partial hospitalization: a review of recent literature. *Hospital and Community Psychiatry*. 1987;38:1291-9.

Ross J. *Occupational Therapy and Vocational Rehabilitation*. Chichester: John Wiley & Sons Ltd; 2008.

Rosser R, Cottee M, Rabin R, Selai C. Index of health-related quality of life. In: Hopkins A, ed. *Measures of the Quality of Life and the Uses to Which Such Measures May Be Put*. London: The Royal College of Physicians; 1992.

Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *Journal of Clinical Psychopharmacology*. 2004;24:70-8.

Roth A, Fonagy P, Parry G. *What Works for Whom? A Critical Review of Psychotherapy Research*. New York: Guilford; 1996.

Royal College of Psychiatrists. *Consensus Statement on High-Dose Antipsychotic Medication*. London: Royal College of Psychiatrists; 2006.

Royal College of Psychiatrists. *Improving services for refugees and asylum seekers: position statement*. London: Royal College of Psychiatrists; 2007.

Royal College of Psychiatrists. *Personal communication with the Prescribing Observatory for Mental Health [2005 data]. Regular Oral Daily Prescriptions*. 2008.

Royal College of Psychiatrists. *Carers and Confidentiality*. 2010; Available from: <http://www.rcpsych.ac.uk/about/campaigns/partnersincarecampaign/carersandconfidentiality.aspx>.

Royal College of Psychiatrists. *Report of the National Audit of Schizophrenia (NAS) 2012*. London: Healthcare Quality Improvement Partnership; 2012.

Ruhrmann S, Bechdolf A, Kuhn KU, Wagner M, Schultze-Lutter F, Janssen B, et al. Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. *The British Journal of Psychiatry*. 2007;51:s88-95.

Ruhrmann S, Schultze-Lutter F, Salokangas R, Heinimaa M, Linszen D, Dingemans P, et al. *Prediction of psychosis in adolescents and young adults at high risk: results*

from the prospective European prediction of psychosis study. *Archives of General Psychiatry*. 2010;67:241.

Russo M, Levine SZ, Demjaha A, Di Forti M, Bonaccorso S, Fearon P, et al. Association between symptom dimensions and categorical diagnoses of psychosis: a cross-sectional and longitudinal investigation. *Schizophrenia Bulletin*. 2013;DOI:10.1093/schbul/sbt055. Published online: 9 May.

Saari K, Koponen H, Laitinen J, Jokelainen J, Lauren L, Isohanni M, et al. Hyperlipidemia in persons using antipsychotic medication: a general population-based birth cohort study. *Journal of Clinical Psychiatry*. 2004;65:547-50.

Saari KM, Lindeman SM, Viilo KM, Isohanni MK, Jarvelin MR, Lauren LH, et al. A 4-fold risk of metabolic syndrome in patients with schizophrenia: the Northern Finland 1966 Birth Cohort study. *Journal of Clinical Psychiatry*. 2005;66:559-63.

Sacco KA, Creeden C, Reutenauer EL, Vessicchio JC, Weinberger AH, George TP. Effects of atomoxetine on cognitive function and cigarette smoking in schizophrenia. *Schizophrenia Research*. 2009;107:332-33.

Saddichha S, Manjunatha N, Ameen S, Akhtar S. Diabetes and schizophrenia - effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. *Acta Psychiatrica Scandinavica*. 2008;117:342-7.

Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry*. 2007;64:1123-31.

Sainsbury Centre for Mental Health. Paper 3: the economic and social costs of mental illness. London: Sainsbury Centre for Mental Health; 2003.

Sainsbury Centre for Mental Health. The Economic and Financial Case for Supported Employment. London: Sainsbury Centre for Mental Health; 2009.

Salkever D, Domino ME, Burns BJ, Santos AB, Deci PA, Dias J, et al. Assertive community treatment for people with severe mental illness: the effect on hospital use and costs. *Health Services Research*. 1999;34:577-601.

Salyers MP, McGuire AB, Rollins AL, Bond GR, Mueser KT, Macy VR. Integrating assertive community treatment and illness management and recovery for consumers with severe mental illness. *Community Mental Health Journal*. 2010;46:319-29.

Salzer MS, Shear SL. Identifying consumer-provider benefits in evaluations of consumer-delivered services. *Psychiatric Rehabilitation Journal*. 2002;25:281-8.

Sartorius N. Iatrogenic stigma of mental illness. *BMJ*. 2002;324:1470-1.

Sass B, Moffat J, Bhui K, Mckenzie K. Enhancing pathways to care for black and minority ethnic populations: a systematic review. *International Review of Psychiatry*. 2009;21:430-38.

Sattelmair JR, Perman J, Ding EL, Kohl III HW, Haskell W, Lee I. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation*. 2011;124:789-95.

Saunders JC, Byrne MM. A thematic analysis of families living with schizophrenia. *Archives of Psychiatric Nursing*. 2002;16:217-23.

