Depression in Adults
(update)

Depression: the treatment and management of depression in adults

National Clinical Practice Guideline Number X

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1 Preface

This guideline was first published in December 2004 (referred to as the ‘previous guideline’). The present guideline (referred to as the ‘update’) updates many areas of the previous guideline. There are also new chapters on service user and carer experience of depression (Chapter 4) and on the treatment and management of subthreshold depression diagnoses (dysthymia and minor depression) which were not part of the scope of the previous guideline (Chapter 10). Recommendations categorised as ‘good practice points’ in the previous guideline were reviewed for their current relevance (including issues around consent and advance directives). Further details of what has been updated and what is left unchanged can be found at the beginning of each evidence chapter. The scope for the update also included updating the NICE technology appraisal (TA59) on the use of electroconvulsive therapy and that for computerised cognitive behaviour therapy (TA97) (NICE, 2003, 2002)1. See Appendix 1 for more details on the scope of this update. Sections of the guideline where the evidence has not been updated are shaded in grey. For the consultation period only, Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.

The previous guideline and this update have been developed to advise on the treatment and management of depression. The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, service users, a carer 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 depression while also emphasising the importance of the experience of care for them and their carers.

Although the evidence base is rapidly expanding, there are a number of major gaps, and further 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, people with depression and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

1.1 National guideline

1.1.1 What are clinical practice guidelines?

Clinical practice guidelines are ‘systematically developed statements that assist clinicians and patients 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

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1 Recommendations from TA59 and TA97 were incorporated into the previous depression guideline according to NICE protocol.
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 limitations 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 with depression.

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 (AGREE: Appraisal of Guidelines for Research and Evaluation Instrument; www.agreecollaboration.org), 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 these disorders and situations. However, there will always be some people 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 depression 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, 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 to 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 Clinical 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 patients, professionals and the public. NICE guidance aims to improve standards of care, to diminish unacceptable variations in the provision and quality of care across the NHS and to ensure that the health service is patient 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 practice guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE has established seven National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare.

1.1.4 The National Collaborating Centre for Mental Health
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 patient 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’ Research and Training Unit and the British Psychological Society’s equivalent unit (Centre for Outcomes Research and Effectiveness).

1.1.5 From national 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.

1.1.6 Auditing the implementation of 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 Healthcare Commission will monitor the extent to which Primary Care Trusts, trusts responsible for mental health and social care and Health Authorities have implemented these guidelines.

1.2 The national depression guideline

1.2.1 Who has developed this guideline?
The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included two service users and a carer, and professionals from psychiatry, clinical psychology, general practice, nursing and psychiatric pharmacy.

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 carer 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 fourteen times throughout the process of guideline development. It met as a whole, but key topics were led by a national expert in the relevant topic. 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 is relevant for adults with depression 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 depression.

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

- occupational health services
- social services
- forensic services
- the independent sector.

The experience of depression can affect the whole family and often the community. The guideline recognises the role of both in the treatment and support of people with depression.

1.2.3 Specific aims of this guideline
The guideline makes recommendations for the treatment and management of depression. It aims to:
• improve access and engagement with treatment and services for people with depression
• evaluate the role of specific psychological and psychosocial interventions in the treatment of depression
• evaluate the role of specific pharmacological interventions in the treatment of depression
• evaluate the role of specific service level interventions for people with depression
• integrate the above to provide best-practice advice on the care of people with depression and their family and carers
• 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 an introduction to guidelines, the topic of depression and to the methods used to update this guideline. Chapters 4 to 12 provide the evidence that underpins the recommendations about the treatment and management of depression, with chapter 4 providing personal accounts from service users and carers, which offer an insight into their experience of depression.

Each evidence chapter begins with 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 the review protocol and studies included in the review. Clinical evidence summaries are then used to summarise the data presented. Health economic evidence is then presented (where appropriate), followed by a section (from evidence to recommendations) that draws together the clinical and health economic evidence and provides a rationale for the recommendations. On the CD-ROM, further details are provided about included/excluded studies, the evidence, and the previous guideline methodology (see for Table 1 for details).

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2 Depression

This guideline is concerned with the treatment and management of adults with depression in primary and secondary care. The terminology and diagnostic criteria used for this heterogeneous group of related disorders has changed over the years and the previous guideline related only to those identified by The ICD-10 Classification of Mental and Behavioural Disorders (ICD-10) (WHO, 1992) as having a depressive episode (F32), recurrent depressive episode (F33) or mixed anxiety and depressive disorder (F41.2). In this guideline update the scope has been widened in the recognition that a substantial proportion of people present with less severe forms of depression so that this guidance in addition considers dysthymia (F34.1) and depression falling below the threshold for depression which does not have a coding in ICD-10 but will be included in other mood [affective] disorders (F38). It should however be noted that much of the research forming the evidence base from which this guideline is drawn has used a different classificatory system – the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, currently in its fourth edition (DSM-IV-TR) (APA, 2000c). The two classificatory systems, while similar, are not identical especially with regard to definitions of severity. After considerable discussion we have take the decision to base the guidelines on the DSM-IV-TR (see Diagnosis *.*) and this covers major depressive disorder single episode (296.2) and recurrent (296.3) together with dysthymic disorder (300.4) and minor depressive disorder (included in 311, depressive disorder not otherwise specified) (APA, 2000c). The effect of this change in practice is discussed in 2.1.4, Diagnosis (see also Diagnosis, Appendix 11) The guideline does not address the management of depression in bipolar disorder, post-natal depression, depression in children and adolescents or depression associated with chronic physical illness, all of which are covered by separate guidelines (**).

2.1 The disorder

2.1.1 Symptoms, presentation and pattern of illness
Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Distinguishing the mood changes between clinically significant degrees of depression (e.g. major depression) and those occurring ‘normally’ remains problematic and it is best to consider the symptoms of depression as occurring on a continuum of severity (Lewinsohn, 2000). The identification of major depression is based not only on its severity but also on persistence, the presence of other symptoms and the degree of functional and social impairment. However there appears no hard-and-fast ‘cut-off’ between ‘clinically significant’ and ‘normal’ degrees of depression; the greater the severity of depression the greater the morbidity and adverse consequences (Lewinsohn, 2000; Kessing, 2007). When taken together with the need to take other aspects that need to be considered such as duration, stage of illness, treatment history there are considerable problems when attempting to classify depression into categories (see discussion under Diagnosis 1.1.4).
Commonly, mood and affect in a major depressive illness are unreactive to circumstance, remaining low throughout the course of each day, although for some people mood varies diurnally, with gradual improvement throughout the day only to return to a low mood on waking. In other cases a person’s mood may be reactive to positive experiences and events, although these elevations in mood are not sustained, with depressive feelings re-emerging, often quickly (Andrews & Jenkins, 1999).

Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, an exacerbation of pre-existing pains, and pains secondary to increased muscle tension and other pains (Gerber et al., 1992), a lack of libido, fatigue and diminished activity, although agitation is common and marked anxiety frequent. Typically there is reduced sleep and lowered appetite (sometimes leading to significant weight loss) but for some people it is recognised that sleep and appetited are increased. A loss of interest and enjoyment in everyday life, feelings of guilt, worthlessness and deserved punishment are common, as are lowered self-esteem, loss of confidence, feelings of helplessness, suicidal ideation and attempts at self-harm or suicide. Cognitive changes include poor concentration and reduced attention, pessimistic and recurrently negative thoughts about oneself, one’s past and the future, mental slowing and rumination (Cassano & Fava, 2002).

Depression is often accompanied by anxiety, and in these circumstances one of three diagnoses can be made: (1) depression, (2) anxiety, or (3) mixed depression and anxiety, dependent upon which constellation of symptoms dominates the clinical picture. In addition, the presentation of depression varies with age, the young showing more behavioural symptoms and older adults more somatic symptoms and fewer complaints of low mood (Serby & Yu, 2003).

Major depression is generally diagnosed when a persistent low mood and an absence of positive affect are accompanied by a range of symptoms, the number and combination needed to make a diagnosis being operationally defined (ICD-10, WHO, 1992; DSM-IV, APA, 2000).

Some people are recognised as showing an atypical presentation with reactive mood, increased appetite, weight gain and excessive sleepiness together with the personality feature of sensitivity to rejection (Quitkin et al., 1991) and this is classified as major depression with atypical features in DSM-IV (APA, 2000). The definition of atypical depression has changed over time and it is not specifically recognised in ICD-10.

Some patients have a more severe and typical presentation, including marked physical slowness (or marked agitation), complete lack of reactivity of mood to positive events, and a range of somatic symptoms including appetite and weight loss, reduced sleep with a particular pattern of waking early in the morning and being unable to get back to sleep. A pattern of the depression being substantially worse in the morning (diurnal variation) is also commonly seen. This presentation is referred to as major depression with melancholic features in DSM-IV and depression with somatic symptoms in ICD-10.

People with severe depressions may also develop psychotic symptoms (hallucinations and/or delusions), most commonly thematically consistent with the negative, self-blaming cognitions and low mood typically encountered in major depression, although...
others may develop psychotic symptoms unrelated to the patient’s mood (Andrews & Jenkins, 1999). In the latter case, these mood-incongruent psychotic symptoms can be hard to distinguish from those that occur in other psychoses such as depression.

2.1.2 Course and prognosis
The average age of the first episode of a major depression occurs in the mid-20s and although the first episode may occur at any time, from early childhood through to old age, a substantial proportion of people have their first depression in childhood or adolescence (Fava & Kendler, 2000). And just as the initial presentation and form of a depressive illness varies considerably, so too does the prodromal period. Some individuals experience a range of symptoms in the months prior to the full illness, including anxiety, phobias, milder depressive symptoms and panic attacks; others may develop a severe major depressive illness fairly rapidly, not uncommonly following a major stressful life event. Sometimes somatic symptoms dominate the clinical picture leading the clinician to investigate possible underlying physical illness until mood changes become more obvious.

Although depression has been thought of as a time-limited disorder lasting on average four to six months with complete recovery afterwards it is now clear that incomplete recovery and relapse are common. The WHO study of mental disorders in 14 centres across the world found that 50% still had a diagnosis of depression a year later (Simon et al., 2002) and at least 10% of patients have persistent or chronic depression (Kessler et al., 2003). At least 50% of people following their first episode of major depression will go on to have at least one more episode (Kupfer, 1991) and after the second and third episodes, the risk of further relapse rises to 70% and 90% respectively (Kupfer, 1991). Early onset depression (at or before 20 years of age) and depression occurring in old age have a significantly increased vulnerability to relapse (Giles et al., 1989; Mitchell and Subramaniam, 2005). Thus, while the outlook for a first episode is good, the outlook for recurrent episodes over the long term can be poor, with many patients suffering symptoms of depression over many years (Akiskal, 1986).

Sometimes, recurrent episodes of depression will follow a seasonal pattern which has been called ‘seasonal affective disorder’ (Rosenthal et al, 1984). DSM-IV includes criteria for a seasonal pattern whereas only provisional criteria are given in the research version of ICD-10. Although a seasonal pattern can apply to both recurrent depression and bipolar disorder it appears most common in the former (70-80%, Rodin & Thompson, 1997; Westrin & Lam, 2007) with recurrent winter depression far more common than recurrent summer episodes (Magnusson & Partonen, 2005; Rodin & Thompson, 1997).

Depression with a seasonal pattern refers to depression which occurs repeatedly at the same time of year (not accounted for by psychosocial stress) with remission in between and without a lifetime predominance of non-seasonal depression. Decreased activity is reported as nearly always present with atypical depressive symptoms being common, particularly increased sleep, weight gain and carbohydrate craving (Magnusson & Partonen, 2005). The onset is reported as usually in the third decade and is commoner in the young (Magnusson & Partonen, 2005; Rodin & Thompson, 1997). Surveys in the UK have found a surprisingly high prevalence in GP practice attenders ranging from 3.5% in Aberdeen (Eagles et al, 1999) to 5.6% in Southern England (Thompson et al, 2004). However the validity of ‘seasonal affective disorder’ has been poorly accepted in
Europe and may be an extreme form of a dimensional ‘seasonality trait’ rather than a specific diagnosis (Kasper et al, 1989). Some patients with non-seasonal mood disorders also report seasonal variation (Bauer & Dunner, 1993) and this also occurs in other disorders such as anxiety and eating disorders (Bauer & Dunner, 1993; Magnusson & Partonen, 2005). After some years follow-up approximately half of those with continuing depressive episodes no longer display a seasonal pattern (Magnusson & Partonen, 2005).

Up to 10% of depressed patients subsequently experience hypomanic/manic episodes (Kovacs, 1996) which emphasises the need to question patients about a history of elevated mood and to be alert to new episodes occurring.

In the WHO study, episodes of depression that were either untreated by the GP or missed entirely had the same outlook as treated episodes of depression; however, they were milder at index consultation (Goldberg et al., 1998). A small longitudinal study (Kessler et al., 2002) found that the majority of undetected individuals either recovered or were diagnosed during the follow-up period; nevertheless, nearly 20% of the identified cases in this study remained undetected and unwell after 3 years.

The term ‘treatment-resistant depression’ was used in the last Guideline to describe depression that has failed to respond to two or more antidepressants at an adequate dose for an adequate duration given sequentially. Although the term is commonly used, and it can be seen as a useful ‘short-hand’ to refer to difficulties in achieving adequate improvement with treatment, it has problems that have led us to a move away from its use in this guideline. The term implies that there is natural cut-off between people who respond to one or 2 antidepressants compared to those who do not and this is not supported by evidence and the term may be taken by both doctors and patients as a perjorative label. It is also not helpful as it does not take into account different degrees of improvement or stage of illness (whether occurring in an ongoing episode or relapse in spite of ongoing treatment). It takes no account of psychotherapeutic treatment and non-antidepressant augmenting agents are not easily incorporated. The limited trial evidence base reflects the lack of a natural distinction and different studies incorporate different degrees of treatment failure. Finally it fails to take into account what psychosocial factors may be preventing recovery (Andrews & Jenkins, 1999). We have preferred to approach the problem of inadequate response by considering sequenced treatment options rather than by a category of patient.

Disability and mortality

Depression is the most common mental disorder in community settings, and is a major cause of disability across the world. In 1990 it was the fourth most common cause of loss of disability-adjusted life years in the world, and by 2020 it is projected to become the second most common cause (World Bank, 1993). In 1994 it was estimated that about 1.5 million disability-adjusted life years were lost each year in the west as a result of depression (Murray et al., 1994). It is even more common in the developing world (for review, see Institute of Medicine et al., 2001). There is a clear dose-response relationship between illness severity and the extent of disability (Ormel & Costa e Silva 1995) and onsets of depression are associated with onsets of disability, with an approximate doubling of both social and occupational disability (Ormel et al., 1999).
Apart from the subjective suffering experienced by people who are depressed, the impact on social and occupational functioning, physical health and mortality is substantial. Depressive illness causes a greater decrement in health state than the major chronic physical illnesses angina, arthritis, asthma, and diabetes (Moussavi et al., 2007). Emotional, motivational and cognitive effects substantially reduce a person’s ability to work effectively, with losses in personal and family income as well as lost contribution to society in tax revenues and employment skills. Wider social effects include: greater dependence upon welfare and benefits with loss of self-esteem and self-confidence; social impairments, including reduced ability to communicate and sustain relationships during the illness with knock-on effects after an episode; and longer term impairment in social functioning, especially for those who have chronic or recurrent disorders. The stigma associated with mental health problems generally (Sartorius, 2002), and the public view that others might view a person with depression as unbalanced, neurotic and irritating (Priest et al., 1996), may partly account for the reluctance of depressed people to seek help (Bridges & Goldberg, 1987).

Depression can also exacerbate the pain, distress and disability associated with physical diseases, as well as adversely affecting outcomes. Depression combined with chronic physical disease incrementally worsens health compared with physical disease alone or even combinations of physical disease (Moussavi et al 2007). In addition, for a range of physical illnesses, findings suggest an increased risk of death when comorbid depression is present (Cassano & Fava, 2002). In coronary heart disease for example, depressive disorders are associated with an 80% increased risk, both of its development, and of subsequent mortality in established disease, at least partly through common contributory factors (Nicholson et al., 2006).

Suicide accounts for just under 1% of all deaths, and nearly two-thirds of this figure occur in depressed people (Sartorius, 2001). Looked at another way, having depression leads to over a four-times higher risk of suicide compared with the general population which this rises to nearly 20-times in the most severely ill (Bostwick & Pankratz, 2000). Sometimes depression may also lead to acts of violence against others, and may even include homicide. Marital and family relationships are frequently negatively affected, and parental depression may lead to neglect of children and significant disturbances in children (Ramachandani & Stein, 2003).

Incidence and prevalence

Worldwide estimates of the proportion of people who are likely to suffer from depression in their lifetime vary widely between studies and settings but the best estimates lie between about 4% and 10% for major depression and between 2.5% and 5% for dysthymia (low grade chronic depressive symptoms) (Waraich et al., 2004) with differences contributed to by real differences between countries and the method of assessment. The estimated point prevalence for a depressive episode (F32/33, ICD-10, WHO, 1992) among 16- to 74-year-olds in the UK in 2000 was 2.6% (males 2.3%, females 2.8%), but, if the less specific and broader category of ‘mixed depression and anxiety’ (F41.2, ICD-10, WHO, 1992) was included, these figures rose dramatically to 11.4% (males 9.1%, females 13.6%) (Singleton et al 2001)

Prevalence rates have consistently been found to be between 1.5 and 2.5 times higher in women than men and also to be fairly stable over the age range of 18-64 years (Waraich et al., 2004) although in the most recent UK survey cited above female preponderance
was only marked for a depressive episode in those under 35-years whereas for mixed anxiety and depression it was across the age range. Compared with adults without a neurotic disorder, those with a depressive episode or mixed anxiety and depression were more likely to be aged between 35 and 54, separated or divorced and living alone or as a lone parent. This pattern was broadly similar between men and women (Singleton et al 2001).

A number of socio-economic factors significantly affected prevalence rates in the UK survey: those with a depressive episode were more likely than those without neurotic disorders to be unemployed, to belong to social classes 4 and below, to have lower predicted intellectual function, to have no formal educational qualifications and to live in Local Authority or Housing Association accommodation, to have moved 3 or more times in the last 2 years and to live in an urban environment (Singleton et al 2001).

No significant effect of ethnic status on prevalence rates of a depressive episode or mixed anxiety and depression were found although numerically there were a higher proportion of South Asians than in those without a neurotic disorder (Singleton et al 2001). Migration has been high in Europe in the last two decades but data on mental health is scarce and results vary between migrant groups (Lindert et al 2008).

An illustration of the social origins of depression can be found in a general practice survey in which 7.2% (range: 2.4% to 13.7%, depending upon the practice) of consecutive attendees had a depressive disorder. Neighbourhood social deprivation accounted for 48.3% of the variance among practices, and the variables that accounted for most of that variance were: the proportion of the population having no or only one car; and neighbourhood unemployment (Ostler et al., 2001).

The evidence therefore overwhelmingly supports the view that the prevalence of depression, however it is defined, varies according to gender and social and economic factors.

2.1.3 Diagnosis

In recent years there has been a greater recognition of the need to consider depression that is ‘subthreshold’, ie does not meet the full criteria for a depressive/major depressive episode. Subthreshold depression causes considerable morbidity and human and economic costs and is more common in those with a history of major depression and is a risk factor for future major depression (Rowe & Rapaport, 2006). There is no accepted classification for this in the current diagnostic systems with the closest being minor depression, a research diagnosis in DSM-IV. At least two but less than 5 symptoms are required and it overlaps with ICD-10 mild depressive episode with 4 symptoms. Given the practical difficulty and inherent uncertainty in deciding thresholds for significant symptom severity and disability, there is no natural discontinuity between minor depression and mild major depression in routine clinical practice. Diagnostic criteria and methods of classification of depressive disorders have changed substantially over the years. Although the advent of operational diagnostic criteria has improved the reliability of diagnosis this does not get around the fundamental problem of attempting to classify a disorder that is heterogeneous and best considered on a number of dimensions. For a fuller discussion see Appendix 11. DSM-IV and ICD-10, have have virtually the same diagnostic features for a ‘clinically significant’ severity
of depression (terming a major depressive episode in DSM-IV or a depressive episode in ICD-10). Nevertheless their thresholds differ with DSM-IV requiring a minimum of 5 out of 9 symptoms (which must include depressed mood and/or anhedonia) and ICD-10 requires 4 out of 10 symptoms (including at least two of depressed mood, anhedonia and loss of energy). This may mean that more people as identified as depressed using ICD-10 criteria compared with DSM-IV (Wittchen et al., 2001) or at least that somewhat different populations are identified (Andrews et al 2008) related to the need for only one of 2 core symptoms for DSM-IV but 2 out of 3 for ICD-10. These studies emphasise that, although similar, the two systems are not identical and that this is particularly apparent at the threshold taken to indicate clinical significance. We have widened the range of depressive disorders to be considered in this guideline update and emphasise that the diagnostic ‘groupings’ we use should be viewed as pragmatic subdivisions of dimensions in the form of vignettes or exemplars rather than firm categories. The guideline development group consider that it is important to acknowledge the uncertainty inherent in our current understanding of depression and its classification and that assuming a false categorical certainty is likely to be unhelpful and worst damaging.