Scheewe TW, Backx FJG, Takken T, Jorg F, van Strater ACP, Kroes AG, et al. Exercise therapy improves mental and physical health in schizophrenia: A randomised controlled trial. *Acta Psychiatrica Scandinavica*. 2013;127:464-73.

Schizophrenia Commission. The abandoned illness: a report from the Schizophrenia Commission. London: Rethink Mental Illness; 2012.

Schneider J, Boyce M, Johnson R, Secker J, Slade J, Grove B, et al. Impact of supported employment on service costs and income of people with mental health needs *Journal of Mental Health*. 2009;18:533-42.

Schneider J, Secker J, Grove B., Floyd M, Boyce M, Practice Partners. The SESAMI evaluation of employment support in the UK: background and baseline data. *Journal of Mental Health* 2007;16:375-87.

Schooler NR. Relapse and rehospitalization: comparing oral and depot antipsychotics. *Journal of Clinical Psychiatry*. 2003;64(Suppl:16):14-7.

Schünemann H, Brożek J, Oxman A, eds. GRADE Handbook: for Grading the Quality of Evidence and Strength of Recommendations. Version 3.2: The GRADE Working Group; 2009. Available from: [www.who.int/hiv/topics/mtct/grade\\_handbook.pdf](http://www.who.int/hiv/topics/mtct/grade_handbook.pdf).

Schünemann HJ, Best D, Vist G, for the GRADE Working Group. Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations. *Canadian Medical Association Journal*. 2003;169:677-80.

Sciolla A, Patterson TL, Wetherell JL, McAdams LA, Jeste DV. Functioning and well-being of middle-aged and older patients with schizophrenia: measurement with the 36-item Short-Form (SF-36) Health Survey. *American Journal of Geriatric Psychiatry*. 2003;11:629-37.

Scocco P, Longo R, Caon F. Weight change in treatment with olanzapine and a psychoeducational approach. *Eating Behaviors*. 2006;7:115-24.

Scottish Recovery Network. The role and potential development of peer support services: Scottish Recovery Network briefing paper. Glasgow: Scottish Recovery Network; 2005.

Seebohm P, Secker J. What do service users want? In: Grove B, Secker J, Seebohm P, eds. *New Thinking about Mental Health and Employment*. Oxford: Radcliffe Publishing; 2005.

Segal SP, Silverman C, Temkin T. Outcomes from consumer-operated and community mental health services: A randomized controlled trial. *Psychiatric Services*. 2011;62:915-21.

Sells D, Davidson L, Jewell C, Falzer P, Rowe M. The treatment relationship in peer-based and regular case management for clients with severe mental illness. *Psychiatric Services*. 2006;57:1179-84.

Serretti A, Mandelli L, Bajo E, Cevenini N, Papili P, Mori E, et al. The socio-economical burden of schizophrenia: a simulation of cost-offset of early intervention program in Italy. *European Psychiatry*. 2009;24:11-6.

Sevy S, Nathanson K, Schechter C, Fulop G. Contingency valuation and preferences of health states associated with side effects of antipsychotic medications in schizophrenia. *Schizophrenia Bulletin*. 2001;27:643-51.

Shalev A, Hermesh H, Rothberg J, Munitz H. Poor neuroleptic response in acutely exacerbated schizophrenic patients. *Acta Psychiatrica Scandinavica*. 1993;87:86-91.

Sharif F, Shaygan M, Mani A. Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia in Shiraz, Iran. *BMC Psychiatry*. 2012;12.

Shepherd G. Social skills training: the generalisation problem-some further data. *Behaviour Research and Therapy*. 1978;16:297-9.

Shern DL, Tsemberis S, Anthony W, Lovell AM, Richmond L, Felton CJ, et al. Serving street-dwelling individuals with psychiatric disabilities: outcomes of a psychiatric rehabilitation clinical trial. *American Journal of Public Health*. 2000;90:1873-78.

Shevlin M, Houston JE, Dorahy MJ, Adamson G. Cumulative traumas and psychosis: an analysis of the national comorbidity survey and the British psychiatric morbidity survey. *Schizophrenia Bulletin*. 2008;34:193-9.

Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, et al. Sulpiride augmentation in people with schizophrenia partially responsive to

clozapine. A double-blind, placebo-controlled study. *The British Journal of Psychiatry*. 1997;171:569-73.

Shon KH, Park SS. Medication and symptom management education program for the rehabilitation of psychiatric patients in Korea: the effects of promoting schedule on self-efficacy theory. *Yonsei Medical Journal*. 2002;43:579-89.

Simon AE, Lauber C, Ludewig K, Braun-Scharm H, Umbricht DS, Swiss Early Psychosis Project. General practitioners and schizophrenia: results from a Swiss survey. *The British Journal of Psychiatry*. 2005;187:274-81.