In contrast to the previous guidelines we have used DSM-IV, rather than ICD-10 to define the diagnosis of depression, because the evidence base for treatments nearly always uses DSM-IV. In addition we have attempted to move away from focussing on one aspect such as severity which can have the unwanted effect of leading to the categorisation of depression, and influencing treatment choice, on a single factor such as symptom count.

The implication of the change in diagnostic system used in the guideline, combined with redefining the severity ranges, is that it is likely to raise the thresholds for some specific treatments such as antidepressants. An important motivation has been to provide a strong steer away from only using symptom counting to make the diagnosis of depression and by extension to emphasise that the use of symptom severity rating scales by themselves should not be used to make the diagnosis, although they can be an aid in assessing severity and response to treatment.

To make a diagnosis of a depression requires assessment of three linked but separate factors, A) severity, B) duration and C) course with four severity groupings

It is important to emphasise that the making of a diagnosis of depression does not automatically imply a specific treatment. A diagnosis is a starting point in considering the most appropriate way of helping that individual in their particular circumstances. The evidence base for treatments considered in this guideline are based primarily on randomised controlled trials in which standardised criteria have been used to determine entry into the trial. Patients seen clinically are rarely assessed using standardised criteria reinforcing the need to be circumspect about an over-rigid extrapolation from randomised trials to clinical practice.

• minor depression (2-4 symptoms with maintained function).
• mild depression (few, if any, symptoms in excess of 5 and only minor functional impairment).
• moderate depression (symptoms or functional impairment are between ‘mild’ and ‘severe’)
• severe depression (several symptoms in excess of 5 and the symptoms markedly interfere with functioning).
Psychotic symptoms can occur and are usually associated with severe depression.

Diagnosis using the three aspects listed above (severity, duration, course) necessarily only provides a partial description of the individual experience of depression. Depressed people vary in the pattern of symptoms they experience, their family history, personalities, pre-morbid difficulties (e.g. sexual abuse), psychological mindedness and current relational and social problems – all of which may significantly affect outcomes. It is also common for depressed people to have a comorbid psychiatric diagnosis, such as anxiety, social phobia, panic and various personality disorders (Brown et al., 2001), and physical co-morbidity. Gender and socio-economic factors account for large variations in the population rates of depression, and few studies of pharmacological, psychological or indeed other treatments, for depression control for or examine these variations. This emphasises that choice of treatment is a complex process and involves negotiation and discussion with patients, and, given the current limited knowledge about what factors are associated with better antidepressant or psychotherapy response, most decisions will rely upon clinical judgement and patient preference until we have further research evidence. Trials of treatment in unclear cases may be warranted but the uncertainty needs to be discussed with the patient and benefits from treatment carefully monitored.

The differential diagnosis of depression can be difficult; of particular concern are patients with bipolar disorder presenting with depression. The issue of differential diagnosis in this area is covered in the NICE guideline on bipolar disorder (**).

2.2  Aetiology

The enormous variation in the presentation, course and outcomes of depressive illnesses is reflected in the breadth of theoretical explanations for their aetiology, including genetic (Kendler & Prescott, 1999), biochemical, endocrine and neuropsychological (Goodwin, 2000; Malhi et al 2005), psychological (Freud, 1917), and social (Brown & Harris, 1978) processes and/or factors. An emphasis upon physical, and especially endocrine, theories of causation has been encouraged by the observation that some physical illnesses do increase the risk of depression, including diabetes, cardiac disease, hyperthyroidism, hypothyroidism, Cushing’s syndrome, Addison’s disease and hyperprolactinaemic amenorrhea (Cassano & Fava, 2002). Advances in neuroimaging have reinforced the idea of depression as a disorder of brain structure and function (Drevets et al 2008) and psychological findings emphasise the importance of cognitive and emotional processes (Beck 2008).

Most people now believe that all these factors influence an individual’s vulnerability to depression, although it is likely that for different people living in different circumstances, precisely how these factors interact and influence that vulnerability will vary between individuals (Harris, 2000). Nevertheless, the factors identified as likely to increase a person’s vulnerability to depression include gender, genetic and family factors, adverse childhood experiences, personality factors and social circumstances. In the stress-vulnerability model (Nuechterlein & Dawson, 1984), vulnerability factors interact with social or physical triggers such as stressful life events or physical illness to result in a depressive episode (e.g. Harris, 2000).
A family history of depressive illness accounts for around 39% of the variance of depression in both sexes (Kendler et al., 2001), and early life experiences such as a poor parent-child relationship, marital discord and divorce, neglect, physical abuse and sexual abuse almost certainly increase a person’s vulnerability to depression in later life (Fava & Kendler, 2000). Personality traits such as ‘neuroticism’ also increase the risk of depression when faced with stressful life events (Fava & Kendler, 2000). However, different personalities have different expectancies of stressful life events, and some personalities have different rates of dependent life events, which are directly related to their personality – such as breaking up a relationship (Hammen et al., 2000). The possession of a specific variation in particular genes has also been reported to make individuals more likely to experience depression when faced with stressful events (e.g. Caspi et al 2003).

The role of current social circumstances in increasing the risk of depression, such as poverty, homelessness, unemployment and chronic physical or mental illness cannot be doubted even from a brief examination of the epidemiology of depression (see above). In the UK, an influential study found that social vulnerability factors for depression in women in Camberwell, South-East London, included: having three or more children under the age of 14 years living at home; not having a confiding relationship with another person; and having no paid employment outside the home (Brown & Harris, 1978). Subsequent studies have found that lack of a confiding relationship is the most replicable of these factors (**).

The neatness of this social model of depression, in which vulnerabilities interact with stressful life events, such as separation or loss of a loved one, triggering a depressive episode, is not always supported by the ‘facts’: some episodes of depression occur in the absence of a stressful event, and conversely many such events are not followed by a depressive disorder in those with vulnerabilities. Having said that, the presence of some factors protects against depression following a stressful life event, such as having a supportive confiding relationship with another person (Brown & Harris, 1978), or befriending (Harris et al., 1999).

In addition to considering the aetiology of the onset of depressive episodes it is equally important to consider factors which maintain or perpetuate depression as these are potential targets for intervention. Although many studies have reported on factors which predict outcome (including earlier age of onset, greater severity and chronicity, ongoing social stresses, comorbidity with other psychiatric or physical disorders and certain types of personality disorder) we lack an understanding of what determines how long a depressive episode lasts, why it varies so much between individuals and why for some it becomes persistent. It is also clinically apparent that depression, especially when it persists, may lead to secondary disability that compounds, and is difficult to distinguish from, the depression itself. Features include loss of self-esteem and independence, feelings of helplessness and hopelessness (which increase the risk of suicide) and loss of engagement in outside activities with social withdrawal. These are aspects that self-help interventions and organisations often target but about which we have little systematic evidence. These are likely to relate to, and benefit from, the non-specific effects of interventions and the placebo effect (see below).
2.3 Economic costs of depression

There is now widespread recognition of the significant burden that depression imposes on individuals and their carers, health services and communities throughout the world. By 2020 Depression is projected to become the second leading cause of disability with estimates indicating that unipolar depressive disorders account for 4.4% of the global disease burden or the equivalent of 65 million disability adjusted life years (DALYs) (Murray & Lopez, 1996; WHO, 2002). Within the UK setting, the Psychiatric Morbidity Survey (PMS) of adults aged 16-74 in 2000 reported a prevalence rate for depression of 26 per 1,000 people with slightly higher rates for women compared to men (Singleton et al., 2001). Due to its high prevalence and treatment costs, its role as probably the most important risk factor for suicide (Knapp & Illson, 2002) as well as its large impact on workplace productivity, depression places an enormous burden on both the health care system and the broader society.

One UK study estimated the total cost of depression in adults in England in 2000 (Thomas & Morris, 2003). A prevalence-based approach was used by applying rates of depression from Office of National Statistics (ONS) data to population data for England in 2000. The study measured the direct treatment costs of depression, including primary and secondary care costs as well as indirect costs of lost working days (morbidity) and lost life-years (mortality). The direct treatment costs were estimated at £370 million, of which 84 per cent was attributable to antidepressant medication. However, the indirect costs of depression were estimated to be far greater: total morbidity costs were £8 billion and mortality costs were £562 million. In comparison with the findings of earlier UK-based cost-of-illness studies, direct treatment costs shifted from hospital admissions (including specialised mental institutions) towards medication, reflecting changes in patterns of care over time away from expensive inpatient care to relatively less expensive outpatient-based care.

A recent review was conducted by the King’s Fund in 2006 to estimate mental health expenditure, including depression, in England for the next 20 years, to 2026 (McCrone et al., 2008). The study combined prevalence rates of depression, taken from PMS data, with population estimates for 2007 through to 2026. It was estimated that there were 1.24 million people with depression in England, and this was projected to rise by 17 per cent to 1.45 million by 2026. Based on these figures, the authors’ estimated total costs for depression including: prescribed drugs, inpatient care, other NHS services, supported accommodation, social services and lost employment in terms of workplace absenteeism. Overall, the total cost of services for depression in England in 2007 was estimated to be £1.7 billion whilst lost employment increased this total to £7.5 billion. By 2026 these figures were projected to be £3 billion and £12.2 billion respectively. In contrast to the study by Thomas & Morris (2003), antidepressant medication accounted for only 1 per cent of total service costs whilst inpatient and outpatient care accounted for over 50 per cent. However, the proportion of lost employment costs (78-90 per cent) of the total costs was similar across both studies.

One of the key findings from the cost-of-illness literature is that the indirect costs of depression far outweigh the health service costs. The paper by Thomas & Morris (2003) suggests that the effect on lost employment and productivity is 23 times larger than the costs falling to the health service. Other studies have also supported these findings. Based on UK labour market survey data, Almond & Healey (2003) estimated that respondents with self-reported depression/anxiety were three times more likely to be
absent from work (equivalent to 15 days per year) than workers without depression/anxiety. Furthermore, a US-based study suggests that depression is a major cause of reduced productivity whilst at work, in terms of “work cut-back days” (Kessler et al., 2001). This reduced workplace productivity is unlikely to be adequately measured by absenteeism rates and further emphasises the “hidden costs” of depression (Knapp, 2003). Other intangible costs of depression include the impact on the quality of life of sufferers and their carers and families.

Certainly, the cost-of-illness calculations presented here show that depression imposes a significant burden on individuals and their carers, the healthcare system and on the broader economy through lost productivity and workplace absenteeism. Furthermore, it is anticipated that these costs will continue to rise significantly in future years. Therefore, it is important that the efficient use of available healthcare resources is used to maximise health benefits for people with depression.

2.4 Treatment and management in the NHS

Treatment for depressive illnesses in the NHS is hampered by the unwillingness of many people to seek help for depression and the failure to recognise depression, especially in primary care. The improved recognition and treatment of depression in primary care is central to the WHO strategy for mental health (WHO, 2001).

2.4.1 Detection, recognition and referral in primary care

Of the 130 cases of depression (including mild cases) per 1000 population only 80 will consult their GP. The most common reasons given for reluctance to contact the family doctor were: did not think anyone could help (28%); a problem one should be able to cope with (28%); did not think it was necessary to contact a doctor (17%); thought problem would get better by itself (15%); too embarrassed to discuss it with anyone (13%); afraid of the consequences (e.g. treatment, tests, hospitalisation, being sectioned – 10%) (Meltzer et al., 2000). The stigma associated with depression cannot be ignored in this context (Priest et al., 1996).

Of the 80 depressed people per 1000 population who do consult their GP, 49 are not recognised as depressed, mainly because most such patients are consulting for a somatic symptom, and do not consider themselves mentally unwell, despite the presence of symptoms of depression (Kisely et al., 1995). This group also have milder illnesses (Goldberg et al., 1998; Thompson et al., 2001). And of those that are recognised as depressed, most are treated in primary care and about one in four or five are referred to secondary mental health services. There is considerable variation between individual GPs in their referral rates to the mental illness services, but those seen by the mental illness service are a highly selected group – they are skewed towards those who do not respond to antidepressants, more severe illnesses, single women and those below the age of 35 (Goldberg & Huxley, 1980).

General practitioners are immensely variable in their ability to recognise depressive illnesses, with some recognising virtually all the patients found to be depressed at independent research interview, and others recognising very few (Goldberg & Huxley, 1992; Üstün & Sartorius, 1995). The communication skills of the GP make a vital contribution to determining their ability to detect emotional distress, and those with superior skills allow their patients to show more evidence of distress during their interviews, thus making detection easy. Those doctors with poor communication skills
are more likely to collude with their patients, who may not themselves wish to complain of their distress unless they are asked directly about it (Goldberg & Bridges, 1988a; Goldberg et al., 1993).

Attempts to improve the rate of recognition of depression by GPs using guidelines, lectures and discussion groups have not improved recognition or outcomes (Thompson et al., 2000), although similar interventions combined with skills training may improve detection and outcomes in terms of symptoms and level of functioning (Tiemens et al., 1999; Ostler et al., 2001). The inference that these health gains are the result of improved detection and better access to specific treatments, while having face validity, has been contested. For example, Ormel et al. (1990) suggested that the benefits of recognition of common mental disorders could not be attributed entirely to specific mental health treatments. Other factors like acknowledgement of distress, reinterpretation of symptoms, providing hope and social support were suggested to contribute to better patient outcomes.

This view has gained confirmation from a Dutch study in which providing skills training for GPs did not improve detection but did improve outcomes. Moreover, about half of the observed improvement in patient outcomes was mediated by the combined improvements in process of care. In combination with the strong mediating effect of empathy and psycho-education they suggest that other, probably also non-specific, aspects of the process of care must be responsible for the training effect on symptoms and disability (Van Os et al., 2002). In addition, the communication skills needed by GPs can be learned and incorporated into routine practice with evident improvement in patient outcomes (Gask et al., 1988; Roter et al., 1995).

In summary, those with more severe disorders, and those presenting psychological symptoms to their doctor, are especially likely to be recognised as depressed, while those presenting with somatic symptoms for which no cause can be found are less likely to be recognised. The evidence suggests that this very undesirable state of affairs, in which large numbers of people each year suffer depression, with all the personal and social consequences and suffering involved, could be changed. With 50% of people with depression never consulting a doctor, 95% never entering secondary mental health services, and many more having their depression going unrecognised and untreated, this is clearly a problem for primary care.

2.4.2 Assessment and co-ordination of care
Given the low detection and recognition rates, it is essential that primary care and mental health practitioners have the required skills to assess the patients with depression, their social circumstances and relationships, and the risk they may pose to themselves and to others. This is especially important in view of the fact that depression is associated with an increased suicide rate, a strong tendency for recurrence and high personal and social costs. The effective assessment of a patient, including risk assessment and the subsequent co-ordination of their care (through the use of the Care Programme Approach in secondary care services), is highly likely to improve outcomes, and should, therefore, be comprehensive.

2.4.3 Non-specific effects of treatment and the placebo
Among those seeking care with depression, those put on waiting lists do improve steadily with time. Posternak & Miller (2001) studied 221 patients assigned to waiting
lists in 19 treatment trials of specific interventions, and found that 20% improved in between four and eight weeks, and 50% improved in six months. They estimate that 60% of placebo responders, and 30% of responders to antidepressants, may experience spontaneous resolution of symptoms (if untreated). An earlier study by Coryell et al. (1994) followed up 114 patients with untreated depression for six months: the mean duration of episode was six months, with 50% remission in 25 weeks. It should be noted that there is a high relapse rate associated with depression (see Section 2.1.2 above).

Despite their greater severity and other differences, Furukawa et al. (2000) showed that patients treated by psychiatrists with antidepressants did better than this: the median time to recovery was three months, with 26% recovering in one month, 63% in six months; 85% in one year, and 88% in two years.

Although there is insufficient space here to allow proper discussion, non-specific/placebo effects apply not only to treatment with medication but also to other treatments. Studies comparing any treatment with a waiting list control or treatment as usual in which there is minimal intervention are therefore difficult to interpret and improvements could simply be to the increased support, engagement and monitoring that the intervention involves. The placebo effect in trials of psychiatric drugs is often so large that specific pharmacological effects can be hard to identify, especially when given to people who fall into one of the larger, more heterogeneous diagnostic categories. There can also be suspicion of publication bias, especially with regard to drug company funded trials (Lexchin et al., 2003; Melander et al., 2003). Antidepressants (or other) treatments for depression may offer little or no advantage, on average, over placebo, for patients with minor and mild depression who often improve spontaneously or who respond well to non-specific measures such as support and monitoring. The evidence does support the efficacy of specific treatments with more severe depression and in those with depression that persists over time. However at present it is not possible to clearly identify people with depression who will respond to the specific aspects of a treatment as opposed to the non-specific effects associated with having a treatment.

2.4.4 Pharmacological treatments

The mainstay of the pharmacological treatment of depression for the last 40 or more years has been antidepressants. Tricyclic antidepressants (TCAs) were introduced in the 1950s, the first being imipramine (Kuhn, 1958). The mode of action of this class of drugs thought to be responsible for their mood-elevating properties is their ability to block the synaptic reuptake of monoamines, including noradrenaline (NA), 5-hydroxytryptymine (5HT) and dopamine (DA). In fact the TCAs predominantly affect the reuptake of NA and 5HT rather than DA (Mindham, 1982). The antidepressant properties of MAOIs were discovered by chance in the 1950s in parallel with TCAs. Although the introduction of the TCAs was welcome, given the lack of specific treatments for people with depression, the side effects resulting from their ability to influence anticholinergics, histaminergic and other receptor systems reduced their acceptability. Moreover, overdose with TCAs (with the exception of lofepramine) carries a high mortality and morbidity, particularly problematic in the treatment of people with suicidal intentions.
In response to the side effect profile and the toxicity of TCAs in overdose, new classes of antidepressants have been developed, including: the specific serotonin reuptake inhibitors (SSRIs) such as fluoxetine; drugs chemically related to, but different from, the TCAs, such as trazodone; and a range of other chemically unrelated antidepressants including mirtazapine (BNF, 4.3). Their effects and side effects vary considerably, although their mood-elevating effects are again thought to be mediated through increasing intra-synaptic levels of monoamines, some primarily affecting NA, some 5HT and others affecting both to varying degrees and in different ways.

Other drugs used either alone or in combination with antidepressants include lithium salts (BNF, 4.2.3), and the antipsychotics (BNF, 4.2), although the use of these drugs is usually reserved for people with severe, psychotic or chronic depressions, or as prophylactics. A full review of the evidence base for the use of the different types of antidepressants is presented in Chapter 8.

In addition, there is preliminary evidence that pharmacogenetic variations may affect the efficacy and tolerability of antidepressant drugs. It is likely that future research on this topic will lead to the development of clinically meaningful pharmacogenetic markers, but at the moment the data is insufficient to make recommendations.

2.4.5 Psychological treatments

In 1917 Freud published Mourning and Melancholia, probably the first modern psychological theory on the causes, meaning and psychological treatment of depression. Since that time, numerous theories and methods for the psychological treatment of psychological disorders have been elaborated and championed, although psychological treatments specifically for depression were developed only over the last 30 to 40 years, and research into their efficacy is more recent still (Roth & Fonagy, 1996). Many, but not all, such therapies are derived from Freudian psychoanalysis, but address the difficulties of treating people with depression using a less rigid psychoanalytic approach (Fonagy, 2003). In any event, the emergence of cognitive and behavioural approaches to the treatment of mental health problems has led to a greater focus upon the evidence base and the development of psychological treatments specifically adapted for people with depression (for example, see Beck et al., 1979).

Psychological treatments for depression currently claiming efficacy in the treatment of people with depressive illnesses and reviewed for this guideline in Chapter 6 include: cognitive behavioural therapy (CBT); behaviour therapy (BT); interpersonal psychotherapy (IPT); problem-solving therapy (PST); counselling; short-term psychodynamic psychotherapy; and couple-focused therapies. Psychological treatments have expanded rapidly in recent years and generally have more widespread acceptance from patients (Priest et al., 1996). In the last 15 years in the UK there has been a very significant expansion of psychological treatments in primary care for depression, in particular primary care counselling.

2.4.6 Service-level and other interventions

Given the complexity of healthcare organisations, and the variation in the way care is delivered (inpatient, outpatient, day hospital, community teams, etc.), choosing the right service configuration for the delivery of care to specific groups of people has gained increasing interest with regard to both policy (for example, see Department of Health, 1999b), and research (e.g. evaluating day hospital treatment, Marshall et al.,
Research using RCT designs has a number of difficulties; for example, using comparators such as ‘standard care’ in the US make the results difficult to generalise or apply to countries with very different types of ‘standard care’.

Service-level interventions considered for review in this guideline include: organisational developments, crisis teams, day hospital care, and non-statutory support and other social supports. Other types of interventions reviewed for this guideline include: exercise, guided self-help, computerised cognitive behavioural therapy (CCBT) and screening.

2.4.7 Stepped care

In Figure 1 a ‘stepped care’ model is developed, which draws attention to the different needs that depressed individuals have – depending on the characteristics of their depression and their personal and social circumstances – and the responses that are required from services. Stepped care provides a framework in which to organise the provision of services supporting both patients and carers, and healthcare professionals in identifying and accessing the most effective interventions.

Figure 1. The stepped care model

<table>
<thead>
<tr>
<th>Focus of the intervention</th>
<th>Nature of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP 1: All known and suspected presentations of depression</td>
<td>Assessment, referral, psychoeducation, active monitoring and support</td>
</tr>
<tr>
<td>STEP 2: Minor, mild to moderate depression</td>
<td>Low intensity psychological and psychosocial interventions, medication, referral</td>
</tr>
<tr>
<td>STEP 3: Mild to moderate depression with limited response to initial interventions, moderate and severe depression</td>
<td>Medication, high intensity psychological interventions, combined treatments, referral</td>
</tr>
<tr>
<td>STEP 4: Severe and complex* depression, risk to life, severe self-neglect</td>
<td>Medication, high intensity psychological interventions, ECT, crisis service, combined treatments, multi-professional and in-patient care.</td>
</tr>
</tbody>
</table>

* Complex includes depression with a poor response to multiple treatments, complicated by psychosis, and/or significant psychiatric comorbidity or psychosocial factors
Of those people whom primary healthcare professionals recognise as having depression, some prefer to avoid medical interventions, and others will improve in any case without them. Thus, in depressions of only mild severity, many GPs prefer a ‘active monitoring approach, which can be accompanied by general advice on such matters as restoring natural sleep rhythms and getting more structure into the day. However, other people prefer to accept, or indeed require, medical, psychological or social interventions, and these patients are therefore offered more complex interventions. Various interventions are effective, delivered by a range of workers in primary care.

Treatment of depression in primary care, however, often falls short of optimal guideline recommended practice (Donoghue & Tylee, 1996a) and outcomes are correspondingly below what is possible (Rost et al., 1995). As we have seen, only about one in five of the patients at this level will need referral to a mental healthcare professional, the main indications being failure of the depression to respond to treatment offered in primary care, incomplete response or frequent recurrences of depression. Those patients who are actively suicidal or whose depression has psychotic features may also benefit from specialist referral.

Finally, there are a few patients who will need admission to an inpatient psychiatric bed. Here they can receive 24 hour care and various special interventions.
3 Methods

3.1 Overview

The update of this guideline drew upon methods outlined by NICE (The Guidelines Manual [NICE, 2007]). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the update of a patient centred, evidence-based guideline. There are six basic steps in the process of updating a guideline:

- define the scope, which sets the parameters of the update and provides a focus and steer for the development work
- update the clinical questions developed for the previous guideline
- develop criteria for updating the literature search and conduct the search
- design validated protocols for systematic review and apply to evidence recovered by search
- synthesise and (meta-) analyse data retrieved, guided by the clinical questions, and produce evidence summaries (for both the clinical and health economic evidence)
- decide if there is sufficient new evidence to change existing recommendations, and develop new recommendations where necessary.

The update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness. 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

The National Institute for Health and Clinical Excellence commissioned the NCCMH to review recent evidence on the management of depression and to update the existing guideline ‘Depression: treatment and management of depression in primary and secondary care’ (NICE clinical guideline 23, 2004). The NCCMH developed a scope for the guideline update (see Appendix 1). The scope for the update also included updating the NICE technology appraisal on the use of electroconvulsive therapy (NICE, 2002), which had been incorporated into the previous guideline.

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 NCC and the remit from the Department of Health/Welsh Assembly Government

- inform the development of updated clinical 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.

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). Comments were invited from stakeholder organisations and Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by the GRP.

3.3 The Guideline Development Group

The GDG consisted of: professionals in psychiatry, psychiatric pharmacy, clinical psychology, nursing, and general practice; academic experts in psychiatry and psychology; and service users (one of whom was also a carer). The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economics 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

Fourteen GDG meetings were held between November 2007 and January 2009. During each day-long GDG meeting, in a plenary session, clinical 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, and service user and carer concerns were routinely discussed as part of a standing agenda.

3.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Four topic groups were formed to cover: 1) pharmacological and physical interventions, 2) psychological and psychosocial interventions, and 3) services. These groups were designed to efficiently manage the large volume of evidence appraisal prior to presenting it to the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the healthcare professionals). Topic groups refined the clinical questions, refined the clinical definitions of treatment interventions, reviewed and prepared the evidence with the systematic reviewer before presenting it to the GDG as a whole and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group’s work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting the section of the guideline relevant to the work of each topic group.
3.3.3 Service users and carers
Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included 3 service users, one of whom was also a carer. They contributed as full GDG members to writing the clinical questions, 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, they contributed to writing the guideline’s introduction and identified recommendations from the service user and carer perspective.

3.3.4 Special advisors
Special advisors, who had specific expertise in one or more aspects of treatment and management relevant to the guideline, or provided expertise in methodological aspects of evidence synthesis, assisted the GDG, commenting on specific aspects of the developing guideline and, where necessary, making presentations to the GDG. Appendix 3 lists those who agreed to act as special advisors.

3.3.5 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 recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the development of the guideline. They informed the group 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 6 lists researchers who were contacted.

3.4 Clinical questions
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, an analytic framework (see Appendix 7) was prepared by NCCMH staff based on the scope and the clinical questions developed for the previous guideline. The framework was used to provide a structure from which the clinical questions were drafted. Both the analytic framework and the draft clinical questions were then discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the framework and questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. Questions submitted by stakeholders were also discussed by the GDG and included where appropriate. For the purposes of the systematic review of clinical evidence, the questions were categorised as primary or secondary. The review focused on providing evidence to answer the primary questions. The final list of clinical questions can be found in Appendix 7.

For questions about interventions, the PICO (patient, intervention, comparison and outcome) framework was used. This structured approach divides each question into four components: the patients (the population under study), the interventions (what is being done), the comparisons (other main treatment options) and the outcomes (the measures of how effective the interventions have been) (see Table 2).
Table 2. Features of a well-formulated question on effectiveness intervention – the PICO guide.

<table>
<thead>
<tr>
<th>Patients/population</th>
<th>Which patients or population of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Which intervention, treatment or approach should be used?</td>
</tr>
<tr>
<td>Comparison</td>
<td>What is/are the main alternative/s to compare with the intervention?</td>
</tr>
<tr>
<td>Outcome</td>
<td>What is really important for the patient? 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; costs?</td>
</tr>
</tbody>
</table>

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 early intervention. In addition, questions related to issues of service delivery are occasionally specified in the remit from the Department of Health (DH)/Welsh Assembly Government. In these cases, appropriate clinical 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 clinical question of relevance to NICE guidelines. These are listed in Table 3. 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 study is likely to always yield a better answer than a single study.

Deciding on the best design type to answer a specific clinical or public health question does not mean that studies of different design types addressing the same question were discarded.

Table 3. Best study design to answer each type of question.

<table>
<thead>
<tr>
<th>Type of question</th>
<th>Best primary study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness or other impact of an intervention</td>
<td>Randomised controlled trial; other studies that may be considered in the absence of an RCT are the following: internally / externally controlled before and after trial, interrupted time-series</td>
</tr>
<tr>
<td>Accuracy of information (e.g. risk factor, test, prediction rule)</td>
<td>Comparing the information against a valid gold standard in a randomised trial or inception cohort study</td>
</tr>
<tr>
<td>Rates (of disease, patient experience, rare side effects)</td>
<td>Cohort, registry, cross-sectional study</td>
</tr>
<tr>
<td>Costs</td>
<td>Naturalistic prospective cost study</td>
</tr>
</tbody>
</table>
3.5 Systematic clinical literature review

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature (updating the existing evidence-base where appropriate) in order to answer the specific clinical 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 (see Section 3.5.7) and the need for future research is specified.

3.5.1 Methodology

A stepwise, hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed this process based on methods set out in The Guidelines Manual (NICE, 2007) and after considering recommendations from a range of other sources. These included:

- Clinical Policy and Practice Program of the New South Wales Department of Health (Australia)
- Clinical Evidence online
- The Cochrane Collaboration
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Healthcare Research and Quality
- Oxford Systematic Review Development Programme.

3.5.2 The review process

During the development of the scope, a more extensive search was undertaken for systematic reviews and guidelines published since the previous depression guideline. These were used to inform the development of review protocols for each topic group. Review protocols included the relevant clinical question(s), the search strategy, the criteria for assessing the eligibility of studies, and any additional assessments.

The initial approach taken to locating primary-level studies depended on the type of clinical question and potential availability of evidence. Based on the previous guideline and GDG knowledge of the literature, a decision was made about which questions were best addressed by good practice based on expert opinion, which questions were likely to have a good evidence base and which questions were likely to have little or no directly relevant evidence. Recommendations based on good practice were developed by informal consensus of the GDG. For questions with a good evidence base, the review process depended on the type of key question (see below). For questions that were unlikely to have a good evidence base, a brief descriptive review was initially undertaken by a member of the GDG.
Searches for evidence were updated between 6 and 8 weeks before 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).

The search process for questions concerning interventions

For questions related to interventions, the initial evidence base (or updated evidence base) was formed from well-conducted randomised controlled trials (RCTs) that addressed at least one of the clinical questions. Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, the RCT remains the most important method for establishing treatment efficacy. For other clinical questions, searches were for the appropriate study design (see above).

Standard mental health related bibliographic databases (i.e., CINAHL, Cochrane Library, EMBASE, MEDLINE, PsycINFO) were used for the initial search for all studies potentially relevant to the guideline. Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 10 for quality criteria used to assess systematic reviews). However, in some circumstances existing data sets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

After the initial search results were scanned liberally to exclude irrelevant papers, the review team used a purpose-built 'study information' database to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). Double checking of all excluded studies was not done routinely, but a selection of abstracts was checked to ensure reliability of the sifting. For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to (a) repeat the search using subject-specific databases (e.g. AMED, ERIC, OpenSIGLE or Sociological Abstracts), (b) conduct a new search for lower levels of evidence or (c) adopt a consensus process (see Section 3.5.7).

In addition, searches were made of the reference lists of all eligible systematic reviews and included studies. Known experts in the field (see Appendix 5), based both on the references identified in early steps and on advice from GDG members, were sent letters requesting relevant studies that were in the process of being published2. In addition, the tables of contents of appropriate journals were periodically checked for relevant studies.

Search filters

Search filters developed by the review team consisted of a combination of subject heading and free-text phrases. Specific filters were developed for the guideline topic and, where necessary, for each clinical question. In addition, the review team used filters developed for systematic reviews, RCTs and other appropriate research designs (Appendix 8).

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2 Unpublished full trial reports were also accepted where sufficient information was available to judge eligibility and quality (see section on unpublished evidence).
Study selection

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility (based on the relevant review protocol) at the time they were being entered into the study database. Eligible systematic reviews and primary-level studies were critically appraised for methodological quality (see Appendix 10 for the quality checklists, and Appendix 17 for characteristics of each study including quality assessment). The eligibility of each study was confirmed by consensus during topic group meetings.

For some clinical questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the topic groups 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 each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context and then decide how they should modify their recommendations.

Unpublished evidence

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 the quality of the research. Second, where evidence was submitted directly to the GDG, it must have been done so with the understanding that details would be published in the full guideline. 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.

3.5.3 Data extraction

Outcome data were extracted from all eligible studies, which met the minimum quality criteria, using Review Manager 4.2.10 (The Nordic Cochrane Centre, 2003) or Review Manager 5 (The Nordic Cochrane Centre, 2008).

For each major area reviewed, the GDG distinguished between outcomes that they considered critical and ones that are important but not critical for the purposes of updating the guideline. Only critical outcomes were initially extracted for data analysis (further details about the critical outcomes can be found in the evidence chapters).

In most circumstances, for a given outcome (continuous and dichotomous), where more than 50% of the number randomised to any group were lost to follow up, the data were excluded from the analysis (except for the outcome ‘leaving the study early’,
in which case, the denominator was the number randomised). Where possible, dichotomous efficacy outcomes were calculated on an intention-to-treat basis (that is, a 'once-randomised-always-analyse' basis). Where there was good evidence that those participants who ceased to engage in the study were likely to have an unfavourable outcome, early withdrawals were included in both the numerator and denominator. Adverse events were entered into Review Manager as reported by the study authors because it was usually not possible to determine whether early withdrawals had an unfavourable outcome. Where there was limited data for a particular review, the 50% rule was not applied. In these circumstances the evidence was downgraded due to the risk of bias.

Where necessary, standard deviations were calculated from, standard errors, confidence intervals or p-values according to standard formulae (see the Cochrane Reviewers' Handbook 4.2.2.). 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 data set. Where possible, data extracted by one reviewer was checked by a second reviewer. Disagreements were resolved with 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 (Jadad et al., 1996; Berlin, 2001).

### 3.5.4 Synthesising the evidence

Where possible, meta-analysis was used to synthesise the evidence using Review Manager. If necessary, re-analyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

Dichotomous outcomes were analysed as relative risks (RR) with the associated 95% CI (for an example, see Figure 1). A relative risk (also called a risk ratio) is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control. In Figure 1, the overall RR of 0.73 indicates that the event rate (that is, non-remission rate) associated with intervention A is about three quarters of that with the control intervention or, in other words, the relative risk reduction is 27%.

The CI shows with 95% certainty the range within which the true treatment effect should lie and can be used to determine statistical significance. If the CI does not cross the 'line of no effect', the effect is statistically significant.
Figure 1: Example of a forest plot displaying dichotomous data

Review: NCCMH clinical guideline review (Example)
Comparison: 01 Intervention A compared to a control group
Outcome: 01 Number of people who did not show remission

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Intervention A</th>
<th>Control</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Intervention A vs. control</td>
<td>Griffiths1994 13/23</td>
<td>27/28</td>
<td>36.79 [0.41, 0.84]</td>
<td>0.59</td>
<td>22.30 [0.58, 1.10]</td>
</tr>
<tr>
<td></td>
<td>Lee1986 12/15</td>
<td>14/15</td>
<td>38.92 [0.66, 1.09]</td>
<td>0.79</td>
<td>100.00 [0.60, 0.88]</td>
</tr>
<tr>
<td></td>
<td>Treasure1994 21/28</td>
<td>24/27</td>
<td>38.32 [0.66, 1.29]</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>45/66</td>
<td>65/70</td>
<td>100.00 [0.61, 0.88]</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 2.83$, df = 2 ($P = 0.24$), $I^2 = 29.3%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.37$ ($P = 0.0007$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous outcomes were analysed as weighted mean differences (WMD), or as a standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect (for an example, see Figure 2). If provided, intention-to-treat data, using a method such as 'last observation carried forward', were preferred over data from completers.

Figure 2: Example of a forest plot displaying continuous data

Review: NCCMH clinical guideline review (Example)
Comparison: 01 Intervention A compared to a control group
Outcome: 03 Mean frequency (endpoint)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Intervention A</th>
<th>Control</th>
<th>SMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Intervention A vs. control</td>
<td>Freeman1988 32</td>
<td>1.30(3.40)</td>
<td>20</td>
<td>3.70(3.60)</td>
<td>25.91</td>
</tr>
<tr>
<td></td>
<td>Griffiths1994 20</td>
<td>1.25(1.45)</td>
<td>24</td>
<td>4.15(2.25)</td>
<td>17.01</td>
</tr>
<tr>
<td></td>
<td>Lee1986 24</td>
<td>3.70(4.00)</td>
<td>14</td>
<td>10.10(7.50)</td>
<td>15.08</td>
</tr>
<tr>
<td></td>
<td>Treasure1994 28</td>
<td>4.23(2.04)</td>
<td>24</td>
<td>41.40(24.37)</td>
<td>27.28</td>
</tr>
<tr>
<td></td>
<td>Wolf1992 15</td>
<td>5.30(5.10)</td>
<td>11</td>
<td>7.10(4.40)</td>
<td>13.90</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>109</td>
<td>91</td>
<td>100.00</td>
<td>-0.74 [-1.04, -0.45]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 6.13$, df = 4 ($P = 0.19$), $I^2 = 34.8%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.98$ ($P &lt; 0.00001$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To check for consistency between studies, both the $I^2$ test of heterogeneity and a visual inspection of the forest plots were used. The $I^2$ statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson, 2002). The $I^2$ statistic was interpreted in the following way:

- > 50%: notable heterogeneity (an attempt was made to explain the variation by conducting sub-analyses to examine potential moderators. In addition, studies with effect sizes greater than two standard deviations from the mean of the remaining studies were excluded using sensitivity analyses. If studies with heterogeneous results were found to be comparable with regard to study and participant characteristics, a random-effects model was used to summarise the results (DerSimonian & Laird, 1986). In the random-effects analysis, heterogeneity is accounted for in both the width of CIs and in the estimate of the treatment effect. With decreasing heterogeneity the random-effects approach moves asymptotically towards a fixed-effects model)

- 30 to 50%: moderate heterogeneity (both the chi-squared test of heterogeneity and a visual inspection of the forest plot were used to decide between a fixed and random-effects model)
• < 30%: mild heterogeneity (a fixed-effects model was used to synthesise the results).

3.5.5 Presenting the data to the GDG
Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the relevant topic group.

Forest plots
Each forest plot displayed the effect size and CI for each study as well as the overall summary statistic. The graphs were organised so that the display of data in the area to the left of the ‘line of no effect’ indicated a ‘favourable’ outcome for the treatment in question.

3.5.6 Forming the clinical summaries and recommendations
After the presentation of evidence, members of the topic group discussed whether there was sufficient evidence to change existing recommendations or drafted new recommendations where necessary. One member of the review team in conjunction with the topic group lead then produced a clinical evidence summary based on the topic group discussion.

3.5.7 Method used to answer a clinical question in the absence of appropriately designed, high-quality research
In the absence of appropriately designed, high-quality research, or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there were unlikely to be such evidence, either an informal or formal consensus process was adopted. This process focused on those questions that the GDG considered a priority.

Informal consensus
The starting point for the process of informal consensus was that a member of the topic group identified, with help from the systematic reviewer, a narrative review that most directly addressed the clinical question. Where this was not possible, a brief review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the clinical question and to lead to written statements for the guideline. The process involved a number of steps:

• A description of what is known about the issues concerning the clinical question was written by one of the topic group members
• Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question
• Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include
studies that did not directly address the clinical question but were thought to contain relevant data

- If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was done
- At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question were developed
- Following this, on occasions and as deemed appropriate by the development group, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements
- Recommendations were then developed and could also be sent for further external peer review
- After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

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 people with depression covered in the guideline, in areas with likely major resource implications. This was achieved by:

- Systematic literature review of existing economic evidence
- Economic modelling, where economic evidence was lacking or was considered inadequate to inform decisions.

3.6.1 Key economic issues

Systematic search of the economic literature was undertaken on all areas that were updated since the previous NICE depression guideline.

Moreover, literature on health-related quality of life of people with depression was systematically searched to identify studies reporting appropriate utility weights that could be utilised in a cost-utility analysis.

In addition to the systematic review of economic literature, the following economic issues were identified by the GDG in collaboration with the health economist as key-priorities for de novo economic modelling in the guideline update:

- Cost effectiveness of psychological therapies (i.e. Cognitive Behavioural Therapy) & Pharmacological therapies in combination or alone
- Cost effectiveness of Collaborative Care versus Usual care in the care of those with moderate and severe depression.

The rest of this section describes the methods adopted in the systematic literature review of economic studies undertaken for this guideline (update). The respective
methodology adopted in the previous NICE depression guideline is provided in Appendix 18. Methods employed in de novo economic modelling carried out for this guideline (update) are described in the respective sections of the guideline.

Search strategy

For the systematic review of economic evidence the standard mental-health-related bibliographic databases (EMBASE, MEDLINE, CINAHL and PsycINFO) were searched. For these databases, a health economics search filter adapted from the Centre for Reviews and Dissemination at the University of York was used in combination with a general search strategy for depression. Additional searches were performed in specific health economics databases (NHS EED, OHE HEED), as well as in the HTA database. For the HTA and NHS EED databases, the general strategy for depression was used. OHE HEED was searched using a shorter, database-specific strategy. Initial searches were performed in November 2007. The searches were updated regularly, with the final search performed in December 2008. Details of the search strategy for economic studies on interventions for people with depression are provided in Appendix 12.

In parallel to searches of electronic databases, reference lists of eligible studies and relevant reviews were searched by hand. Studies included in the clinical evidence review were also screened for economic evidence.

The systematic search of the literature identified approximately 35 thousand references (stage 1). Publications that were clearly not relevant were first excluded (stage 2). The abstracts of all potentially relevant publications were then assessed against a set of selection criteria by the health economist (stage 3). Full texts of the studies potentially meeting the selection criteria (including those for which eligibility was not clear from the abstract) were obtained (stage 4). Studies that did not meet the inclusion criteria, were duplicates, were secondary publications to a previous study, or had been updated in more recent publications were subsequently excluded (stage 5). Finally, all papers eligible for inclusion were assessed for internal validity and critically appraised (stage 6). The quality assessment was based on the checklists used by the British Medical Journal to assist referees in appraising full and partial economic analyses (Drummond & Jefferson, 1996) (Appendix 13).