Simpson A, Janner M. Star Wards Survey Report 2009/2010. London: Star Wards; 2010. Available from:  
[http://www.starwards.org.uk/images/stories/user\\_files/marion/Star\\_Wards\\_Survey\\_Report\\_Final\\_05052010\\_1.pdf](http://www.starwards.org.uk/images/stories/user_files/marion/Star_Wards_Survey_Report_Final_05052010_1.pdf).

Singh SP, Fisher HL. Early intervention in psychosis: obstacles and opportunities. *Advances in Psychiatric Treatment*. 2005;11:71-78.

Singleton N, Bumpstead R, O'Brien M, Lee A, Meltzer H. Psychiatric morbidity among adults living in private households, 2000. *International Review of Psychiatry*. 2003;15:65-73.

Skovholt TM. The client as helper: a means to promote psychological growth. *The Counseling Psychologist*. 1974;4:58-64.

Skrinar GS, Huxley NA, Hutchinson DS, Menninger E, Glew P. The role of a fitness intervention on people with serious psychiatric disabilities. *Psychiatric Rehabilitation Journal*. 2005;29:122-27.

Slade E, McCarthy J, Valenstein M, Visnic S, Dixon L. Cost savings from assertive community treatment services in an era of declining psychiatric inpatient use. *Health Services Research*. 2013;48:195-217.

Slade M. 100 Ways to Support Recovery: a Guide for Mental Health Professionals. London: Rethink; 2009.

Slade M, Rosen A, Shankar R. Multidisciplinary mental health teams. *The International Journal of Social Psychiatry*. 1995;41:180-9.

Slade PD, Bentall RP. *Sensory Deception: A Scientific Analysis of Hallucination*. London: Croom Helm; 1988.

Sledge WH, Lawless M, Sells D, Wieland M, O'Connell MJ, Davidson L. Effectiveness of peer support in reducing readmissions of persons with multiple psychiatric hospitalizations. *Psychiatric Services*. 2011;62:541-4.

Small N, Harrison J, Newell R. Carer burden in schizophrenia: considerations for nursing practice. *Mental Health Practice*. 2010;14:22-25.

Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. *BMJ*. 2013;3.

Smith JV, Birchwood MJ. Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *The British Journal of Psychiatry*. 1987;645-52.

Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *The British Journal of Psychiatry*. 2008;192:406-11.

Snyder SH, Greenberg D, Yamumura HI. Antischizophrenic drugs: affinity for muscarinic cholinergic receptor sites in the brain predicts extrapyramidal effects. *Journal of Psychiatric Research*. 1974;11:91-5.

So HW, Chen EYH, Chan RCK, Wong CW, Hung SF, Chung DWS, et al. Efficacy of a brief intervention for carers of people with first-episode psychosis: A waiting list controlled study. *Hong Kong Journal of Psychiatry*. 2006;16:92-100.

Solomon P. Peer support/peer provided services underlying processes, benefits, and critical ingredients. *Psychiatric Rehabilitation Journal*. 2004;27:392-401.

Solomon P, Draine J. One-year outcomes of a randomized trial of consumer case management. *Evaluation and Program Planning*. 1995;18:117-27.

Solomon P, Draine J, Mannion E, Meisel M. Impact of brief family psychoeducation on self-efficacy. *Schizophrenia Bulletin*. 1996;22:41-50.

Solomon P, Draine J, Meyerson A. Jail recidivism and receipt of community mental health services. *Hospital and Community Psychiatry*. 1994;45:793-97.

Spiegelhalter D, Thomas A, Best N. WinBUGS Beta Version 1.4 User Manual. Cambridge: University of Cambridge: MRC Biostatistics Unit, Institute of Public Health; 2001.

Squires H, Rick J, Carroll C, Hillage J. Cost-effectiveness of interventions to return employees to work following long-term sickness absence due to musculoskeletal disorders. *Journal of Public Health*. 2012;34:115-24.

Stack-Sullivan H. *Schizophrenia as a Human Process*. London: Norton; 1974.



Stack Sullivan H. Conceptions of Modern Psychiatry. Washington, DC: William Alanson White Psychiatric Foundation; 1947.

Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. *BMJ*. 2013;346:f185.

Stahl SM. Focus on antipsychotic polypharmacy: evidence-based prescribing or prescribing-based evidence? *The International Journal of Neuropsychopharmacology*. 2004;7:113-6.

Startup M, Jackson MC, Bendix S. North Wales randomized controlled trial of cognitive behaviour therapy for acute schizophrenia spectrum disorders: outcomes at 6 and 12 months. *Psychological medicine*. 2004;34:413-22.

Startup M, Jackson MC, Evans KE, Bendix S. North Wales randomized controlled trial of cognitive behaviour therapy for acute schizophrenia spectrum disorders: two-year follow-up and economic evaluation. *Psychological medicine*. 2005;35:1307-16.

Steel C. The relationship between trauma and psychosis: a CBT perspective. Reading: Charlie Waller Institute of Evidence Based Psychological Treatment: University of Reading; 2011. Available from: <http://www.ukpts.co.uk/site/assets/Steel-UKPTS-Oxford-2011.pdf>.