3.6.2 Selection criteria

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

- only papers published in English language were considered
- studies published from 1998 onwards were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs
- only studies from the UK were selected as the aim of the review was to identify economic information transferable to the UK context and this is in keeping with selection criteria from the previous depression guideline
- selection criteria based on types of clinical conditions and patients were identical to the clinical literature review
• 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 and abstracts were excluded from the review

• full economic evaluations that compared two or more relevant options and considered both costs and consequences (that is, cost–consequence analysis, cost-effectiveness analysis, cost–utility analysis or cost–benefit analysis) were included in the review

• studies were included if they used clinical effectiveness data from an RCT, a prospective cohort study, or a systematic review and meta-analysis of clinical studies. Studies were excluded if they had a mirror-image or other retrospective design, or if they utilised efficacy data that were based mainly on assumptions

3.6.3 Data extraction
Data were extracted by the health economist using a standard economic data extraction form (Appendix 14).

3.6.4 Presentation of economic evidence
The economic evidence identified by the health economics systematic review is summarised in the respective chapters of the guideline, following presentation of the clinical evidence. The references to included studies and to those potentially eligible that were excluded at stage 5 of the review, as well as the evidence tables with the characteristics and results of economic studies included in the review, are provided in Appendix 15. Methods and results of economic modelling on psychological therapies / psychosocial interventions are reported in the respective economic sections of chapters 6 and 7. Methods and results of economic modelling on pharmacological, psychological and service configuration interventions are presented in chapter 6 to 11.

All economic evidence reported in the previous NICE depression guideline, on areas that were not covered in the guideline update, has been retained in the guideline update, highlighted in grey colour.

In some areas updated in this guideline, the systematic search of economic literature did not identify economic studies meeting the criteria for inclusion in the systematic review set for the guideline update. In such cases, the economic evidence reported in the previous NICE depression guideline, which adopted more relaxed inclusion criteria for economic studies, has been retained in the guideline update, highlighted in grey colour.

3.7 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/carer stakeholders: the national service user and carer organisations that represent people whose care is described in this guideline
• professional stakeholders: the national organisations that represent health care professionals who are providing services to service users
• commercial stakeholders: the companies that manufacture medicines used in the treatment of depression
• Primary Care Trusts
• Department of Health and Welsh Assembly Government.

Stakeholders have been involved in the guideline’s development at the following points:
• commenting on the initial scope of the guideline and attending a briefing meeting held by NICE
• contributing possible clinical questions and lists of evidence to the GDG
• commenting on the draft of the guideline.

3.8 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 others were responded to, and the guideline updated as appropriate. The GRP 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. NICE then formally approved the guideline and issued its guidance to the NHS in England and Wales.
4 The experience of depression

4.1 Introduction
This chapter provides an overview of the experience of people with depression and their families/carers. In the first two sections are first-hand personal accounts written by service users and carers, which provide some experiences of having the diagnosis, accessing services, having treatment and caring for someone with depression. It should be noted that these accounts are not representative of the experiences of people with depression and therefore can only ever be illustrative. This is followed by a review of the qualitative literature of service user experience. There is then a summary of the themes emerging from the personal accounts and the literature review, which provides a basis for the recommendations, which appear in the final section.

4.2 Personal accounts—service users

4.2.1 Introduction
The writers of the personal accounts were contacted primarily through the service user and carer representatives on the GDG though various agencies that had access to people with depression. The people who were approached to write the accounts were asked to consider a number of questions when composing their narratives. These included:

- When were you diagnosed with depression and how old were you?
- How did you feel about the diagnosis? How has your diagnosis affected you in terms of stigma and within your community?
- Do you think that any life experiences led to the onset of the condition? If so, please describe if you feel able to do so.
- When did you seek help from the NHS and whom did you contact? (Please describe this first contact.) What helped or did not help you gain access to services? If you did not personally seek help, please explain how you gained access to services.
- What possible treatments were discussed with you?
- Do you have any language support needs, including needing help with reading or speaking English? If so, did this have an impact on your receiving or understanding a diagnosis of depression or receiving treatment?
- What treatment(s) did you receive? Please describe both drug treatment and psychological therapy.
- Was the treatment(s) helpful? (Please describe what worked for you and what didn’t work for you.)
- How would you describe your relationship with your practitioner(s)? (GP/community psychiatric nurse/psychiatrist, etc.)
• Did you use any other approaches to help your depression in addition to those provided by NHS services, for example private treatment? If so please describe what was helpful and not helpful.
• Did you attend a support group and was this helpful? Did any people close to you help and support you?
• How has the nature of the condition changed over time?
• How do you feel now?
• If your condition has improved, do you use any strategies to help you to stay well? If so, please describe these strategies.
• In what ways has depression affected your everyday life (such as schooling, employment and making relationships) and the lives of those close to you?

Each author signed a consent form allowing the account to be reproduced in this guideline. Seven personal accounts from service users were received in total. Although the questions were aimed at people with any form of depression, all of the personal accounts received were from people who have/have had severe and chronic depression, spanning many years. The themes that are most frequently expressed in the testimonies include trauma or conflict in childhood as a perceived cause of depression; the need for long-term psychotherapy for people with severe and chronic depression; the need to take personal responsibility for and understand the illness to improve outcomes; issues around diversity; paid and unpaid employment as an important part of the recovery process; the negative impact on daily functioning; concerns regarding stigma and discrimination in the workplace and the relationship between service users and professionals.

4.2.2  Personal account A
I was 23 when I was first diagnosed with depression, 35 when diagnosed with major depressive disorder and 43 when diagnosed with dysthymia. However, my first experience of suffering with depression was most probably as a teenager, living in a chaotic household with a parent with alcoholism and a narcissistic personality disorder.

The first treatment I had was when I was 23 with a wonderful GP who told me he had had depression and a breakdown at medical school. He enabled me to go to see him whenever I wanted, to talk to him for 10 to 15 minutes every week. I was also on an antidepressant and tranquilliser for instant tranquilisation whenever I felt miserable. The depression passed within 4 to 5 months. I always think of the GP fondly as a life saver.

For the next few years I used therapy to deal with my depression, low self-esteem and my underlying childhood issues, each year becoming more confident. During my childhood I had had to deal constantly with my mother’s tempers, mood swings and cruelty, so I had to learn in therapy how to deal with my own emotions, from scratch. Initially I had 3 years of gestalt therapy with a wonderful therapist who came recommended by a friend. I then had psychodynamic psychotherapy for 4 years (while I also ran a self-help group for women). I found this psychotherapist from the UKCP
list. During this period I also worked with teenagers and I found hard work to be a great help in having something to focus on and enhance my self-esteem.

In my thirties, however, I had a major depressive episode and I booked myself into hospital which I now see as a big mistake as it was not therapeutic by any means, but my understanding of what hospital offered was not known to me. I had been having some housing problems, family life was difficult and I had been working very long hours at work to solve all of these problems. I knew that I was at danger point. I was given antidepressants, an antipsychotic, a mood stabiliser, and benzodiazepines. I was offered no therapeutic help and I found the system of nursing within the ward very damaging—they just observed the patients and didn’t talk to us. So I was just left with my depressed thoughts for 11 weeks. I came out and went back to work.

I also didn’t realise that there was stigma around these matters, and I had been open with my friends about being depressed and in hospital. Overnight I lost two thirds of my friends and social contacts. This left me feeling very distressed, ashamed and humiliated. Also, within my family, my illness was exploited by my still crazy mother, to undermine and separate me from any compassion I could expect. This has changed gradually over the years, but it took a long time to heal.

At work, although I was employed in the care environment, some people were not keen about me returning to work. I was marginalised from external meetings for quite some time and my role was confined to writing policy. This changed over time, but I don’t think I should have had to ‘re-prove’ myself as if I had been in prison. But I kept quiet and got on with it. I learnt that it’s best to hide having depression, to avoid the stigma. Subsequently, I have discovered through my own experience and working with service users, that it’s still best to hide having depression (or indeed any other mental illness) if you want to get a job and keep it.

I have had two recurrences of major depressive disorder. I had to give up work in 1998 to battle with it full time for a couple of years. I begged to have psychotherapy, but I now couldn’t afford to pay for it myself. I was tried on a series of drugs over a 7 year period: six different antidepressants and various mood stabilisers, tranquillisers, and so on. I got a job in 2000, but I could barely hold a conversation I was so drugged up. It was sheer force of will that got me up and out each day. I was swimming and eventually was able to pay for my own psychotherapy and gradually the major depression I had been in for 4 to 5 years lifted in 2002. Throughout this time I had battled with pervasive suicidal feelings and only my personal strength got me through. Just getting off the huge amounts of medication was a feat I am proud of in itself, in addition to overcoming the depression caused by childhood issues and living a normal positive life which the medication, not to mention the illness, nearly took from me completely.

I also had a wonderful GP in 2002 to 2003, who took it upon himself to (in his words) ‘have a go at’ my consultant psychiatrist for half an hour on the phone about the cocktail of drugs I was taking. Being on a level of medication that was unnecessary and toxic, I had put on seven and a half stone since 2005 and I was , threatened with high blood pressure and impaired glucose syndrome. My GP helped me get off this cocktail of unnecessary medication.
Not being drugged up freed me and enabled me to function at work, as I had previously done, and it ‘woke’ me up. The threatened ‘relapse’ has never happened. My self-esteem issues over my depression and weight had left me anxious though, and after an 18-month battle involving MIND and my psychiatrist, I got CBT in 2004. This was even more wonderful in aiding my recovery and I had one session per week for a year working on my anxiety phobias. The psychologist was a wonderful professional who had faith in me and together we worked very hard overcoming the deep beliefs that I had held and which prevented me leading a full, well life.

I have been having psychotherapy again since 2005, working on the final bits of damage done to me by my alcoholic, narcissistic mother. It is hard work but my personal stamina increases all the time. This therapy would not be available in the local mental health trust— there is only one course of psychotherapy available (1 year per patient). Even with lifelong illness you get one ‘go’ at it. Where I currently live patients cannot choose whether they would prefer a male or female therapist, nor the style of training they would want their therapist to have had. Choosing a therapist is as important as choosing a GP. Within the NHS there is still a culture that if you don’t take any therapist, you are treatment resistant. I have always preferred a woman therapist, and one psycho dynamically or psychoanalytically trained.

My psychotherapist is helping me with positive attachment and parenting techniques get to the point I should have been at and forming a positive attachment in the psychotherapeutic environment. This enables me to build confidence and be the person I should be, making the most of my abilities and relationships in the present. I am also learning self-analysis and skills building to enable me to keep an eye on stresses and challenges, to self manage and keep well.

My psychiatrist, who I had from 1995 to 2005, now agrees with me that psychotherapy, building my career and not being on any drugs, have been the best for me in my recovery. She is of the ‘old school’ and took a lot of convincing, but at some point, she turned her ideas around about me and what I was able to achieve. She still confirms I was very ill, but that with my hard work I have completely changed my life around and, in her terms, I am unlikely to relapse. My psychiatrist put this in writing to my GP in 2006.

Stigma remains a problem however. It is worse if the negative attitudes are expressed by GPs and other medical practitioners. Even now assumptions seem to be made when I have outpatients appointments for physical ailments because computerisation of records has meant even though I am recovered, major depressive disorder is on my records everywhere. I can sometimes see a doctor’s face drop when they get to that point— some are not very good at hiding it. In 2006 I was turned away from a gastro clinic and told that my stomach pain and weight loss were because of depression and that the NHS couldn’t help me. I complained and the resulting CT scan showed I had cancer which when removed 6 weeks later was at stage 2. I feel quite sick thinking of how many people with depression and mental illness, especially those who are less articulate and bolshy than me, could be being turned away because of the lack of understanding. If I had listened to that doctor in 2006, I would be dead now—and all because I have had depression, not for any other reason.
4.2.3 Personal account B

I first consulted my original GP in the spring of 2006, when I was 55, because of symptoms of what I felt was very severe and prolonged depression. I had experienced a rapid series of distressing life events (a complex bereavement leading to feelings of alienation and isolation) and I had no support. I was working freelance as a trainer but no longer able to seek work and so I was without an income.

I had already tried to help myself for 6 months and had bought many so-called self-help books. I have a masters degree in social work and at one time taught counselling skills. I am familiar with rational emotive therapy, CBT, person-centred therapy, transactional analysis, and so on. I understand the efficacy of exercise, diet, positive thinking and relaxation. The major problem is that one cannot actually do these things when depressed and I believe those who have not been depressed cannot truly comprehend this at all. I am also conscious that any so-called emotional problems affect the way one is perceived and addressed. Because of this, I was very reluctant indeed to seek help and many of my fears were in fact confirmed.

The GP whom I first saw spent more time looking at his computer than me. He asked ‘are you depressed?’ I told him I was sufficiently distressed to consult a GP. Having said he could refer me to the mental health team, he said that ‘they were not very good’ and gave me a card for a private counsellor. He told me to complete a ‘HADS’ test in the waiting room and put it under his door. He offered no medication and no follow-up appointment. I sat in my car in the car park crying for 2 hours before I could drive home.

However, I made an appointment with the private counsellor, although I was anxious about the cost. But I felt I had to try and help myself. The counsellor was a very nice woman but I felt I was not being assessed. She talked a great deal about her upcoming wedding and for half a session explained the essentials of transactional analysis (which I’ve taught). I also felt that conclusions were drawn rapidly and inaccurately. She told me to keep a diary of angry feelings and never referred to it again. She explained that ‘if you haven’t had an adolescent rebellion you have one in middle age’ and told me to ‘get rid of’ people who were draining me. This is not entirely bad advice but much too crude. I got the impression she was talking about her own life, not mine. I felt very much more unsettled at the end of each session than when I had arrived.

After three sessions I found another counsellor, who was better than the first but I could not afford to continue the sessions or to travel to see him. Again I found that the counsellor seemed to have a favourite model of human behaviour. I was later even more annoyed when the difficulties with the counsellors were explained away by a mental health team worker as a disturbance of mine in facing the issues. I felt much worse afterwards knowing this and that I could not improve the situation.

Eventually I began a method of self-counselling: occasionally speaking aloud to myself in a deliberate effort to calm myself down since I knew that depression can be a result of over-stimulation.
Fortunately, in the summer of 2006, I was able to change my GP. The new GP provided much more help but unfortunately the initial medication (citalopram), which I took for 4 months made no difference to me at all.

My new GP referred me again for counselling at the surgery. There was a waiting list: I attended the first session and then there was a gap of some weeks (which was at the end of 2006). I found having to talk with a stranger yet again disturbing. The sessions often ended with an emotionally laden question or the advice given was more appropriate for a much older bereaved person. I did very little talking and I could not summon the energy to constantly correct the assumptions being made which, again seemed based on the counsellor’s own life. I attended just a few sessions and then decided that this was a waste of resources.

I felt that if someone would just skilfully listen and question (as I thought good counselling did) I could sort things out myself. My own reasonably sound knowledge of counselling actually seemed to be a disadvantage to me and I had to learn to keep quiet. I still needed help, had very little external support, and my GP was offering what was available so I felt I had to accept it, but it was not even close to what I needed.

In February 2007 I got into a very distressed state but could not get an appointment with any GP although I phoned the surgery four times. The one friend who knows about my condition then took me to the surgery. I now know that I was quite seriously ill at this point. But one can only go to the surgery when one feels capable of doing so. Appointments had to be made on the day at 8.30am which was one of the worst times for me. So then appointments had to be made a few days ahead. One needs to be able to access help when one needs it during the bad times. In the end it was a registrar GP who saw me in this deeply distressed state. Even then I felt guilty for someone seeing me ‘as an emergency’ and I felt very bad about that. He was, however, quite good and he referred me again to the mental health team.

The registrar changed my medication to escitalopram. I was deeply grateful as my GP kept telling me to continue the citalopram and wait for it to take effect. The escitalopram was beneficial and I have continued with it for over a year. I still seem to need this medication. I feel that getting the medication right and promptly at the virulent stage of the depression is vital. I also feel that I was quite poorly and was left to ‘wait’ to see if I would get better.

Prior to my MHT assessment interview in May 2007 (the GP registrar I saw in February had written again to the MHT to ask for an early appointment) I was in a very foggy state and was particularly vulnerable. However, I think that I expressed the issues quite clearly in the limited time. The interviewer described himself as a nurse, said he was trying to clarify why I was there and at one point told me I looked ‘alright’, which was frustratingly puzzling to me and based on no knowledge of me whatsoever. I quickly lost confidence in my interviewer. I was told, ‘Yes, I’ve had bereavements too’ and said ‘I don’t know why you have been referred’, which was very unhelpful. He also told me I had to ‘negotiate’ if the counselling is not right. How can someone who is seriously depressed negotiate?
I was also given the Aaron Beck tick box type diagnostic tool which I found confusing. (For example ‘loss of appetite’ is difficult to answer; a lot of people who are depressed have ‘abnormal appetite’.) I find these tools very simplistic.

I left this appointment and begin crying immediately – again I could not drive home for an hour. I took extra medication to try and cope. I called the mental health team and was told that I was bound to get upset ‘as I was talking about upsetting things’. Again, the problem is presented as being because of the vulnerability of the patient rather than the competence of the interviewer.

My GP had said that she would be able to refer me to a psychologist but that first I had to be referred to the mental health team. I found this very disappointing and also embarrassing. I was going to have to tell yet another person about my life. When after many weeks I got to see the MHT counsellor in June 2007 she told me the sessions were for 6 weeks so I knew immediately I could not be helped in this short time: I was taught ‘relaxation training’ which was inadequate for my needs. It was like offering aspirin for appendicitis. I had to miss one of the six sessions because I was not well enough to attend.

With every other (physical) condition for which I have been referred I have been seen by a consultant at least once. But with a mental health problem, which was the one life-threatening condition which I had, I was referred by a GP and seen by a nurse (who thought I ‘looked ok’). This meant that I had problems getting my pension (money problems started to become a major factor when my savings diminished). The occupational health professional said I had to have a consultant diagnosis; but it was almost a year before I could see a psychiatrist for a formal diagnosis, which my former employer paid for.

I at last saw a consultant psychiatrist privately in January 2008. She diagnosed me with post-traumatic stress (I had been severely bullied at work before I left 10 years ago) leading to severe depression. While perhaps dismal, it was a relief to have the diagnosis and it does validate my experience. The psychiatrist saw me for two sessions but explained that she could not see me again (as this was, I expect, very expensive). She did provide details of a freelance psychologist, but told me that I would have to see her privately. I saw this psychologist twice paying £75 each session but just could not afford any further sessions. I have had no further treatment other than the medication. As my GP said very recently, there is no other help available, just ‘short fix’ stuff.

Over the past 2 years I have had to share my personal details over and over again with about 12 strangers, half of them doctors ‘assessing’ me. My GP has done her best, but has only so much time, and one wants to be a ‘good’ patient. At one point I stopped driving as I knew that I was not safe to do so. I told my GP about this but she said I would feel a sense of achievement if I continued to drive! This greatly concerned me. Also, I felt no ‘sense of achievement’: a lack of achievement is not one of my problems. I felt that my self-report was not being taken seriously and I was very confused about how I could present myself to make myself understood.

I was never clear about the role of the mental health team or what the ‘variety of options on offer’ actually were (in fact other than counselling there was ‘nothing else available’). It was not recognised that I was in a deep fog, akin to being in another
universe, and was finding it very hard to concentrate on what was being said. The more contacts I had, the more distressed I felt.

Up until 6 or 7 months ago I was feeling as if in a parallel universe, and at one point as if I was living under water. I could not ‘wake up’ from dreams, and very unusually for me I could not get up until 10 am on some days. I felt profound grief. I now have far less faith in getting help so I do not know what I would do if things become worse. I was helped by seeing the consultant psychiatrist and I felt much better having been taken seriously. One problem was being not being able to work.

My own coping strategies are mainly avoiding known triggers, self-monitoring and trying to get proper nutrition. I also swim every day. Distraction helps if I can stop the circularity of thoughts. My everyday life is affected as I am much less outgoing now. I have been ‘let down’ so many times that I do not want to make the approach now. I am mostly happier on my own though I am also gregarious and socially skilled. I feel a little embarrassed that I do not have the things other people of my acquaintance have (family relationships and so on) and so I cannot talk the currency of that group (children and grandchildren). But I am more accepting of my own isolation/difference from other people. However, I do fear being destabilised by even small life events in the future as I know I am vulnerable and don’t manage such challenges well.

4.2.4 Personal account C

Life experiences have definitely led to the onset of depression. I had an accident as a child which affected my eyesight and I have been visually impaired all my teenage and adult life. After I lost my sight I felt I was rejected as a child and teenager by my family, which was exacerbated by being sent away from home to be educated at a school for blind people. As the eldest of four children I bore the brunt of my father’s aggression and when I was older had to work in the family business for long hours and was punished at whim.

Because of my impaired sight I have had problems with sensitive hearing that made my life hell. I felt like a prisoner and as if I was being tortured by everybody and everything with so much noise around me.