Stein LI, Test MA. Alternative to mental hospital treatment. I. Conceptual model, treatment program, and clinical evaluation. *Archives of General Psychiatry*. 1980;37:392-7.

Stein LI, Test MA, Marx AJ. Alternative to the hospital: a controlled study. *American Journal of Psychiatry*. 1975;132:517-22.

Steingard S, Allen M, Schooler NR. A study of the pharmacologic treatment of medication-compliant schizophrenics who relapse. *Journal of Clinical Psychiatry*. 1994;55:470-2.

Strakowski SM, Johnson JL, Delbello MP, Hamer RM, Green AI, Tohen M, et al. Quality of life during treatment with haloperidol or olanzapine in the year following a first psychotic episode. *Schizophrenia Research*. 2005;78:161-9.

Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-12.

Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, et al. The national institute of mental health clinical antipsychotic trials of intervention

effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophrenia Bulletin*. 2003;29:15-31.

Stuckler D, Basu S, Suhrcke M, Coutts A, McKee M. Effects of the 2008 recession on health: a first look at European data. *The Lancet*. 2011;378:124-5.

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*. 2003;60:1187-92.

Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. *Current Medical Research and Opinion*. 2007;23:2305-12.

Suvisaari JM, Saarni SI, Perala J, Suvisaari JV, Harkanen T, Lonnqvist J, et al. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. *Journal of Clinical Psychiatry*. 2007;68:1045-55.

Sytema S, Wunderink L, Bloemers W, Roorda L, Wiersma D. Assertive community treatment in the Netherlands: a randomized controlled trial. *Acta Psychiatrica Scandinavica*. 2007;116:105-12.

Szmukler G, Kuipers E, Joyce J, Harris T, Leese M, Maphosa W, et al. An exploratory randomised controlled trial of a support programme for carers of patients with a psychosis. *Social Psychiatry and Psychiatric Epidemiology*. 2003;38:411-18.

Szmukler GI, Herrman H, Colusa S, Benson A, Bloch S. A controlled trial of a counselling intervention for caregivers of relatives with schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*. 1996;31:149-55.

Talwar N, Crawford MJ, Maratos A, Nur U, McDermott O, Procter S. Music therapy for in-patients with schizophrenia: exploratory randomised controlled trial. *The British Journal of Psychiatry*. 2006;189:405-9.

Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia Research*. 2008;102:1-18.

Tang YL, Mao P, Li FM, Li W, Chen Q, Jiang F, et al. Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *British Journal of Clinical Pharmacology*. 2007;64:49-56.

Tanskanen S, Morant N, Hinton M, Lloyd-Evans B, Crosby M, Killaspy H, et al. Service user and carer experiences of seeking help for a first episode of psychosis: a UK qualitative study. *BMC Psychiatry*. 2011;11:157.

Tarricone I, Ferrari-Gozzi B, Serretti A, Grieco D, Berardi D. Weight gain in antipsychotic-naïve patients: a review and meta-analysis. *Psychological medicine*. 2010;40:187-200.

Tarrier N, Beckett R, Harwood S, Baker A, Yusupoff L, Ugarteburu I. A trial of two cognitive-behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenic patients: I. Outcome. *The British Journal of Psychiatry*. 1993;162:524-32.

Tarrier N, Lowson K, Barrowclough C. Some aspects of family interventions in schizophrenia. II: financial considerations. *The British Journal of Psychiatry*. 1991;159:481-84.

Tauscher J, Kapur S. Choosing the right dose of antipsychotics in schizophrenia: lessons from neuroimaging studies. *CNS Drugs*. 2001;15:671-8.

Taylor D, Mace S, Mir S, Kerwin R. A prescription survey of the use of atypical antipsychotics for hospital inpatients in the United Kingdom. *International Journal of Psychiatry in Clinical Practice*. 2000;4:41-46.

Taylor D, Mir S, Mace S, Whiskey E. Co-prescribing of atypical and typical antipsychotics – prescribing sequence and documented outcome. *Psychiatric Bulletin*. 2002;26:170-72.

Taylor D, Young C, Mohamed R, Paton C, Walwyn R. Undiagnosed impaired fasting glucose and diabetes mellitus amongst inpatients receiving antipsychotic drugs. *Journal of Psychopharmacology*. 2005;19:182-6.

Taylor MF, Brice J, Buck N, Prentice-Lane E. *British Household Panel Survey User Manual Volume B*. Colchester: University of Essex; 2003.

Taylor PJ, Gunn J. Homicides by people with mental illness: myth and reality. *The British Journal of Psychiatry*. 1999;174:9-14.

Test MA, Knoedler WH, Allness DJ, Burke SS. Long-term community care through an assertive continuous treatment team. In: Tamminga C, Schultz S, ed. *Advances in Neuropsychiatry and Psychopharmacology, Schizophrenia Research*. NY: Raven Press; 1991.