I was admitted to a psychiatric unit at the age of 30 because I was suicidal. This was due to a variety of reasons which had been building up to that time. The main complication was that my wife was expecting a baby and we were not getting on and constantly arguing. I felt totally lost, I had no friends and there was no support for my depression. Because of my past experience I couldn’t go to my parents or brother or sisters who lived near me. I felt totally isolated and not wanted by anybody. Although I received a diagnosis of depression this was not fully explained to me and it didn’t do any good because ultimately the staff weren’t equipped to help me or my family. They couldn’t give proper information in a manner that my family could accept or understand, or communicate with them effectively, and there has been no support since then. I spent 6 days there and was medicated. The treatment was ultimately not helpful because there was no follow up support.

In 1992 I attended a college for the blind for training in the hope that I would be able to get a job. Unfortunately this didn’t happen because I was so unprepared, was having
emotional breakdowns, and had too much to cope with at college. I was sent to a local hospital by a doctor from the college and was diagnosed with problematic depression and was given more practical help than previously: I had some psychotherapy, relaxation classes and exercise for my neck. At the end of the college year I was advised to take a break of a few months. This was a very hard time and a struggle for me—both the college and the job centre rejected me by saying they couldn’t help me until I was stable.

There is a definite stigma towards mental health problems in my community, which is a Muslim community. Nobody seemed to want to understand about my diagnosis and I didn’t feel I could talk to anybody because people are not equipped to provide support. They believe in leaving it to the power of prayer. When I approached an Imam in a local mosque about a personal problem within the family I was told that religion would resolve it. He stirred up more trouble by visiting the family member with whom I was having difficulties.

I have felt like an outsider and have suffered rejection after rejection. I have been rejected from services, society, and family. I feel like my life is messed up physically, mentally, socially and financially and in terms of work and education.

I had a severe breakdown last year and am concerned about relapse and was referred twice by my GP to the community mental health team. I was not seen by them. I feel like I am wasting my time trying. I feel like I am being pushed back. I am in a situation where I need the support of a therapeutic community or at the very least a safe place where I am able to go away from family pressures.

My relationship with my current GP is better at the moment. I don’t have regular check ups or practical support but I get help with medication and an occasional chat if I bring the subject up. My GP was a bit more helpful when I had my breakdown. The CMHT did not do a good job of giving practical help: instead I was passed on to voluntary groups who were not fully equipped to offer support in a crisis or if I need help for referral from my GP to the CMHP again. It feels like a vicious circle: I have had a total of five breakdowns and have attempted suicide. But this seems to mean nothing to them. The only psychiatrist I have ever met told me that I would have to sort my problems out for myself. He literally let me wander the streets. I felt so bad I could have jumped off the roof. But perhaps God saved me.

I have therefore spent the last 15 years working on complementary therapies and any improvement in my condition is due to the work that I have done. It is more to do with faith and spirituality rather than religion. I feel closer to God now and feel protected. Many times I wanted to die and take the jump and I was saved. So I think I am meant to live and survive—there is a purpose for me otherwise I would have given up long ago or gone to prison or got on drugs and alcohol. So I thank God I have not gone down those roads.

The self-help techniques I have used have included positive affirmation, relaxation and emotional freedom therapy. I have also received qualifications in holistic therapies. I have been instrumental in setting up a local mental health drop-in centre and I am also a Director of a local division of Mind and standing as the BME representative on Mind Link. (I was able to access some CBT through Mind.) I have joined different groups, for
example, a bowls club for blind people, and I have friends who have provided me with support.

But despite all this activity I am still disillusioned by the attitude of organisations that are meant to be dealing with mental health problems. I have a lot to offer despite no help being offered to me.

My feelings of alienation and isolation are exacerbated by family members who appear to have little appreciation of how difficult life is for me. I feel very isolated because my sensitive hearing makes me nervous and anxious in public places.

Depression has infected every part of my life. It has slowed me down, led to loss of self-esteem and made it difficult for me to get work.

4.2.5 Personal account D

The depression started when I was young (I am now 57). I came from a poor background—my father was diagnosed with bipolar disorder when he was in army during the Second World War and after being discharged he spent a year in a psychiatric hospital. He couldn’t work most of the time. My father also suffered from agoraphobia, so I ran errands for him—I was his ‘skivvy’. My father had bad mood swings, which affected my mother, my siblings and me. He never gave any praise, and he never once said that he loved me or my mother. I missed school in order to care for him or because he had hit me so hard I had a black eye and couldn’t go to school. I found it hard to learn at school and later I found out that I had dyslexia.

When I started puberty I felt different from other people. I felt as though I was not as good as the next person, which stemmed from my upbringing. There were a lot of kids at school living in poverty but life with my father made me feel very inadequate. When I was 15 or 16 years old my father tried to kill my mother when he found out she was having a relationship with another man. I felt as if I was always protecting my mother from my father. Both my siblings, who are older than me, married young to get away from my father.

I knew my feelings were different from those of other people so I went to see the doctor by myself when I was 16. The doctor knew immediately that I was suffering from depression. Because of my low self-esteem I couldn’t hold a job down because I felt as if I was not good enough to do anything. I was constantly comparing myself to other people. I felt at the time that life wasn’t worth living – I thought that practically it would be better to throw myself under a bus. If I hadn’t gone to the doctor I would have killed myself. It was a relief to know that my depression could be understood, if not treated, and to speak to someone who knew what I was talking about.

I was first prescribed diazepam, which made me feel good because I was out of it. I was prescribed one tablet a day but I took three or four. I couldn’t work but at least it was a lift and that is what I felt I needed. I was on diazepam for about 6 to 9 months and then I came off it. I tried to look for job but my feelings of inadequacy and paranoia returned: I felt as if people were looking at me and talking about me. I found it difficult to go outside and became agoraphobic.
Nothing else was offered to treat me so I treated myself by using cannabis, speed and barbiturates. Eventually I found a job I liked and when I was 18 years old I started having serious relationships. I was still living at home then and stayed to protect my mother as my father was still beating her, and I didn’t want to take anyone home as I was ashamed of my father.

I finally left home at age 21 when I got married; I felt as if life was taking off. I was happily married and away from my father and it felt like depression was behind me. I loved my wife and that was enough in life. Children completed the marriage. By the time I was in my early 30s I was working in the building trade as a site manager and I was earning good money for the first time. I was determined not to be like my father and I appreciated what I had. I felt that there was a crater in my life where my father should have been. I didn’t have anyone to look up to – no one to build a personality around. My personality only grew when I got married.

My Dad died in 1983. I stood by his grave and I couldn’t cry. I battered myself with questions: what is the matter with me? I was consumed with all the thoughts of what had happened in the past. I felt numb about it all; it seemed like there was a massive void. I felt like I had never had a Dad and I became very good friends with a man in his 60s who I tried to adopt as a father.

In the following year my wife was diagnosed with schizophrenia. She was 28 at the time. My wife’s illness made me feel depressed but I couldn’t show it. I felt as though I had lost my wife and there was just a shell of a person there who used to be my wife. The illness was like bereavement. I was offered antidepressants but I didn’t take them as I didn’t want my wife to see them. I was trying to keep it together but she believed I was having a nervous breakdown. Throughout her illness I was on an adrenaline rush. I was working flat out and didn’t have time to think about myself. I was a machine trying to keep my family together: looking after my wife and kids and working. In the end I took time off work. I needed some emotional help and I needed someone to talk to. There was no time for myself and I stopped communicating with people.

After my wife had sufficiently recovered from her first episode of schizophrenia (it took about 9 or 10 months), I realised how badly it had affected me. I thought about what it had taken out of me and I would sink into depression and phone up the Samaritans. I went to see my GP a few times during this time and they were sympathetic to what I was going through. I started taking amitriptyline and I also saw a counsellor for 3 months. The counsellor was better than the antidepressants. It gave me a good lift. This lasted for a few months before I began to feel low again. For a few years I was in a cycle of relapsing and recovering – I was up and down like a yoyo. I couldn’t set a course for a life; everything had been completely obliterated by illness.

But my wife was feeling better and we wanted more children so the doctors took her off her depot antipsychotics and antidepressants. When she became pregnant she was happy and like she used to be before the illness. In 1987 my youngest son was born but 4 months after his birth my wife became very ill; she was hearing voices and it was as if the gates of hell were opened and everything came out. She was hospitalised and I stopped working and looked after the baby – it was like being a one-parent family.

Shortly after this I was diagnosed with asthma, which was considered by my doctors to be my major illness rather than depression. The asthma hit me hard as I was my wife’s...
carer and I looked after the children. I also began to have panic attacks. Although I was convincing my wife that I was coping, this was just a mask. I felt as if I had become invisible, that my purpose was to make someone else become well. I did not see that there was something wrong with me. Then one day I was pushing a trolley around the supermarket and I thought ‘I don’t want to die in a supermarket; I don’t want to die in between the bleach and the biscuits.’ This happened several times around this period. I didn’t go to doctors as I thought they would think I was nuts.

In 1997 my wife relapsed again and it affected our youngest son very badly as he had not seen his mother this way before. He was badly bullied at school for having a mother who was a ‘nutter’ and got very depressed. When he was 15 (in 2003) our son was also diagnosed with schizophrenia. I got depressed about what was happening to my son because I didn’t want him to go through the same things that his mother and I had been through.

Although people think that I am stable, I recognise that I will never be free of depression but as I get older I understand more about it. I don’t want to kill myself. I care for both my son and my wife and I will never turn away from them. I become more depressed when there is a crisis – and there always seems to be a crisis in my family. But I have accepted my depression as I have lived with it for so long; it’s like an old nemesis. It’s a part of me.

Eighteen months ago I was taking venlafaxine but I am not currently been treated for depression. To be honest, I hate taking tablets. When I was first ill I thought I was a lunatic because I was taking a tablet. If I do need help I find that counselling is best for me, although I have not seen a therapist for a few years. I can now recognise when I am becoming depressed. It’s a waiting game. I get black days when I wake up in the morning and I am totally unmotivated and I couldn’t even care if I won the lottery—it would make no difference because I feel so lousy. If I feel like this for more than one day then I start to worry and I know I am depressed. To try and cope with the symptoms I grin and bear it or I try doing something different – getting away from mundane routine.

I am now able to talk to my wife about being depressed rather than trying to hide it from her and I talk to lots of other depressed people, which, for me, is like a form of counselling. I got involved with voluntary groups when my wife got schizophrenia: I am the chair of one voluntary organisation and I work for another, and I do a lot of media work. The horrid feeling of not being as good as other people is not there now because I feel that I am helping.

I am particularly interested in the political side of how people with mental health problems are treated. I believe that my depression was caused by my childhood experiences, but depression is such an individual illness — it has got many different faces and it can be caused by many different things. Therefore should people with depression be treated in the same way? I am encouraged to see that a lot of resources are being put into providing CBT for people with depression, but CBT is not the right treatment for everyone with depression and this needs to be recognised.
4.2.6 *Personal account E*

I was 27 years old when I was first diagnosed with depression, 14 years ago. I think I started to get depressed 6 years prior to diagnosis, I just didn't know it at the time. At the time, I was relieved at the diagnosis. I had gone to the doctors knowing something was wrong, but not knowing what it was. I was offered counselling and/or medication. I knew that I had to have medication, as it would make me feel better more quickly. I had already withdrawn from my friends and community (due to the depression) so in terms of stigma, there was none, though I didn't tell family, because they wouldn't understand.

I knew that this 'breakdown' occurred due to the events that had happened the previous 18 months: the sudden deaths of two close friends and my grandmother, being made redundant from my part time job, ending a 6 year relationship with my boyfriend, and then being physically assaulted.

Without doubt, my childhood experiences have also contributed to a life of depression. My mother died when I was 5 and after that my two younger brothers and I were not allowed to talk about her. My Dad remarried a woman with three children, but it was not long before my Dad and stepmother hated each other, and were physically and emotionally cruel to each other. My Dad hated her children, and was physically and emotionally cruel to them, and my stepmother hated my brothers and me, and was physically and emotionally cruel to us. One of my stepsisters sexually abused my youngest brother and me.

A month or so after starting medication, I did not feel any better, so was given counselling immediately. I established a good and trusting relationship with the counsellor who helped me to understand what was happening to me. However, I plummeted further, and was seen by a psychiatrist who allocated me a CPN, who I saw for around 18 months, until I was able to slowly start rebuilding my life. When my 'time' was up seeing the counsellor, I saw a psychologist for the following 18 months. I was also prescribed an antipsychotic drug, but I felt like a zombie and could not look after my daughter, so did not take it often.

Of the professionals listed above, without doubt the CPN helped the most; I had a good relationship with her. When I was at my most depressed, I was seeing the Psychologist, but I was in no fit state to engage in any meaningful therapy, as I was too ill.

As well as the treatments listed above, while I was having counselling I was told that I should attend a women's group, run by my counsellor through the NHS. I attended and it helped much more than I realised at the time in that I formed friendships that were very supportive. However, in terms of therapeutic input it did nothing—people would talk about their week and how awful life was, but I couldn't do that. How could I tell people that I had spent the week trying not to kill myself, when that was all I wanted to do? It was not that I wanted to die, but I could see no other way of stopping the pain. Depression filled every second of every minute of every day, and it was unbearable. I was fortunate in that I was able to sleep a lot (up to 15 hours a day), though time still went slowly. Reading books about depression and self-help gave me an understanding of what was happening to me.
On one occasion I went to a voluntary agency support group, but I couldn’t accept at that time that depression would be part of my life forever: I found it difficult to listen to others about how they were managing their lives living with depression. I thought I was going to get better and it would never come back again—how naïve was I?

Over the years, I have been prescribed most of the SSRIs. They worked to varying degrees, but the most distressing aspect for me is that they all seem to affect my memory and articulation. I have learnt to live with this, but am aware of the limitations this poses for me, especially at work. I did receive further counselling on one occasion, by the NHS, but it was not particularly helpful, as it did not get to the root of the depression.

Over the last 2 years I have paid privately to see a psychotherapist and had psychodynamic therapy. This has been the most helpful in terms of trying to repair and understand the damage I experienced as a child. Financially, though, this has been difficult, and I have had to get another job, in addition to my full time job to pay for this.

Depression for me has changed over time, I believe due to the psychodynamic therapy I have had. For years when I was depressed I needed to sleep a lot and I also put on weight. Now I struggle to sleep (which has its obvious disadvantages) and I tend to lose weight. I didn’t recognise I was depressed for a long while and by the time I went to see my doctor, it was too late to treat successfully, and so took 2 years to recover from. Whereas now it can very quickly become severe, but on a positive note it can ease quickly as well.

Depression is with me all the time, rather like chronic back ache it is always there, but some times are better than others. I have managed to qualify at university in the career I have always wanted, and I love my job, and know that I am pretty good at it. However, there is always the fear that I will get too ill to work. I have had to have the odd day/week off over the last few years, but with the help of my GP (who has been very supportive and allows me to manage my depression my way) I have not had to say it is because of depression. There is a general acceptance at my place of employment to have had depression, so long as it doesn’t interfere with one’s work.

However, I have an excellent manager at work with whom I can be honest. On one occasion I told him that I was going to have to take sick leave as I was very depressed and could not work. He advised me that I could take time off of work, but that if I wanted, he would go through everything I needed to do. He told me that anything I felt unable to do, he would get someone else to do. I went through my work with him, and was able to do everything because he took the pressure off me. He told me to see him at any time I felt unable to do something. Every morning for about a month after that, he would come into my office in the morning to see how I was, and I never took any sick leave.

I have had to build my life around periods of depression, for which I am resentful. I often feel that my life is hanging by a thread—that at any moment, my life, that I have worked so hard to build up, could be taken away from me. It is on this basis that I choose not to engage in a long-term relationship. I am currently seeing someone, but because of his commitments, I do not see him often. This suits me as it means I am under no obligations or pressure from him.
I feel frustrated that there are no services available to me now. On the surface, I function very well; no one would ever believe that I have depression as I am a good actress. But when it is severe, it would be helpful to be able to access services immediately from a team that knows me and can support me without me having to go through a series of assessments and then being told ‘well you can go on the waiting list for this service, but you can only have this service for a particular length of time’. I also feel that long-term psychodynamic therapy should be available, on the NHS, which can get to the root of the issues that cause depression. I now know that I will have depression until I can resolve my childhood issues.

4.2.7 Personal account F

I was first diagnosed with depression in 1999 when I was 44 years old and was feeling suicidal. Because of the way I had been feeling I was relieved to have a diagnosis. Only my close friends knew that I had depression—I didn’t want people to know because there is very little understanding within my community.

My mother died when I was 15 years old. My father then attempted suicide and was on a life support machine for 2 weeks. He was brain damaged and I looked after him for 25 years until his death. I was married at 18 and my first child was kidnapped by her father after I left him. My daughter was 3 months old at the time and I never got her back. I married for a second time, to a man who became a violent alcoholic. Because of his drinking he lost a lot of jobs because he was too hung over to turn up and we were often in debt and lived in poverty. We had four children but we could not provide them with much at Christmas and for birthdays. We struggled financially to provide food and the basics.

When I became suicidal I went to see my GP. He was very attentive and took me very seriously and referred me to a psychiatrist and a mental health clinic. Antidepressants and counselling were discussed as possible treatment options and I was referred for counselling but had to wait 18 months, which was useless. I tried various medications, such as Prothiaden, which made me worse. In the end I was put on Prozac which did help to improve my symptoms. When I finally saw a counsellor, I was offered hypnotherapy, which I didn’t want. I wanted counselling. My relationship with my psychiatrist is non-existent. My doctor doesn’t have a clue who I am. I’m just another number in a long queue.

I have attended a Christian counselling organisation in the city where I live which has been brilliant. There were well-trained counsellors available who were very supportive. Two of the counsellors maintained contact in between appointments.

Depression devastated my life. I shut out a lot of people because I could not socialise when I was so ill. I didn’t want to make relationships because I lost trust in people. My family suffered as I was not really there for them and I couldn’t work because my illness was too severe for me to function normally. The house became a tip.

However things have improved over the years. At the current time I am still on antidepressants but I am ready to come off them. I am now very seldom depressed. After 9 years of being off work because of illness I am now getting back to work on a
job placement. If I have any low moods I go back to my counsellor and exercise regularly and eat healthier food to stay well.

4.2.8 Personal account G

I was first diagnosed with depression in 2000 at the age of 42. At the time I was diagnosed, I was unemployed having been made redundant several months previously and also my marriage was in difficulties. I think that these things contributed to triggering my depression but neither were the responsible in its own right. On reflection there were signs of problems a couple of years previously.

The diagnosis was not a surprise as it had taken a few months for me to decide to go to see my GP as I tried to cope with it as best as I could. At first my GP was reluctant to do anything but after several visits she relented and prescribed me an antidepressant. Unfortunately, this antidepressant did not work and a few months later I returned to see my GP and asked to see someone. Fortunately my wife at the time had accompanied and backed me up otherwise I don't think the GP would have referred me to a psychologist/ psychiatrist.

Initially I had three sessions with a psychologist who said that she could not help and referred me to a psychiatrist. He changed my antidepressant and I then saw him on a monthly basis. This second antidepressant did not work and it was changed again. Eventually I was prescribed a mix of a tricyclic antidepressant and lithium carbonate that proved more effective at controlling the symptoms. However this took 18 months, during which time I was unable to work, my marriage broke up, and because of how I was feeling, I isolated myself from my family. Up until that point I had no experience of mental illness or knew anyone who suffered from it. I was given no information about it from my GP, psychologist or psychiatrist. I think that was the reason I isolated myself from my family more and more as time went on.

During the 8 years I have been ill, I have been on medication and although no longer on lithium I feel that it is only over the last year or so that I have been listened to by my GP and psychiatrist. Since being ill I have changed my GP four times due to moving around the area (one GP retired). Their approach has differed, and has often been inconsistent, and it is only my most recent GP who I feel has listened to me and worked with me dealing with any medical issues around my condition, such as side effects. The one real issue I have about my treatment is that over the 8 years I have only had three sessions with a psychologist and the rest of the time it has been purely medication. I feel this has slowed my recovery and has left me to deal with several issues that I feel could have been dealt with by a psychologist or psychiatrist. Once my condition had stabilised the only contact I had with my GP and psychiatrist was to either get my prescription renewed, or seeing my psychiatrist every 3 months for 10 minutes. Other than that the only other contact I had was with the nurse that who took blood samples to check my lithium levels. Also it concerns me that I was never offered any help or advice on managing my condition. I have obtained such information from what I have discovered on the internet and from fellow service users and the voluntary sector.

As my condition improved I started to research my illness online and also made online contact with others from across the world suffering from mental illness. I have found
the internet very useful for getting information about my condition and when I was very ill and needed to talk, I could usually find someone somewhere in the world to talk to 24 hours a day. The other advantage was that when I didn’t feel like talking, I didn’t have to. Over the years I have formed an online network of fellow sufferers and we keep each other up to date on anything of interest happening in the various countries regarding mental illness and its treatment.

The biggest effect depression has had on my life is when it comes to employment. Since being diagnosed I have only worked for 8 months in paid employment. I’ve also done voluntary work for 18 months with a variety of organisations involved with disability and mental health. Although I did not have a problem getting work before being diagnosed, since then I have found it difficult. In October 2002 I went to university as part of my ‘recovery’ graduating with an MSc in 2003. Although this did not help me find work I found it very beneficial to me in that it kept my mind active and this is something I have continued to try and do since then.