Thakore JH. Metabolic syndrome and schizophrenia. *The British Journal of Psychiatry*. 2005;186:455-6.

The Cochrane Collaboration. Review Manager (RevMan) [Computer programme]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2011.

The Health and Social Care Information Centre. Hospital Episode Statistics 2011–12. London: The Health and Social Care Information Centre; 2012; Available from: <http://www.hesonline.nhs.uk>

The International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 2008;455:237-41.

The NHS Information Centre, Lifestyles Statistics. Statistics on smoking: England. The Health and Social Care Information Centre; 2011; 1-126:[Available from: <https://catalogue.ic.nhs.uk/publications/public-health/smoking/smok-eng-2011/smok-eng-2011-rep.pdf>.

The Royal College of Psychiatrists Social Inclusion Scoping Group. Mental Health and Social Inclusion: making psychiatry and mental health services fit for the 21st century. London: Royal College of Psychiatrists 2009.

The Work Foundation. Working with Schizophrenia: Pathways to Employment, Recovery and Inclusion. London: The Work Foundation; 2013.

Thieda P, Beard S, Richter A, Kane J. An economic review of compliance with medication therapy in the treatment of schizophrenia. *Psychiatric Services*. 2003;54:508-16.

Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Medical Research Methodology*. 2008;8:45.

Thorne B. Carl Rogers. London: Sage; 1992.

Thornicroft G. Shunned: discrimination against people with mental illness. Oxford and New York: Oxford University Press; 2006.

Thornicroft G, Tansella M. The balanced care model for global mental health. *Psychological medicine*. 2012;11:1-15.

Thornicroft G, Tansella M, Becker T, Knapp M, Leese M, Schene A, et al. The personal impact of schizophrenia in Europe. *Schizophrenia Research*. 2004;69:125-32.

Tiihonen J, Wahlbeck K, Lonnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ*. 2006;333:224.

Tilden D, Aristides M, Meddis D, Burns T. An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. *Clinical Therapeutics*. 2002;24:1648-67.

- Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. *Schizophrenia Bulletin*. 2012;38:642-7.
- Totman J, Mann F, Johnson S. Is locating acute wards in the general hospital an essential element in psychiatric reform? The UK experience. *Epidemiologia e Psichiatria Sociale*. 2010;19:282-6.
- Tranvag O, Kristoffersen K. Experience of being the spouse/cohabitant of a person with bipolar affective disorder: a cumulative process over time. *Scandinavian Journal of Caring Sciences*. 2008;22:5-18.
- Trower P, Birchwood M, Meaden A, Byrne S, Nelson A, Ross K. Cognitive therapy for command hallucinations: randomised controlled trial. *The British Journal of Psychiatry*. 2004;184:312-20.
- Tsang HW, Chan A, Wong A, Liberman RP. Vocational outcomes of an integrated supported employment program for individuals with persistent and severe mental illness. *Journal of Behavior Therapy and Experimental Psychiatry*. 2009;40:292-305.
- Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database of Systematic Reviews*. 2013;2.
- Tunis SL, Croghan TW, Heilman DK, Johnstone BM, Obenchain RL. Reliability, validity, and application of the medical outcomes study 36-item short-form health survey (SF-36) in schizophrenic patients treated with olanzapine versus haloperidol. *Medical Care*. 1999;37:678-91.
- Tunis SL, Faries DE, Nyhuis AW, Kinon BJ, Ascher-Svanum H, Aquila R. Cost-effectiveness of olanzapine as first-line treatment for schizophrenia: results from a randomized, open-label, 1-year trial. *Value in Health*. 2006;9:77-89.
- Tuomilehto J, Schwarz P, Lindstrom J. Long-term benefits from lifestyle interventions for type 2 diabetes prevention: time to expand the efforts. *Diabetes Care*. 2011;34 (Suppl):S210-S14.
- Turkington D, Kingdon D, Turner T. Effectiveness of a brief cognitive-behavioural therapy intervention in the treatment of schizophrenia. *The British Journal of Psychiatry*. 2002;180:523-7.
- Turner AP, Barlow JH, Elliot CH. Lay-Led, Self-Management for People with a Long-Term Health Condition: UK Results. T. Kroll edn. *Disability and Health*, Hauppauge, New York: Nova Science Publishers, Inc.; 2008.
- Turner N, Browne S, Clarke M, Gervin M, Larkin C, Waddington JL, et al. Employment status amongst those with psychosis at first presentation. *Social Psychiatry and Psychiatric Epidemiology*. 2009;44:863-9.

Twamley EW, Vella L, Burton CZ, Becker DR, Bell MD, Jeste DV. The efficacy of supported employment for middle-aged and older people with schizophrenia. *Schizophrenia Research*. 2012;135:100-4.

Tyrer P, Evans K, Gandhi N, Lamont A, Harrison RP, Johnson T. Randomised controlled trial of two models of care for discharged psychiatric patients. *BMJ*. 1998;316:106-09.

Udechuku A, Olver J, Hallam K, Blyth F, Leslie M, Nasso M, et al. Assertive community treatment of the mentally ill: service model and effectiveness. *Australasian Psychiatry*. 2005;13:129-34.

Ulrich G, Houtmans T, Gold C. The additional therapeutic effect of group music therapy for schizophrenic patients: a randomized study. *Acta Psychiatrica Scandinavica*. 2007;116:362-70.

Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatrica Scandinavica*. 2010;122:211-8.

Usher K, Park T, Foster K, Buettner P. A randomized controlled trial undertaken to test a nurse-led weight management and exercise intervention designed for people with serious mental illness who take second generation antipsychotics. *Journal of Advanced Nursing*. 2013;69:1539-48.

Valmaggia LR, McCrone P, Knapp M, Woolley JB, Broome MR, Tabraham P, et al. Economic impact of early intervention in people at high risk of psychosis. *Psychological medicine*. 2009;39:1617-26.

van Dam DS, van der Ven E, Velthorst E, Selten JP, Morgan C, de Haan L. Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis. *Psychological medicine*. 2012;42:2463-74.

van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *Journal of Clinical Epidemiology*. 1998;51:367-75.

Van Gent EM, Zwart FM. Psychoeducation of partners of bipolar-manic patients. *Journal of Affective Disorders*. 1991;21:15-8.

Van Gestel-Timmermans H, Brouwers EPM, Van Assen MALM, Van Nieuwenhuizen C. Effects of a peer-run course on recovery from serious mental illness: a randomized controlled trial. *Psychiatric Services*. 2012;63:54-60.

Van Nimwegen LJ, Storosum JG, Blumer RM. Hepatic insulin resistance in antipsychotic naive schizophrenic patients: stable isotope studies of glucose metabolism. *The Journal of Clinical Endocrinology and Metabolism*. 2008;572-77.

van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010;468:203-12.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological medicine*. 2009;39:179-95.

van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Screening for diabetes and other metabolic abnormalities in patients with schizophrenia and schizoaffective disorder: evaluation of incidence and screening methods. *Journal of Clinical Psychiatry*. 2006;67:1493-500.

van Winkel R, De Hert M, Wampers M, Van Eyck D, Hanssens L, Scheen A, et al. Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder. *Journal of Clinical Psychiatry*. 2008;69:472-79.

Vancampfort D, Probst M, Sweers K, Maurissen K, Knapen J, De Hert M. Relationships between obesity, functional exercise capacity, physical activity participation and physical self-perception in people with schizophrenia. *Acta Psychiatrica Scandinavica*. 2011;123:423-30.

Varambally S, Gangadhar BN, Thirthalli J, Jagannathan A, Kumar S, Venkatasubramanian G, et al. Therapeutic efficacy of add on yogasana intervention in stabilized outpatient schizophrenia: randomized controlled comparison with exercise and waitlist. *Indian Journal of Psychiatry*. 2012;54:227-32.

Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophrenia Bulletin*. 2012;38:661-71.

Varghese D, Scott J, Welham J, Bor W, Najman J, O'Callaghan M, et al. Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophrenia Bulletin*. 2011;37:389-93.

Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. *Schizophrenia Bulletin*. 2012;38:1118-23.

Vaughn CE, Leff JP. The influence of family and social factors on the course of psychiatric illness. A comparison of schizophrenic and depressed neurotic patients. *The British Journal of Psychiatry*. 1976;129:125-37.

Vauth R, Corrigan PW, Clauss M, Dietl M, Dreher RM, Stieglitz RD, et al. Cognitive strategies versus self-management skills as adjunct to vocational rehabilitation. *Schizophrenia Bulletin*. 2005;31:55-66.

Vera-Llonch M, Delea TE, Richardson E, Rupnow M, Grogg A, Oster G. Outcomes and costs of risperidone versus olanzapine in patients with chronic schizophrenia or schizoaffective disorders: a Markov model. *Value in Health*. 2004;7:569-84.

Viguera AC, Baldessarini RJ, Hegarty JD, van Kammen DP, Tohen M. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Archives of General Psychiatry*. 1997;54:49-55.

von Hausswolff-Juhlin Y, Bjartveit M, Lindstrom E, Jones P. Schizophrenia and physical health problems. *Acta Psychiatrica Scandinavica Supplementum*. 2009;15-21.

Vreeland B, Minsky S, Yanos PT, Menza M, Gara M, Kim E, et al. Efficacy of the team solutions program for educating patients about illness management and treatment. *Psychiatric Services*. 2006;57:822-28.

Wahlbeck K, Cheine MV, Essali A. Clozapine versus typical neuroleptic medication for schizophrenia (Cochrane Review). *The Cochrane Library*, Issue 3. Oxford: Update Software; 1999.

Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. *The British Journal of Psychiatry*. 2011;199:453-8.

Wahlberg KE, Wynne LC, Oja H, Keskitalo P, Pykalainen L, Lahti I, et al. Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish adoptive family study of schizophrenia. *American Journal of Psychiatry*. 1997;154:355-62.