Although I feel well at present, it is noticeable to me that my mood is more variable than when I was on lithium, but the strategies I have in place help me cope with this. Also keeping my mind active helps and doing voluntary work gives me a feeling of having ‘value’ in society. I still have some issues due to the depression, but know that it will take time to resolve these so I try not to let this affect me.

4.3 Personal accounts—carers

4.3.1 Introduction

The methods used for obtaining the carers’ accounts was the same as outlined in section 1.2, but for carers of people with depression, the questions included:

- How long have you been a carer of someone with depression?
- How involved are/were you in the treatment plans of the person with depression?
- Were you offered support by the person’s practitioners?
- Do you yourself have any mental health problems? If so, were you offered an assessment and treatment by a healthcare professional?
- How would you describe your relationship with the person’s practitioner(s)? (GP/community psychiatric nurse/psychiatrist, etc.)
- Did you attend a support group and was this helpful? Did any people close to you help and support you in your role as a carer?
- In what ways has being a carer affected your everyday life (such as schooling, employment and making relationships) and the lives of those close to you?

Two personal accounts from carers of people with depression were received.

4.3.2 Personal account H
Firstly, I must say that caring for someone is one of the most rewarding things I have done. It can be frustrating, exhausting, challenging to one’s own physical and mental health, but ultimately helping someone make the most of their lives by helping them in their most vulnerable moments, is rewarding.

This applies to any caring. I was my mother’s carer when I was a child and teenager and I made sure she ate properly and took her tablets. But most of all I provided practical and emotional support. But I think it can be damaging for children to care for an adult without support, because childhood is when we should be able to expect to be nurtured ourselves.

I then became a carer to my partner. My partner has had two long periods of depression; at present he has been ill since 2005. They have tried the newer stuff on him but one of the old favourites seems to be doing the trick. I attend his reviews and make sure he is looking after himself as regards diet and exercise. I also emotionally support him by listening, working through problems with him, and trying to encourage him to be positive. His best male friend and I have decided to only respond to positive subjects that he brings up, as a way of trying to create positive thoughts in his repertoire. I have struggled for 2 years to try and get him CBT without success, as I can see he desperately needs to be helped with changing his thought patterns to positive thoughts, which would help his overwhelming depression.

As his carer, the pressure of his overwhelmingly negative thoughts and depressed ways of thinking can be a burden. He doesn’t want to think about bills and money, and runs up huge phone bills when he is depressed. I have to constantly nag him to get him to try and keep an eye on his expenditure as it is a risk to his welfare.

As a result of this illness, we can’t live together anymore. I see him two or three times a day at either his home or my home, but the pressure of 24-hour depression wasn’t doing me any good and I had to move house to be able to care for him again. It actually has the good effect of getting him out of the house at least once a day, to come and see me. I plan trips out, organise things and occasionally exert pressure to get him out of bed and even out of the house, because sometimes he would rather sleep 18 hours a day every day.

His physical health is suffering as a result of extreme weight gain because of the medication and a lowering of his activity levels both because of medication and depression. I battle with his doctor and social worker over this, trying to get them to take this seriously because his father had two strokes at his age and he himself has been warned about fat around his heart. I am trying to get him a review of his medication plus a referral to an occupational therapist for support around physical exercise.

It’s hard for me seeing him suffer, and sometimes I get angry with his social worker, when they can’t see that physical health and other risks are associated with his depression, and that these things should be included in his care plan. It’s a constant battle to not get services withdrawn. At one point last year he hadn’t seen a social worker or a housing support worker for 3 months, so it’s an up hill struggle.

I have neuropathy and sometimes this overwhelms me and I have to lie down for a couple of days to let it ‘wear off’. My partner is able to get my shopping and visit me and strangely this seems to take his mind off his own suffering for an hour or two, as
he still has physical strength. If it goes on too long though he gets cross, and wants me there to support him.

In a way, as a carer, I am more like a mother than a partner, and though I wouldn’t say this to him, it has changed the dynamic between us forever. Most carers I have met also say this.

When my partner was depressed previously, I was able to support him and get him back to full time work within a year. Now he has been off work since 2006, and his employers have given him until December 2009 to get through this depression, but I know it is a real risk for him and not working in the long run would not help his self-esteem.

I have built my career around being self-employed, and working from home in the mental health and housing fields, mostly regarding carer, resident or service user issues at strategic level. This means I have the time to care, but I am able to keep myself busy and to have time for myself through work. Work is very, very important to most carers: I have heard other carers say that they go to work to get a rest from the overwhelming nature of caring.

The role of being a carer for someone with severe depression has added to my own symptoms of dysthymia over the years because of the sheer pressure of coping with someone who turned down treatment, stopped their antidepressants at one point and crashed into a psychotic depression. This was a huge burden and local services left me to cope with this on my own 24 hours a day, and it nearly broke me.

Carers who become ill with depression or anxiety, or who have a previous history of depression, should be offered support. As I have said, caring is rewarding but it can also be tiring and frustrating.

4.3.3 Personal account I

My Mum has been depressed on and off since I was a 7-year-old boy (I am now 15) and I have been caring for her since then. She’s not depressed all of the time, and it’s fun when she’s well, and normal, like, – we do normal things then and she’s the normal bossy Mum.

When I was small it was just making her a cuppa now and again, or telling her about school with funny bits to try and make her laugh. Or telling my Nan and Granddad about how she was so they could come and help, but now it’s more. I sit down and talk with her, make sure I get in straight away from school because I worry about her when I am out. I get her tablets, make appointments, sort out food shopping, nag her to get dressed when she’s depressed, answer the phone. I am more of a grown up than when she’s well.

Mostly she’s well but now and again she gets depression. I know the signs. Then she goes quiet and stops going out and seeing her friends and I try and cheer her up and make things better for her. I wish she was like other Mums sometimes, and, well, all the time. But I wouldn’t be without her or want to leave her on her own – she’s my Mum!
I try and be positive and jokey, behave myself and be there for her, and make sure she
sees her therapist even when she doesn’t want to go out and sometimes get her friends
around for a surprise to make time pass for her. I hope she gets better soon. I go to my
room when I feel cross and sometimes talk to my friends. I go out and do usual things
too so that she doesn’t worry about me. I do well in school.

My Mum takes tablets and sees her therapist but I think seeing people really helps her.
When her friends come round and take her mind off it for a while, she laughs. Don’t
forget your friends when they are depressed, I say. And chocolate sometimes helps too!

For a while I had no support but now I go to the Young Carers’ Centre in our town,
and I meet other people like me caring for their parents. I play pool and we have days
out – we went to Alton Towers which was fun. It’s good meeting other young people
like myself who are carers too, but we don’t talk about it all the time. We want to get
away from it just for a few hours, fool about, be normal. Sometimes we watch films,
have pizza, and there’s a support worker if you do want to chat. I had a carer’s
assessment there too.

People sometimes think or say my life is sad, but I know its not my Mum’s fault, she
can’t help being depressed. I love her and where else would I want to be? She helps me
too.

### 4.4 Review of the literature

#### 4.4.1 Introduction

To capture the experience of care for people with depression, a systematic search for
published reviews of relevant qualitative studies was undertaken. The aim of the
review was to explore the experience of care for service users, families and carers in
terms of the broad topics of receiving the diagnosis, accessing services and having
treatment.

#### 4.4.2 Evidence search

Reviews were sought of qualitative studies that used relevant first-hand experiences of
service users, families/carers. The GDG did not specify a particular outcome. Instead
the review was concerned with any narrative data that highlighted the experience of
care. For more information about the databases searched see Table 4.

| Table 4. Databases searched and inclusion/exclusion criteria for clinical evidence. |
|---------------------------------|---------------------------------------------------------------------------------|
| Electronic databases            | CINAHL, EMBASE, MEDLINE, PSYCINFO, HMIC, PsycEXTRA_PsycBOOKS                   |
| Date searched                   | Database inception to February 2009                                            |
| Study design                    | Systematic reviews of qualitative studies, surveys, observational studies     |
| Population                      | People with depression and families/carers                                    |
| Outcomes                        | None specified                                                                 |
The search found one systematic review that explored the experience of care for people with depression that met the inclusion/exclusion criteria. The review team then looked at primary qualitative studies identified by the search and identified a further 6 studies. See Table 5 for details of these studies. Themes from the studies are described below.

Table 5. Studies of service user views of services

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Diagnosis</th>
<th>Research design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chew-Graham et al., 2002</td>
<td>31</td>
<td>Not reported</td>
<td>Framework analysis of data from four focus group interviews</td>
</tr>
<tr>
<td>Elgie, 2006</td>
<td>Not reported</td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Khan et al., 2007</td>
<td>Not reported</td>
<td>Depression</td>
<td>Metasynthesis of published qualitative research in guided self-help in primary care mental health</td>
</tr>
<tr>
<td>MaGPIe Research Group, 2005</td>
<td>775 patients; 70 GPs</td>
<td>Not reported – common mental disorders</td>
<td>Cross-sectional survey using structured, in-depth interviews</td>
</tr>
<tr>
<td>Rogers et al., 2001</td>
<td>27 patients; 10 GPs</td>
<td>Depression</td>
<td>Semi-structured interviews</td>
</tr>
<tr>
<td>Ridge &amp; Ziebland, 2006</td>
<td>38</td>
<td>Depression</td>
<td>Unstructured and semi-structured one-to-one interviews; modified grounded theory approach</td>
</tr>
<tr>
<td>van Schaik et al., 2004</td>
<td>12,655</td>
<td>Depressed and non-depressed populations</td>
<td>Systematic review</td>
</tr>
</tbody>
</table>

4.4.3 Experience of depression

Khan and colleagues (2007) in their meta-synthesis of qualitative research in guided self-help in primary care mental health services found that family conflict, problems at work, chronic physical health problems, childhood events, financial hardship and racism were the most frequent reasons given for causes for depression. People taking part in the studies spoke about their depression in terms of effect on functioning and ability to cope rather than feelings or symptoms. The most common means of expressing their feelings was through metaphor: being ‘on edge’, boxed in’, ‘a volcano bursting’, ‘broken in half’, ‘prisoner in my own home’, and so on.

In their qualitative study of the management of depression in primary care, in which 27 service users and 10 GPs were interviewed, Rogers and colleagues (2001) found that contact with primary care, while necessary in terms of assessing and identifying depression, was ‘relatively unimportant, given the range of pressing problems and adverse circumstances that respondents reported’. These problems were predominantly ‘material and cultural disadvantage and abusive relationships’. Most of the respondents had multiple difficulties and these were seen as the reason why they
were depressed. Fifty per cent said that they were ‘unable to cope’ with everyday life because of multiple pressures.

4.4.4 Accessing help and stigma
Khan and colleagues (2007) found that accessing help from primary care could be difficult, with very little time spent having one-to-one contact with a primary care professional. Because of feelings of shame and ‘lack of legitimacy’ people may not have presented their problems in an open manner. There was a possibility that seeking help would ‘threaten an already weakened sense of self’ if treatments were discussed that might be unacceptable to the person, such as medication.

In Rogers and colleagues’ study (2001) accessing services and issue of stigma are closely entwined. Respondents said that they felt anxious when waiting to see their GP, and in particular that they worried about how they were going to introduce the idea that they had a problem that they themselves found difficult to understand. Some felt shame and others believed that they did not have a medical condition. Most people said that they experienced difficulty in saying that they were unable to cope, but that this was especially evident in the interviews with male service users. There was also a feeling that there was limit to what GPs could do to help, but others expressed an anxiety that seeing a GP would lead to further and more serious intervention. For some receiving a diagnosis of depression was a confirmation of their own personal belief, but for others the diagnostic attribution ‘involved re-conceptualising ideas about illness and adapting to them’.

In the MaGPIe study (2005), a ‘substantial proportion’ of the respondents with a common mental problem said that they had not talked to a doctor about their psychological problems. Reasons for this included not wanting to disclose personal information, a belief that their GP was not the right person to talk to, and concerns about their relationship with their GP. About 25% of the patients interviewed for the study said that mental health problems should not be discussed with anyone. Some were worried that if they spoke to their GP they would be prescribed medication.

Chew-Graham and colleagues (2002) in their research into the self-reported needs of South Asian women suffering distress and mental health problems, highlighted how Asian women experienced disadvantage as a result of their gender within their families and community. Furthermore, outside their communities, they were disadvantaged because of their race and gender. In addition, the research identified further barriers to receiving appropriate help and support for illnesses such as depression: language barriers, the ‘community grapevine’ (a powerful deterrent) and Izzat (family or personal honour/respect, status or prestige). The overall theme to emerge from this work was the increased isolation Asian women felt when suffering from emotional distress.

4.4.5 Relationships with professionals
Elgie (2006) described patients’ perspectives of depression and antidepressants in primary care based on research by the Global Alliance of Mental Illness Advocacy Networks (GAMIAN-Europe). The research highlights the inaccurate perceptions of depression in Europe and the often conflicting relationships between patients and their
healthcare professionals regarding the treatment and management of depression. It is noted that a lack of dialogue between professionals and patient, combined with a lack of available ‘user friendly’ information about the condition and its treatment has significantly contributed to non-compliance of antidepressant treatment. Conversely, patients need to accept responsibility for the management of their depression by being open and honest with their GPs and other primary care practitioners by complying with treatment and changing problematic lifestyle factors.

In a cross-sectional survey of patients attending GP practices in New Zealand (MaGPle Research Group, 2005), interventions such as screening and GP education may be ineffective in improving primary mental health care unless accompanied by educational programs for the general public to increase mental health literacy, de-stigmatise mental illness and to promote the role of the GP in providing mental health care and the effectiveness of medication.

Rogers and colleagues (2001) found that service users spent very little time with their primary care doctors or with other healthcare professionals. On the whole they viewed primary care positively but this was in the context of relatively low expectations. Primary care practitioners did not ensure ongoing contact and care and the service users did not make requests for continuing care. Service users did however expect GPs to listen closely to their histories, and were aggrieved if they did not. But, interestingly, some service users clearly differentiated their GP from their counsellor and were reluctant to talk of feelings and problems with their GP.

4.4.6 Treatments

Khan and colleagues (2007) found that taking medication could lead to ambivalent feelings: on the one hand people felt relief because medication helped them cope with difficulties in their day-to-day life; on the other they felt a lack of control. There was also a moral component regarding personal responsibility and the fear of not being able to function in daily life. When the GP or others (family or friends) offered advice to relieve this ambiguity, people were more willing to accept medication as a possible treatment, but only on the understanding that it would be for short-term use. People were cautious about telling other people that were taking medication because of perceived stigma. There was a feeling amongst the people in the studies that they were in some way ‘deficient’ because they needed to take antidepressants. Feelings of guilt, of letting themselves and others down, and concerns about long-term changes to their personality were also expressed.

As noted above, compliance with antidepressant medication may be adversely affected by a lack of dialogue and information about antidepressant medication (Elgie, 2006).

Ridge and Ziebland (2006) found that people with deep-seated and complex problems needed longer-term psychological therapy.

4.4.7 Patient preference
A review was conducted by van Schaik and colleagues (2004) of literature about patient preference regarding treatment of depression in primary care. It should be noted that their review also included surveys conducted in non-depressed populations. In studies that compared counselling with antidepressants, 23-38% more people preferred counselling. In two studies in which psychotherapy and antidepressants, ‘the differences were 6% and 13% favouring psychotherapy’. In one study in which both counselling and psychotherapy were compared, counselling was preferred more often. In general, all studies included in the review demonstrated that the respondents were more positive about psychotherapy or counselling than antidepressants.

Most people mentioned risk of unpleasant side effects and the fear of becoming addicted to their medication as a reason for not favouring psychotropic drugs. When compared with non-psychotropic medication (that is, medication for physical complaints), the prevailing belief among patients was that psychotropic medication caused more side effects and was more associated with ‘losing control’. Those who preferred antidepressant medication were more likely to have severe depression, have experienced psychotropic medication previously, and be older.

A popular reason given for favouring psychotherapy was that this presented the service user with the chance for a ‘personal exchange’ and the ‘cause’ of the problem ‘could be solved’. A number of negative comments were also made about psychotherapy, including a belief that it was not effective and that problems would be exacerbated by discussing them with a therapist.

Factors that influenced a preference for counselling included female gender, ethnicity, greater knowledge about the treatment, having paid sick leave and not currently being treated with antidepressants.

When healthcare professionals supported people regarding their preferences for medication as part of a quality improvement intervention programme, it was found that service users could be encouraged to have the treatment that was thought to suit them best. People who strongly favoured counselling but were not referred for it were likely to remain untreated.

Schaik and colleagues (2004) noted that the review had highlighted that more information was needed about depression because of the number of incorrect assumptions about depression and its treatments (such as the addictive properties of antidepressants).

In the study by Rogers and colleagues (2001), service users were ‘passively accepting’ of decisions made by their primary care practitioners, although some patients were reluctant to start treatment with antidepressants. But on the whole service users understood that medication was the primary treatment available from their GP.

4.4.8 Self-help and other coping strategies

Kahn and colleagues (2007) synthesised qualitative studies of patient experiences of depression management in primary care to develop a framework for a guided self-help intervention with the aim of providing a potential solution to the problem of the gap between demand for CBT and supply of trained therapists. A number of themes were
highlighted, including feelings of control and helplessness in engaging with treatment, which might influence the success of a self-help intervention for people with depression in primary care. People said that they used coping strategies such as distraction or thinking of places that were associated with feeling safe and in control. They saw accessing help as an indication that their personal coping strategies had failed.

4.4.9 Employment

Clinical research, government reports and anecdotal evidence suggest that employment plays a part both in exacerbating stress leading to depression, but also, conversely, that it can be a crucial component in aiding the recovery process.

The Health and Safety Executive (2008) reported that in 2006/07, an estimated 530,000 people in the UK reported they were suffering from stress, depression or anxiety that was caused or exacerbated by their current or past employment. It was estimated that 13.8 million working days (full-day equivalent) were lost in 2006/07 through work-related stress, depression or anxiety. The Sainsbury Centre for Mental Health (2007) also identified another problem: the loss in productivity that occurs when employees come to work but function at less than full capacity because of ill health (termed ‘presenteeism’). Fearing possible stigma or discrimination, people with mental health problems may turn up for work even if they are feeling unwell rather be labelled as mentally ill by their employers and co-workers.

Once people with depression become too ill to work, they may remain absent from their place of employment or unemployed for considerable periods of time. The anecdotal evidence from the personal accounts suggests, however, that for people with depression a return to work, or continuing with work, can aid the recovery process. A report by Waddell and Burton (2006) concluded that work was generally beneficial for both physical and mental health and well-being. It advised that the type of employment should be healthy, safe and offer the individual some influence over how the work is done and a sense of self-worth. Overall, the beneficial effects of work were shown to outweigh the risks and to be much greater than the harmful effects of long-term unemployment or prolonged absence because of sickness.

There was limited evidence specifically relating to depression and employment issues (such as accessing employment opportunities and job retention), but there was more evidence around employment and mental illness in general. A report by the Royal College of Psychiatrists (2008) confirmed that ‘there has been relatively little research about the effectiveness of interventions that assist people with common mental disorders to remain in work or return to work after a sickness absence’. Two studies were identified that analysed employment schemes in people with mental health problems.

In a systematic review of 11 RCTs comparing prevocational training or supported employment for people with severe mental illness with each other or with standard community care, Crowther and colleagues (2001), found that participants who received supported employment were more likely to be in competitive employment than those who received prevocational training (34% compared with 12% at 12 months). Rinaldi
and colleagues (2008) examined a supported employment scheme run by South West London and St George’s Mental Health Trust. The results showed that following the integration of employment specialists into CMHTs there was a significant increase in the number of clients with various diagnoses (31% with depression – unspecified severity) engaged in mainstream work or educational activity at both 6 and 12 months. The conclusion drawn supports the use of individual placement specialists in clinical practice in CMHTs.

4.4.10 Recovery

Ridge and Ziebland (2006) interviewed 38 men and women who, in the main, had had severe depression, to explore the approaches and meanings attributed to overcoming depression. The focus was on the specific components involved in recovery: authenticity, responsibility and ‘rewriting depression into the self’. Recovery involved the need to understand the ‘authentic self’. The main findings of the study were that people needed to understand a language and framework of longer-term recovery to tell their own story of improvement; that getting better meant different things to different people; and that people needed to assume responsibility for their own recovery. The majority of the interviewees had used and valued talking therapies as a means of gaining insight into their thoughts and feelings.

4.5 Summary of themes

This section is a combined summary of themes from the personal accounts and the literature review. It should be noted that most of the personal accounts received were from people who have/have had severe and/or chronic depression. Therefore, it is acknowledged that the themes that run through the personal accounts may not be applicable to people who suffer other forms of depression. The literature search produced studies that also had a relatively narrow focus, with the majority emanating from primary care settings. However, despite the focus of both the personal accounts and the literature review, there is some overlap in the themes around depression and its treatment and associated concerns, as outlined below.

Both the personal accounts and the literature reveal that lack of information from professionals is a barrier to coming to a full understanding of depression, the range of treatments available and the role of the mental health team. There was also a concern that when a person is severely depressed they may find it difficult to concentrate on what is being said. Therefore written information is crucial. One person (B) said that it would be helpful if professionals could be clear about the purpose of any appointments offered. Lack of clarity about how care is organised may increase the person’s distress. One person (G), who had been given no information, had empowered himself through the internet and had built up a wide network of fellow sufferers. Lack of information is a particular issue for people from black and Asian minority ethnic groups, as evidenced by personal account C.