Wainwright L, Glentworth D, Haddock G, Bentley R, Lobban F. What do relatives experience when supporting someone in early psychosis. In press.

Walburn J, Gray R, Gournay K, Quraishi S, David AS. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *The British Journal of Psychiatry*. 2001;179:300-7.

Walker J, Craissati J, Batson S, Amos T, Knowles P. How to get better value from psychiatric units. *Health Service Journal* 2012.



Walker R, Winick W, Frost ES, Lieberman JM. Social restoration of hospitalized psychiatric patients through a program of special employment in industry. *Rehabilitation Literature*. 1969;30:297-303.

Wallace CJ, Nelson CJ, Liberman RP, Aitchison RA, Lukoff D, Elder JP, et al. A review and critique of social skills training with schizophrenic-patients. *Schizophrenia Bulletin*. 1980;6:42-63.

Wardle M, Drage L, Spencer H, Brabban A, Turkington D, Morrison A. Internalised stigma, emotional dysfunction and psychotic experiences in people with psychosis. In press.

Warner R. *Recovery from Schizophrenia* 2nd edn. NY: Routledge; 1994.

Warner R. The Prevention of Schizophrenia: what interventions are safe and effective? *Schizophrenia Bulletin*. 2001;27:551-62.

Weimand BM, Hedelin B, Hall-Lord M-L, Sallstrom C. "Left alone with straining but inescapable responsibilities": Relatives' experiences with mental health services. *Issues in Mental Health Nursing*. 2011;32:703-10.

Weinberger AH, George TP, Perkins KA, Chengappa KN. Effects of topiramate on smoking in patients with schizoaffective disorder, bipolar type. *Journal of Clinical Psychopharmacology*. 2008;28:247-8.

Weinberger DR, Berman KF, Illowsky BP. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. *Archives of General Psychiatry*. 1988;45:609.

Weiner E, Ball MP, Buchholz AS, Gold JM, Evins AE, McMahon RP, et al. Bupropion sustained release added to group support for smoking cessation in schizophrenia: a new randomized trial and a meta-analysis. *Journal of Clinical Psychiatry*. 2012;73:95-102.

Weiner E, Buchholz A, Coffay A, Liu F, McMahon RP, Buchanan RW, et al. Varenicline for smoking cessation in people with schizophrenia: a double blind randomized pilot study. *Schizophrenia Research*. 2011;129:94-95.

Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. *Schizophrenia research*. 2009;113:1-11.

Welham J, Isohanni M, Jones P, McGrath J. The antecedents of schizophrenia: a review of birth cohort studies. *Schizophrenia Bulletin*. 2009;35:603-23.

Wexler BE, Bell MD. Cognitive remediation and vocational rehabilitation for schizophrenia. *Schizophrenia Bulletin*. 2005;31:931-41.

Wiersma D, Kluiter H, Nienhuis F, Ruphan M, Giel R. Day-treatment with community care as an alternative to standard hospitalisation: an experiment in the Netherlands. A preliminary communication. Groningen: Department of Social Psychiatry, University of Groningen. 1989.

Wiersma D, Nienhuis FJ, Sloof CJ, Giel R. Natural course of schizophrenic disorders: a 15-year follow-up of a Dutch incidence cohort *Schizophrenia Bulletin*. 1998;24:75-85.

Wiersma D, Wanderling J, Dragomirecka E, Ganey K, Harrison G, An Der Heiden W, et al. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. *Psychological medicine*. 2000;30:1155-67.

Wigman JT, van Nierop M, Vollebergh WA, Lieb R, Beesdo-Baum K, Wittchen HU, et al. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity-implications for diagnosis and ultra-high risk research. *Schizophrenia Bulletin*. 2012;38:247-57.

Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, et al. A randomized, doubleblind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychiatry and Clinical Neurosciences*. 2012a;73:654-60.

Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *Journal of Clinical Psychiatry*. 2012b;73:654-60.

Williams JM, Gandhi KK, Foulds J, Steinberg M, Lou S, Masumova F. No advantage for high dose compared to regular dose nicotine patch on short-term abstinence rates in schizophrenia (PA2-3). Society for Research on Nicotine and Tobacco 13th Annual Meeting:2007; Austin, Texas.

Winterbourne S, Knapp M, McCrone P, Bell N, Campion J, Clark M, et al. Preventing future physical morbidity and premature mortality in people with first-episode psychosis: an economic evaluation of the possible benefits of weight management interventions. 2013a;In press.

Winterbourne S, Knapp M, McCrone P, Bell N, Campion J, Clark M, et al. Quitting smoking for young people with schizophrenia – is it worth it? Economic evaluation of smoking cessation interventions. 2013b;In press.

Wirshing DA, Pierre JM, Wirshing WC, Guzik LH, Resnick SA, Goldstein D, et al. Community re-entry program training module for schizophrenic inpatients improves treatment outcomes. *Schizophrenia Research*. 2006;87:338-9.

Witheridge TF. The "active ingredients" of assertive outreach. *New Directions for Mental Health Services*. 1991;52:47-64.

Witheridge TF, Dincin J, Appleby L. Working with the most frequent recidivists: a total team approach to assertive resource management. *Psychosocial Rehabilitation Journal*. 1982;5:9-11.

Wolkon GH, Karmen M, Tanaka HT. Evaluation of a social rehabilitation program for recently released psychiatric patients. *Community Mental Health Journal*. 1971;7:312-22.

Wong K, Chiu R, Tang B, Mak D, Liu J, Chiu SN. A randomized controlled trial of a supported employment program for persons with long-term mental illness in Hong Kong. *Psychiatric Services*. 2008;59:84-90.

Wood C. The history of art therapy 1938-95. In *Art, Psychotherapy and Psychosis*. K. Killick & S. Schaverien edn. London: Routledge; 1997.

World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines*. Geneva: World Health Organization; 1992.

Worthington A, Rooney P, Hannan R. *The Triangle of Care*. Second Edition. London: Carers Trust; 2013.

Wright C, Burns T, James P, Billings J, Johnson S, Muijen M, et al. Assertive outreach teams in London: models of operation. Pan-London Assertive Outreach Study, part 1. *The British Journal of Psychiatry*. 2003;183:132-8.

Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. *Journal of Clinical Psychiatry*. 2005;66:1122-9.

Wu MK, Wang CK, Bai YM, Huang CY, Lee SD. Outcomes of obese, clozapine-treated inpatients with schizophrenia placed on a six-month diet and physical activity program. *Psychiatric Services*. 2007;58:544-50.

Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2008;299:185-93.

Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: Long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*. 2013;onlinefirst.

Wykes T, Reeder C. *Cognitive Remediation Therapy for Schizophrenia: Theory and Practice*. London: Routledge; 2005.

Wykes T, van der Gaag M. Is it time to develop a new cognitive therapy for psychosis – cognitive remediation therapy (CRT)? *Clinical psychology review*. 2001;21:1227-56.

Xiang Y, Weng Y, Li W, Gao L, Chen G, Xie L, et al. Training patients with schizophrenia with the community re-entry module: a controlled study. *Social Psychiatry and Psychiatric Epidemiology*. 2006;41:464-69.

Xiang YT, Weng YZ, Li WY, Gao L, Chen GL, Xie L, et al. Efficacy of the Community Re-Entry Module for patients with schizophrenia in Beijing, China: outcome at 2-year follow-up. *The British Journal of Psychiatry*. 2007;190:49-56.

Yagcioglu AEA, Akdede BBK, Turgut TI, Tumuklu M, Yazici MK, Alptekin K, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: Efficacy and safety. *Journal of Clinical Psychiatry*. 2005;66:63-72.

Yang LH, Wonpat-Borja AJ, Opler MG, Corcoran CM. Potential stigma associated with inclusion of the psychosis risk syndrome in the DSM-V: an empirical question. *Schizophrenia Research*. 2010;120:42-8.

Yang W, Li Z, Weng Y, Zhang H, Ma B, Yang W. Psychosocial rehabilitation effects of music therapy in chronic schizophrenia. *Hong Kong Journal of Psychiatry*. 1998;8:38-40.

Yoshii H, Watanabe Y, Kitamura H, Nan Z, Akazawa K. Effect of an education program on improving help-seeking among parents of junior and senior high school students in Japan. *Global Journal of Health Science*. 2011;4:33.

Young JL, Spitz RT, Hillbrand M, Daneri G. Medication adherence failure in schizophrenia: a forensic review of rates, reasons, treatments, and prospects. *J Am Acad Psychiatry Law*. 1999;27:426-44.

Young JL, Zonana HV, Shepler L. Medication noncompliance in schizophrenia: codification and update. *Bull Am Acad Psychiatry Law*. 1986;14:105-22.

Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin*. 1996;22:283-303.

Yung AR, Organ BA, Harris MG. Management of early psychosis in a generic adult mental health service. *The Australian and New Zealand Journal of Psychiatry*. 2003;37:429-36.

Yung AR, Phillips LJ, Nelson B, Francey SM, PanYuen H, Simmons MB, et al. Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. *Journal of Clinical Psychiatry*. 2011;72:430-40.

Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, et al. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophrenia Bulletin*. 2007;33:673-81.

Zhu B, Ascher-Svanum H, Shi L, Faries D, Montgomery W, Marder SR. Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia. *Psychiatric Services*. 2008;59:315-7.

Ziegenbein M, Wittmann G, Kropp S. Aripiprazole augmentation of clozapine in treatment-resistant schizophrenia: a clinical observation. *Clinical drug investigation*. 2006;26:117-24.

Zubin J, Spring B. Vulnerability--a new view of schizophrenia. *Journal of Abnormal Psychology*. 1977;86:103-26.

Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *International Clinical Psychopharmacology*. 2002;17:141-3.