Recognition of depression and the severity of symptoms was also an emergent theme. Two people (B and G) commented that they felt that the severity of their depression was not properly recognised within primary care. One person (B) felt that her diagnosis should have been made by a qualified and experienced professional.
Most of the personal accounts spoke about the relationship with the GP, who is usually
the first point of contact when a person realises that they need help. Most found their
GPs were helpful and understanding, for instance one person (E) had a GP who
enabled her to manage her depression ‘her way’. The main area of criticism concerned
the quality of contact with the GP (see Khan and colleagues, 2007): a GP appointment
lasts for 10 minutes only, and in times of distress this is not long enough. Due to the
nature of depression, sufferers are unlikely to ask for a longer appointment. The
literature also reviewed service users experience of primary care; one study (Rogers et
al., 2001) highlighted the low expectations of service users with depression regarding
what their primary care practitioner could offer them and how they could support
them. But within the context of low expectation, service users’ responses to their
primary care practitioners was positive.

Most of the personal accounts spoke of the importance of a relationship with
professionals that was non-judgemental and supportive. But as one person (B) pointed
out, sometimes being well-meaning and supportive is not enough. She felt that while
her primary care practitioners and counsellors were pleasant and accommodating, her
self-report was not listened to closely enough and that the severity of her depression
was underestimated. A number of people commented that the relationship between
patient and therapist is of prime importance, and that ideally there should be some
choice in terms of the gender of the therapist and their therapeutic approach. Two
people (A and B) commented that it is often seen as the patient’s ‘fault’ if they did not
benefit from psychological treatment, when the counsellor or therapist should take
some responsibility for lack of therapeutic effect.

Accessing help was also a prevalent theme in the literature and the personal accounts.
Two people (B and E) found it difficult to access support when needed. It was felt that
an emergency number to call would be a lifeline for people who live alone and have no
carer support. It would also be helpful for people with long-term, severe depression.

Stigma was frequently discussed in the personal accounts and in the literature. This
was experienced both externally and internally. External stigma was felt from
employers and colleagues; but many people also felt internal stigma and kept their
depression concealed from friends, family and work associates. In a number of the
studies, feelings of shame were expressed, and also an anxiety that asking for help
would lead to being offered interventions that they did not want, such as medication
(the person in account D says that the idea of taking tablets accentuates the feeling of
being mentally unwell).

The majority of the personal accounts reported childhood trauma or conflict of one
form or another, and many of them linked this directly with the onset of their
depression. For many people, complex problems in childhood were compounded by
multiple difficulties in adulthood. For the person in account D being a carer of
someone with schizophrenia meant that he had to hide his symptoms of depression in
order to fulfil his role as a carer. Khan and colleagues (2007) found that family conflict
and childhood events were among the most frequent reasons given for causes for
depression. Howe (1995) explains that:

Internal psychological states and our ability to cope with the external
demands of life have roots which reach right back into childhood. The
robustness of our early internal representations of self and others lays down
the pattern of our future psychological strengths and weaknesses. When children feel that no matter what they think, say or do, they are not able to control what happens to them, physically or emotionally, a feeling of fatalism and helplessness sets in. Attachment relationships in which sexual or physical abuse took place often leave the individual with feelings of passivity and worthlessness. Early attachment relationships that were lost or broken leave people feeling that they cannot control the important things in their lives. Without support they remain emotionally vulnerable to setbacks and upsets. For those who feel hopeless and helpless, depression is often the psychological result.

Research by Brown and Harris (1986) concluded that ‘lack of care’ in childhood proved to be the childhood adversity that was most likely to result in depression in adulthood.

From the perspective of service users involved in this guideline, most have had a course of CBT and it has proved effective to some degree. However, there has been strong feeling amongst the service user and carer topic group that the quote by Howe (1995) highlights the reasons that many people have had to opt for private therapy. It is felt that psychological treatment offered by the NHS in the form of CBT does not go far enough in addressing the trauma experienced in childhood. Research by Ridge and Ziebland (2006) confirms the opinions of the service user group and the testimony from the personal accounts that people with ‘deep and complex problems felt the need for longer term therapy’. Those that have had long-term psychodynamic therapy report that it has been helpful in their understanding of themselves and their depression and that until they have worked through and repaired the damage experienced in childhood, depression will be a major factor in the person’s life. The service user and carer topic group do acknowledge, however, that as there has been little research into the efficacy of long-term psychodynamic therapy, it cannot be recommended as a course of treatment in this guideline.

There were mixed reports regarding medication. Some people did not find antidepressants helpful, particularly in the form of a ‘drug cocktail’. One person (A) commented on the weight gain associated with the medication leading to self-esteem issues and feeling more depressed. Others benefited from it; one person (B) felt strongly that getting the medication right and promptly is vital and that there should be intense support before the antidepressive effects are experienced.

The literature strongly stated that patient preference favoured ‘talking treatments’ such as psychotherapy and counselling over antidepressant medication. Psychotherapy and counselling were preferred because they gave service users the opportunity to have a ‘personal exchange’.

It is evident from the personal accounts and the literature review that people who have had depression for a long time develop coping mechanisms that enable them to manage their illness. These mechanisms range from self-help, finding the right medication regime and therapist, to exercise (A), personal faith (C), support groups (D, E, F and G) and readjusting one’s life in order to be able to manage their depression. However it should be acknowledged that some of these activities may be difficult if a person is severely depressed.
From the personal accounts and the literature it can be seen that there are issues for those with long-standing depression when it comes to accessing and remaining in employment. Several personal accounts spoke of difficulties in getting paid employment: one person (C) stated that both their college and job centre could not help until their condition was stable and another (B) was self-employed when she became ill, was unable to work, and had no income. In personal account G, the person had only worked in paid employment for 8 months in the 8 years he had had depression, but was doing voluntary work with mental health and disability organisations.

Other personal accounts spoke of their experiences in work. Personal account A spoke of colleagues not being keen for them to return to work, and instead of returning to their normal activities was marginalised from external meetings and confined to certain tasks. Personal account E expressed the fear of getting too ill to work, but with the help of her GP did not have to say that the occasional day or week off with illness was because of depression. However she also had the support of her manager in whom she confided and who helped with work pressures.

The issue of employment is also important to carers: in personal account H, the carer has built her career around self-employment so that she has time to care, but is also able to maintain a life outside caring.

The literature highlighted that depression in the workforce is widespread and on the increase, that it has health and social care costs and can affect work productivity. Obtaining or staying in work can be difficult for people with depression. There can be a stigma associated with ‘declaring’ depression in the work place. Staying in employment can be difficult for people with depression and work-related stress may exacerbate the problem. However, work can be beneficial for physical and mental well being. Support and confidentiality from an employer and healthcare professionals can be very helpful in coping with and maintaining employment, as is a more flexible pattern of working. Supported employment is likely to be more beneficial than prevocational training in helping people with depression to return to fully paid employment.

In the study by Ridge and Ziebland (2006), the term ‘recovery’ is used to describe the process by which people learn to understand and then manage their illness. They explain that as the process of recovery develops, the person is able to assume responsibility for their illness, through gaining insight into themselves, their thought processes, their concept of themselves and others around them, and their place in the world. Treatments and professionals were seen as the ‘tools’ needed to aid recovery. The term ‘recovery’ was the cause of significant debate among the service user and carer topic group and had different meanings for different people. For some it meant an absence of depressive symptoms and an ability to function fully to one’s potential. But for other long-term sufferers, ‘recovery’ was a term that they would not use (‘self-management’ being perhaps a more appropriate term). For others the term ‘recovery’ was important in demonstrating the positive shift from being severely depressed with an inability to ‘function normally’, to perhaps currently living with dysthymia, where the user is able to live a full and productive life, with just a few residual symptoms that are manageable.

Zimmerman and colleagues (2008) argue that the return of normal functioning and quality of life should be as fundamental to the concept of recovery or ‘remission’ as is
symptom resolution because the presence of both symptoms and impaired functioning are core constructs in the diagnosis of depression. However, currently remission is defined according to scores falling below a threshold on symptom severity scales.

The literature search did not identify studies of carer experience and the two personal accounts offer very different perspectives, one from an adult caring for her partner (H) and one from a teenage boy caring for his mother (I). But several themes did emerge. The personal accounts both conveyed the experience that caring is rewarding but challenging. Both carers also spoke of the different aspects of caring: undertaking practical tasks for the person, and offering emotional support. Caring can radically change the relationship between partners and between parents and children. The carer in account H felt more like a mother than a partner and the young carer (I) said that he became an adult when he cared for his mother, but that she became a ‘normal bossy Mum’ again when she was well. Both carers reported that having interests that took them away from caring for a few hours was extremely important.

The needs of young carers should be recognised and addressed and recent publications from the Social Care Institute for Excellence and the Department of Health (Roberts et al., 2008; Greene et al., 2008; Department of Health et al., 2008) provide guidance on how this can be achieved. It should be recognised that young carers might marginalise themselves from their peer group and experience other social and educational disadvantage. The report by Roberts and colleagues (2008) suggests that the needs of young carers could be more effectively addressed by respecting their anxieties and acknowledging their input and skills. It is also recommended that young carers should be included in their family member’s care planning.

### 4.6 Clinical practice recommendations

#### 4.6.1 Information and consent

**4.6.1.1** When working with people with depression and their families and carers practitioners should:

- build a trusting relationship and work in an open, engaging and non-judgemental manner
- explore treatment options in an atmosphere of hope and optimism, explaining the different courses of depression and that recovery is possible
- be aware that stigma and discrimination can be associated with a diagnosis of depression.

**4.6.1.2** When working with people with depression and their carers practitioners should:

- avoid clinical language without adequate explanation
- ensure that comprehensive written information is available in the appropriate language and in audio format if possible
- provide and work proficiently with independent interpreters where needed.
4.6.1.3 Practitioners should be aware of, and inform people with depression and their families and carers about, self-help groups, support groups and other local resources.

4.6.1.4 Practitioners should make all efforts necessary to ensure that a person with depression can give meaningful and informed consent before treatment is initiated. This is especially important when a person with depression has a more severe depression or is subject to the Mental Health Act.

4.6.1.5 Although there are limitations with advance directives about the choice of treatment for people who are depressed, it is recommended that they are developed and documented in care plans, especially for people who have recurrent severe or psychotic depression, and for those who have been treated under the Mental Health Act.

4.6.2 Supporting families and carers

4.6.2.1 When families and carers are involved in supporting a person with severe or persistent depression, practitioners should consider offering:
- written and verbal information on depression and its management, including how families and carers can support the person
- a carers’ assessment of their caring, physical and mental health needs where necessary
- information about and facilitate access to local carer and family support groups and relevant voluntary organizations.
They should be able to negotiate confidentiality and the sharing of information between the person with depression and their carers.

4.6.3 Working with people from diverse ethnic and cultural backgrounds

4.6.3.1 Practitioners working with people with depression from diverse ethnic and cultural backgrounds should ensure they are competent in:
- culturally appropriate assessment skills
- using different explanatory models of depression
- addressing cultural and ethnic differences in the formulation of treatment plans and the expectations of and adherence to treatment
- working with families from diverse ethnic and cultural backgrounds

4.6.3.2 Where available, consideration should be given to providing all interventions in the preferred language of the person with depression.
5 Case identification and service delivery

5.1 Introduction

The starting point for providing effective treatment for depression is the recognition of the problem and the first point of access is usually primary care, with the majority of people continuing to be managed in primary care. There is evidence, however, that many cases go unrecognised (Del Piccolo et al., 1998; Raine et al., 2000). Where depression is recognised, care often falls short of optimal recommended practice (Donoghue & Tylee, 1996; Katon et al., 1992) and outcomes are correspondingly below what is possible (Rost et al., 1994). This is a cause of considerable concern. More recent studies, however, suggest that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient-doctor relationship and it is milder forms, which are more likely to recover spontaneously, that go undetected and un-treated. (Kessler et al, 2003, Thompson et al, 2002)

In addition to efforts to improve recognition of depression, a number of responses have been developed over the past 20 or so years to address the problem of sub-optimal treatment. These responses have included developments in the treatment of depression in primary and secondary care; the organisational and professional structures of primary and secondary care mental health services; and the development and adaptation of models for the management of chronic medical conditions, for example diabetes (Von Korff et al., 1997; Von Korff & Goldberg, 2001). Since the publication of the original guideline in 2004 in the UK these developments have included the introduction of graduate mental health workers (DH, 2002) which has contributed to an increased access to low intensity psychosocial interventions including computerised cognitive behavioural therapy, (NICE 2002, NICE 2005). The concept of ‘stepped care’ advocated in the original guideline has been embraced by many commissioners and providers in the NHS and is now being taken forward by the Improving Access to Psychological Therapies programme (DH, 2007). It is this later development with £340 million of funding over six years along with 3,400 new psychological therapists that will bring the single biggest change in the provision of effective treatments for depression in primary and secondary care.

This chapter focuses on two main issues; the identification of depression in primary and secondary care and the range of different service delivery mechanisms that have emerged in recent years. These approaches to service delivery fall under a number of broad headings including systematic approaches for organising care and making

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3 For this update (2009), all sections of the previous delivery of services chapter were reviewed. The following sections: case identification, organisational developments (now re-named enhanced care) non-statutory, support and crisis service remain in this chapter. The updated reviews for guided self-help, computerised cognitive behavioural therapy and exercise have been moved to Chapter 6 and the updated review for ECT can be found in Chapter 9.
available appropriate treatment choices, the development of new and existing staff roles in primary care and the introduction of mental health specialists into primary care.

### 5.2 The identification of depression in primary care and community settings

#### 5.2.1 Introduction

As stated above the accurate identification of depression is an essential first step in the management of people with depression. This includes both people who have sought treatment because of depression symptoms and those being treated for other problems, including physical health conditions. The identification of depression in the latter is covered in another NICE guideline, depression in people with chronic physical health problems (NICE, 2009). This guideline focuses on identifying depression in primary care and community settings.

Studies indicate that up to 50% of depressed patients are not recognised in primary care (Williams et al., 1995), a view which is supported by a recent meta-analysis of 37 studies of GPs’ unassisted ability to detect depression (Mitchell et al, 2009). Mitchell et al suggest that GPs’ are able to rule-out depression in most people who are not depressed with reasonable accuracy but may have difficulty diagnosing depression in all true cases. Although as noted in section 1.2.2 this under-recognition of depression is focused more on mild depression than on moderate or severe depression (Kessler et al, 2003).

#### 5.2.2 Identifying Depression - the Primary Care Perspective

For over 40 years, it has been suggested that GPs fail to accurately diagnose depression (Goldberg et al., 1992; Kessler et al., 2002). Some studies, however, suggest (Kessler et al., 2002; Thompson, Kinmonth & Stevens, 2000) that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient-doctor relationship and it is milder forms, which may recover spontaneously, that go undetected and un-treated. More recent studies suggest in primary care the probability of prescribing antidepressants was associated to the severity of the depression, although almost half of the patients who were prescribed antidepressants were not depressed (Kendrick et al., 2005). Other authors draw attention to the dangers of the erroneous diagnosis of depression in patients with a slight psychological malaise and little functional repercussion leads to the risk of unnecessary and potentially dangerous medicalization (Aragones, Pinol and Labad, 2006). Mitchell (personal communication; under review) conducted a systematic search, meta-analysis and Bayesian analysis of 107 studies that examined the diagnostic accuracy of general practitioners unassisted clinical ability to detect robustly defined depression, using expert structured or semi-structured interviews as a gold standard. He suggested that General Practitioners are able to rule-out depression in most people who are not depressed with reasonable accuracy but have difficulty diagnosing depression in all true cases. Yet given the modest prevalence of depression in most primary care settings the number of false positive errors is larger than the number of false negatives. Further work is needed to examine the subsequent outcome...
of those false positive and false negative diagnoses and also to clarify the accuracy of general practitioners in diagnosing anxiety disorders, adjustment disorders and broadly defined distress.

Reasons for lack of recognition fall into four themes: the patient, practitioner, organisational and societal.

**Patient factors**

People may have difficulty in presenting their distress and discussing their concerns with their doctor, especially when they are uncertain that depression is a legitimate reason for seeing the doctor (Gask et al., 2003). The MaGPIe Research Group (2005a; 2005b) suggests that the relationship is important, and that GPs are, in fact, effective at identifying mental health problems in patients they know and that some people believe that the GP is not the right person to talk to, or that such symptoms should not be discussed at all. Negative perceptions about the value of consulting a GP for mental distress may explain low rates of help-seeking among young adults, including those with severe distress (Biddle, et al., 2006). The depressed person may feel that they do not deserve to take up the doctor's time, or that it is not possible for doctors to listen to them and understand how they feel (Gask et al., 2003; Pollock & Grime, 2002).

When depressed, older adults in particular may complain less of depressed mood and instead somatise (Rabins, 1996). Physical co-morbidity may also make the interpretation of depressive symptoms difficult. People may have beliefs that prevent them from seeking help for depression such as a fear of stigmatisation, or that antidepressant medication is addictive or they may misattribute symptoms of major depression for ‘old age’, ill health or grief. Although depression is more frequent in women, differential reporting of symptoms may lead to depression being under-diagnosed in men. From the patient perspective, contact with primary care has been reported to be of little significance when set against the magnitude of their other experienced problems (Rogers, May & Oliver, 2001).

**Practitioner factors**

The construction of ‘depression’ as a clinical condition is contested amongst GPs (Pilgrim & Dowrick, 2006; Chew-Graham et al., 2000; May et al., 2004). Primary care practitioners may lack the necessary consultation skills or confidence to correctly diagnose late-life depression. They may be wary of opening a ‘Pandora’s box’ in time-limited consultations and instead collude with the patient in what has been called ‘therapeutic nihilism’ (Burroughs et al., 2006). In deprived areas primary care physicians have been shown to view depression as a normal response to difficult circumstances, illnesses or life events (May et al., 2004) and depression may be under-diagnosed because of dissatisfaction with the types of treatment that can be offered, especially a lack of availability of psychological interventions.

**Organisational factors**

The trend in the United Kingdom (UK) for mental health services to be ‘carved out’ from mainstream medical services may disadvantage depressed people who may have difficulties in attending different sites for mental and physical disorders.
The role of the organisation within which these health professionals work has been cited as a major barrier to encouraging disclosure of symptoms and a lack of resources, both personal and places to refer women to, added to professionals’ reluctance to encourage patients to disclose their distress (Chew-Graham et al., 2008; Popay et al, 2007).

Societal factors

The barriers described are likely to be particularly difficult for economically poor and minority populations who tend to have more ill-health and are more disabled. The often-described barrier of stigma is to be set against the arguments that depression is a social construction with the medicalisation of chronic distress or unhappiness (Pilgrim & Bentall, 1999; Ellis, 1996). Thus, it is suggested that chronic unhappiness is not "treatable" in the normal curative or therapeutic sense, but this should not prevent the doctor’s quest to diagnose and cure, but enlarges horizons to recognizing and accepting our own human reactions to patients and understanding how the physician can meet their needs.

Case identification of depression in people with some chronic conditions is now part of routine clinical work for general practitioners as stipulated by the GMS Contract (Ellis, 1996). Evidence however, suggests that such ultra-short screening instruments may fail to detect depression (Mallen & Peat, 2008). It has been suggested that using an additional question “is this something with which you would like help?” (Arroll, 2005) may improve the performance of the screening questions. Others, however, caution that the use of such screening instruments may encourage practitioners to take a reductionist, biomedical approach, diverting them from a broader bio-psychosocial approach to both diagnosis and management of depression (Dowrick, 2004).

5.2.3 Shifting the emphasis from screening to identification

The identification of people with a disease is often referred to as screening. Screening has been defined as the systematic application of a test or enquiry to identify individuals at high risk of developing a specific disorder who may benefit from further investigation or preventative action (Peckham & Dezateux, 1998). Screening programmes detect people at risk of having the condition or at risk of developing the condition in the future. They do not establish a diagnosis but give some indication of any action that may be required, such as further diagnostic investigation, closer monitoring or even preventative action. Screening is not necessarily a benign process (Marteau, 1989). Since screening tools are never 100% accurate, people who are incorrectly identified as being at risk of developing a condition (false positives) can be subject to further possibly intrusive, harmful or inappropriate investigations, management or treatment. Those falsely identified as not being at risk of developing a condition (false negatives) will also suffer by not being given the further investigation they need.

Critics of routine screening for depression have advanced a number of arguments against it. These include the low positive predictive value of the instruments (that is, many patients who screen positive do not have depression), the lack of empirical evidence for benefit to patients, the expenditure of resources on patients who may gain little benefit (many patients who are detected by such an approach may be mildly
depressed and recover with no formal intervention), and the diversion of resource away from more seriously depressed and known patients who may be inadequately treated as a result. These issues are well covered by Palmer and Coyne (2003) in their review of screening for depression in medical settings. Palmer and Coyne also go on to make a number of suggestions for improving recognition, including ensuring effective interventions for those identified, focusing on patients with previous histories of depression and people known to have a high risk of developing depression such as those with a family history of the condition or chronic physical health problems with associated functional impairment. Other (e.g. Pignone et al, 2002; MacMillan et al, 2005) have, however, recommend the use of screening of depression for the general adult population but it should be noted that the systematic review of interventions conducted in support of the recommendations by these groups have included the need for follow–up interventions. The effectiveness of such interventions (e.g. feedback to patients or case management) is considered below and the GDG felt it important first address the value of case identification systems alone, before going on to consider the benefits of integrated systems.

5.2.4 Targeting identification

The original NICE guideline on depression, in addition to other NICE mental health guidelines, considered the case for general population screening for a number of mental health disorders and concluded that it should only be undertaken for specific high-risk populations where benefits outweigh the risks (for example, NICE, 2004a, 2005a). These were those with a history of depression, significant physical illnesses causing disability, or other mental health problems, such as dementia.

A history of depression has been identified a significant factor in future episodes. For example, a study of 425 primary care patients found that 85% of those who were depressed have had at least one previous episode (Coyne et al., 1999). In fact, having a history of depression produced a positive predictive value (see below) roughly equal to that produced by using a depression case-finding instrument (CES-D) (0.25 compared with 0.28). This suggest that careful assessment of relevant instruments is required if a number currently in use appear to have no more predictive value that a history of depression. (It should be noted that depression can frequently be comorbid with other mental health problems, including borderline personality disorder (e.g. Skodol et al., 1999; Zanarini et al., 1998), and dementia (Ballard et al., 1996a, b)).

The following sections review available case identification instruments.

Definition and aim of topic of review

Case identification instruments were defined in the review as validated psychometric scales that were used to identify people with depression. The review was limited to identification tools likely to be used in UK clinical practice, that is, the Beck Depression Inventory, Patient Health Questionnaire, General Health Questionnaire, Centre of Epidemiology Studies-Depression, Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Zung Self Rated Depression Scale, and any 1 or 2 item measures. The identification tools were assessed in consultation (which included primary care and general medical services) and community populations. ‘Gold standard’ diagnoses were defined as DSM-IV or ICD-10 diagnosis of depression. Studies were sought which compared case identification with one of the above instruments with diagnosis of depression based on DSM-IV or ICD-10 criteria. Studies that did not clearly state the
comparator to be DSM-IV or ICD-10, used a scale with greater than 28 items, or did not provide sufficient data to be extracted in the meta-analysis were excluded.

**Summary statistics used to evaluate identification instruments**

**Sensitivity, specificity, positive predictive validity, negative predictive validity**

The terms sensitivity and specificity are used in relation to identification methods discussed in this chapter.

The sensitivity of an instrument refers to the proportion of those with the condition who test positive. An instrument that detects a low percentage of cases will not be very helpful in determining the numbers of patients who should receive a known effective treatment, as many individuals who should receive the treatment will not do so. This would lead to an under-estimation of the prevalence of the disorder, contributes to inadequate care and makes for poor planning and costing of the need for treatment. As the sensitivity of an instrument increases, the number of false negatives it detects will decrease.

The specificity of an instrument refers to the proportion of those without the condition being tested for who test negative. This is important so that well individuals are not offered treatments they do not need. As the specificity of an instrument increases, the number of false positives will decrease.

To illustrate this: from a population in which the point prevalence rate of depression is 10% (that is, 10% of the population has depression at any one time), 1,000 people are given a test which has 90% sensitivity and 85% specificity. It is known that 100 people in this population have depression, but the test detects only 90 (true positives), leaving 10 undetected (false negatives). It is also known that 900 people do not have depression, and the test correctly identifies 765 of these (true negatives), but classifies 135 incorrectly as having depression (false positives). The positive predictive value of the test (the number correctly identified as having depression as a proportion of positive tests) is 40% (90/90+135), and the negative predictive value (the number correctly identified as not having depression as a proportion of negative tests) is 98% (765/765 +10). Therefore, in this example, a positive test result is correct in only 40% of cases, whilst a negative result can be relied upon in 98% of cases.

The example above illustrates some of the main differences between PPVs and NPVs in comparison with sensitivity and specificity. For both PPVs and NPVs prevalence explicitly forms part of their calculation (see Altman and Bland, 1994a). When the prevalence of a disorder is low in a population this is generally associated with a higher NPV and a lower PPV. Therefore although these statistics are concerned with issues probably more directly applicable to clinical practice (for example, the probability that a person with a positive test result actually has depression) they are largely dependent on the characteristics of the population sampled and cannot be universally applied (Altman and Bland, 1994a).

On the other hand, sensitivity and specificity do not necessarily depend on prevalence of depression (Altman and Bland, 1994b). For example, sensitivity is concerned with the performance of an identification test conditional on a person having depression. Therefore the higher false positives often associated with samples of low prevalence will not affect such estimates. The advantage of this approach is that sensitivity and
specificity can be applied across populations (Altman and Bland, 1994b). However, the main disadvantage is that clinicians tend to find such estimates more difficult to interpret.

When describing the sensitivity and specificity of the different instruments, the GDG defined ‘excellent’ as values above 0.9, ‘good’ as 0.8 to 0.9, ‘moderate’ as 0.5 to 0.7, ‘low’ as 0.3 to 0.5, and ‘poor’ as less than 0.3.

**Receiver operating curves**

The qualities of a particular tool are summarised in a receiver operator characteristic (ROC) curve, which plots sensitivity (expressed as %) against (100-specificity) (Figure 3).

![ROC curve](image)

**Figure 3**

A test with perfect discrimination would have an ROC curve that passed through the top left hand corner that is it would have 100% specificity and pick up all true positives with no false positives. Whilst this is never achieved in practice, the area under the curve (AUC) measures how close the tool gets to the theoretical ideal. A perfect test would have an AUC of 1, and a test with AUC above 0.5 is better than chance. As discussed above, since these measures are based on sensitivity and 100-specificity theoretically these estimates are not affected by prevalence.

**Negative and positive likelihood ratios**

Negative (LR-) and positive (LR+) likelihood ratios are thought not to be dependent on prevalence. LR- is calculated by sensitivity/1-specificity and LR+ is 1-sensitivity/specificity. A value of LR+ >5 and LR- <0.3 suggests the test is relatively accurate (Fischer et al., 2003).

**Diagnostic Odds ratios**

The diagnostic odds ratio is LR+/LR-, a value of 20 or greater suggests a good level of accuracy (Fischer et al., 2003).

**Databases searched and inclusion/exclusion criteria**
The review team conducted a new systematic search for cross-sectional studies to assess tools for identifying depression. This was undertaken as a joint review for this guideline and the guideline for depression in chronic physical health problems (NICE, 2004). Information about the databases searched and the inclusion/exclusion criteria used are in Table 6.

Table 6 Databases searched and inclusion/exclusion criteria for the effectiveness of case identification instruments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, Cochrane Library</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to February 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>Cross-sectional studies</td>
</tr>
<tr>
<td>Patient population</td>
<td>People in primary care, community, and general hospital settings</td>
</tr>
<tr>
<td>Instruments</td>
<td>Beck Depression Inventory, Patient Health Questionnaire, General Health Questionnaire, Centre of Epidemiology Studies-Depression, Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Zung Self Rated Depression Scale, and any 1 or 2 item measures of depression</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Sensitivity, Specificity, area under the curve, diagnostic odds ratio, positive likelihood, negative likelihood</td>
</tr>
</tbody>
</table>

Studies considered

A total of 126 studies met the eligibility criteria of the review, 54 studies were conducted in consultation samples, 45 were on people with chronic physical health problems, and 50 were on older people (over 65 years of age). Of these studies 16 were on the PHQ-9, five on the PHQ-2, six on the Whooley, 19 on the BDI, 9 on the BDI: short form, two on the GHQ-28, 12 on the GHQ-12, 17 on CES-D, 20 on the GDS, 11 on the GDS-15, 16 on HADS-D, five on HADS-total, seven on one item measures (see appendix 17 for further details).

In addition, 251 studies were excluded from the analysis. The most common reason for exclusion was a lack of a gold standard (DSM/ICD) comparator (see appendix 17 for further details).

5.2.5 Evaluating identification tools for depression

A bivariate diagnostic accuracy meta-analysis was conducted using Stata 10 with the midas (Dwamena, 2007) commands in order to obtain pooled estimates of sensitivity, specificity, likelihood ratios and diagnostic odds ratio (for further details, see Methods Chapter). To maximize the available data we extracted the most consistently reported and recommended cut-off points for each of the scales (Table 7).

Heterogeneity is usually much greater in meta-analyses of diagnostic accuracy studies compared with randomised controlled trials (Cochrane Collaboration, 2008; Gilbody et al., 2007). Therefore a higher threshold for acceptable heterogeneity in such meta-
analyses is required. However when pooling studies resulted in I² >90%, meta-
analyses were not conducted.

Table 7 Cut off points used (if available) for each of the identification tools (adapted from Pignone et al., 2002; Gilbody et al., 2007)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Cut off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td></td>
</tr>
<tr>
<td>21 items</td>
<td>13</td>
</tr>
<tr>
<td>13 items</td>
<td>4</td>
</tr>
<tr>
<td>Primary care version</td>
<td>4</td>
</tr>
<tr>
<td>PHQ</td>
<td></td>
</tr>
<tr>
<td>9 items</td>
<td>10</td>
</tr>
<tr>
<td>2 items</td>
<td>3</td>
</tr>
<tr>
<td>2 items (Whooley version)</td>
<td>1</td>
</tr>
<tr>
<td>GHQ</td>
<td></td>
</tr>
<tr>
<td>28 items</td>
<td>5</td>
</tr>
<tr>
<td>12 items</td>
<td>3</td>
</tr>
<tr>
<td>HADS-D</td>
<td>8-10 mild, 11-14 moderate</td>
</tr>
<tr>
<td></td>
<td>15+severe</td>
</tr>
<tr>
<td>CES-D</td>
<td>16</td>
</tr>
<tr>
<td>GDS</td>
<td></td>
</tr>
<tr>
<td>30 item</td>
<td>10</td>
</tr>
<tr>
<td>15 items</td>
<td>5</td>
</tr>
<tr>
<td>5 items</td>
<td>?</td>
</tr>
<tr>
<td>Zung</td>
<td>50 mild, 60 moderate, 70 severe</td>
</tr>
</tbody>
</table>

Table 7 summarizes the results of the meta-analysis in terms of pooled sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, and diagnostic odds ratios. Additional sub-group analyses were conducted for older adults.

**Patient Health Questionnaire (PHQ)**

The patient health questionnaire developed out of the more detailed PRIME-MD (Spitzer, Williams, Kroenke et al., 1994). There are three main instruments that have been developed from this scale; the PHQ-9 (Spitzer, Kroenke & Williams, 1999), PHQ-2 (Kroenke, Spitzer & Williams, 2003) and the “Whooley questions” (Wholley et al, 1997).

The PHQ-9 has nine items and has a cut off of 10. Although the PHQ-2 and the Whooley questions use the same two items the difference is that while the PHQ-2 follows the scoring format of the PHQ-9 (Likert scales) the Whooley version dichotomizes the questions (yes/no) and has a cut of 1 compared with 3 for the PHQ-2.

For the PHQ-9 in consultation samples (people in primary care or general medical settings) there was relatively high heterogeneity (although of a similar level to most other scales) (I²= 74.04 %). The PHQ-9 was found to have good sensitivity (0.84, CIs 0.77, 0.88) and specificity (0.87, CIs 0.78, 0.93). The diagnostic odds ratio (35.1, CIs 14.61, 84.33) indicated a high level of diagnostic accuracy.

The PHQ-2 could not be meta-analysed as there was very high heterogeneity. The Whooley questions analysis included studies both on consultation and chronic physically ill samples as there were too few studies to break down by population. This
scale was found to have high sensitivity (0.92, CIs 0.89, 0.95) but lower specificity (0.63, CIs 0.50, 0.75). The diagnostic odds ratio (20.67; 12.00, 35.61) suggested a relatively good level of accuracy.

It was not possible to conduct meta-analysis on the effects of any of the PHQ scales or the Whooley questions on older adults due to a lack of data (one study each on the PHQ-9, PHQ-2, and Whooley).

**Beck Depression Inventory (BDI)**

Beck originally developed the BDI in the 1960s (Beck et al 1961) and subsequently updated the original 21-item version (Beck et al 1979; Beck et al., 1996). This scale has been used widely as a depression outcome measure and is also used to provide data on the severity of depression, commonly 13 is used a cut-off in identification studies.

In addition, the cognitive-affective sub-scale of the BDI has often been used to identify depression. Furthermore, the BDI-fast screen has been specifically developed for use in primary care (Beck, et al., 1997).

For the 21 item BDI there was high heterogeneity for consultation samples (I² =88.61%). The BDI appeared to perform relatively well in terms of sensitivity (0.85, CIs 0.79, 0.90) and specificity (0.83, CIs 0.70, 0.91). This was also consistent with the diagnostic odds ratio (29.29, CIs 15.103, 56.79). However, this is based on only four studies so it is difficult to draw firm conclusions. Subgroup analyses on older adults were also not possible as there were only two studies for this population.

**BDI non-somatic items**

Data from BDI fast-screen (Beck et al., 1997) and BDI: short form (Beck et al., 1979; Beck et al., 1996) were combined to assess the impact of removing somatic items as data from both scales were relatively sparse. There was sufficient, although relatively low, consistency between studies to assess these scales (BDI: non-somatic) in consultation (I² = 75.71%) populations. There was high sensitivity (0.92, CIs 0.61, 0.99) but less specificity (0.76, CIs 0.65, 0.84). The diagnostic odds ratio indicated a high level of accuracy (36.01, CIs 3.81, 340.47). A meta-analysis was not possible for older adults as there were only two studies.

**General Health Questionnaire (GHQ)**

The GHQ (Goldberg & Williams, 1991) was developed as a general measure of psychiatric distress and measures a variety of constructs such as depression and anxiety. The main version used for identification purposes are the GHQ-28 (cut-off of 5) and GHQ-12 (cut-off of 3).

There were only two trials of the GHQ-28, therefore meta-analysis was not conducted. In addition, while there were more studies on the GHQ-12 there was very high heterogeneity (I² >90%) for studies on consultation populations therefore these studies were also not meta-analysed. Moreover, a meta-analysis specifically for older adults was not possible due to a lack of studies (two studies).

**Hospital Anxiety and Depression Scale (HADS)**
The HADS (Zigmund & Snaith, 1983) is a measure of depression and anxiety developed for people with physical health problems. The depression sub-scale has 7 items and the cut-off is 8-10 points.

A total of 21 studies were included in the review, however meta-analysis could not be conducted due to very high heterogeneity ($I^2 > 90\%$) for all subgroups including consultation populations and older adults.

**Center for Epidemiological Studies Depression Scale (CES-D)**

The CES-D (Radloff, 1977) has 20 items and the cut-off is 16. This measure is also relatively commonly used as an outcome measure. There are various short forms of the CES-D including an 8-, 10- and 11-item scale.

There was high heterogeneity in the consultation ($I^2 = 84.63\%$) sample. For the older adult population, Harringsma and colleagues (2004) was removed from the analysis resulting in acceptable heterogeneity ($I^2 = 61.09\%$).

For consultation samples sensitivity was high (0.86, CIs 0.78, 0.92) but specificity was lower (0.75, CIs 0.68, 0.81). The diagnostic odds ratio indicated less of accuracy (18.71, CIs 12.23, 28.62).

For older adults, there was relatively low sensitivity (0.78, CIs 0.68, 0.86) and higher specificity (0.83, CIs 0.76, 0.88) and a slightly lower diagnostic odds ratio (17.48, CIs 10.73, 28.46).

**Geriatric Depression Scale (GDS)**

The GDS was developed to assess depression in older people. The original 30 item scale (cut-off of 10 points) was developed by Yesavage and Brink (1983) and more recently a 15 item (cut-off 5 points) versions has been validated.

Despite the large number of studies (18 studies), there was very high heterogeneity ($I^2 > 90\%$) for the GDS therefore no meta-analyses could be conducted. However, it was possible to analyse studies on the GDS-15.

In the consultation population there was higher sensitivity (0.87, CIs 0.80, 0.91) but specificity (0.75, CIs 0.69, 0.80) was relatively low. The diagnostic odds ratio was just below 20 (18.98, CIs 10.85, 33.20). Heterogeneity was relatively acceptable ($I^2 = 70.96\%$).

No sub-group analyses for older people were conducted as all participants were over 65 years of age.

**Zung Self-Rating Depression Scale**

The self-rating depression scale was developed by Zung (Zung, 1965) and has been revised (Guy, 1976). This has 20 items where a cut off of 50 is typically used. It is sometimes used as an outcome measure as well.
There were five studies using the Zung self rating depression scale. Data could only be combined across populations as there were not enough studies to conduct sub-group analyses (two studies on older adults, three studies on consultation samples). There was relatively good sensitivity (0.83, CIs 0.68, 0.91) and specificity (0.85, CIs 0.68, 0.91). In addition, the diagnostic odds ratio suggested relatively good overall accuracy (27.61, CIs 12.43, 61.38). However, heterogeneity was relatively high (I² = 86.33%).

**One item measures**

There were five studies found to assess a one-item measure in consultation samples. There was a relatively good sensitivity (0.84, CIs 0.78, 0.89) but very low specificity (0.65, CIs 0.55, 0.73). The diagnostic odds ratio indicated a lack of accuracy (9.67, CIs 5.35, 17.46). It was not possible to conduct a subgroup analysis of older adults as there were only two studies.

**Table 8. Evidence summary of depression identification instruments in primary care, chronic physical health, and older populations**

<table>
<thead>
<tr>
<th>Population and instrument</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio+</th>
<th>Likelihood ratio -</th>
<th>Diagnostic Odds ratio</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ9 Consultation samples: 8 studies</td>
<td>0.84 (0.77, 0.88)</td>
<td>0.87 (0.78, 0.93)</td>
<td>6.61 (3.59, 12.19)</td>
<td>0.19 (0.13, 0.27)</td>
<td>35.10 (14.61, 84.33)</td>
<td>0.90 (0.87, 0.92)</td>
</tr>
<tr>
<td>Whooley* all populations: 6 studies</td>
<td>0.95 (0.91, 0.97)</td>
<td>0.69 (0.56, 0.79)</td>
<td>3.02 (2.06, 4.43)</td>
<td>0.08 (0.04, 0.15)</td>
<td>39.46 (14.76, 105.46)</td>
<td>0.94 (0.92, 0.96)</td>
</tr>
<tr>
<td>BDI Consultation samples: 4 studies</td>
<td>0.85 (0.79, 0.90)</td>
<td>0.83 (0.70, 0.91)</td>
<td>5.14 (2.83, 9.32)</td>
<td>0.18 (0.12, 0.24)</td>
<td>29.29 (15.10, 56.79)</td>
<td>0.90 (0.87, 0.92)</td>
</tr>
<tr>
<td>BDI-non somatic items Consultation sample: 5 studies</td>
<td>0.92 (0.61, 0.99)</td>
<td>0.76 (0.65, 0.84)</td>
<td>3.75 (2.37, 5.95)</td>
<td>0.10 (0.02, 0.70)</td>
<td>36.01 (3.81, 340.47)</td>
<td>0.86 (0.82, 0.88)</td>
</tr>
<tr>
<td>CES-D Consultation sample: 8 studies</td>
<td>0.86 (0.78, 0.92)</td>
<td>0.75 (0.68, 0.81)</td>
<td>3.41 (2.78, 4.19)</td>
<td>0.18 (0.12, 0.29)</td>
<td>18.71 (12.23, 28.62)</td>
<td>0.86 (0.83, 0.89)</td>
</tr>
<tr>
<td>Older adults: 5 studies</td>
<td>0.78 (0.68, 0.86)</td>
<td>0.83 (0.76, 0.88)</td>
<td>4.56 (3.31, 6.27)</td>
<td>0.26 (0.18, 0.38)</td>
<td>17.48 (10.73, 28.46)</td>
<td>0.88 (0.84, 0.90)</td>
</tr>
<tr>
<td>GDS-15: Consultation sample: 11 studies</td>
<td>0.87 (0.80, 0.91)</td>
<td>0.75 (0.69, 0.80)</td>
<td>3.40 (2.73, 4.24)</td>
<td>0.18 (0.12, 0.27)</td>
<td>18.98 (10.85, 33.20)</td>
<td>0.86 (0.83, 0.89)</td>
</tr>
<tr>
<td>Zung* All populations: 5 studies</td>
<td>0.83 (0.68, 0.91)</td>
<td>0.85 (0.68, 0.91)</td>
<td>5.64 (2.63, 12.11)</td>
<td>0.20 (0.11, 0.37)</td>
<td>27.61 (12.43, 61.38)</td>
<td>0.90 (0.88, 0.93)</td>
</tr>
<tr>
<td>1-item Consultation sample: 6 studies</td>
<td>0.84 (0.78, 0.89)</td>
<td>0.65 (0.55, 0.73)</td>
<td>2.38 (1.81, 3.13)</td>
<td>0.25 (0.17, 0.36)</td>
<td>9.67 (5.35, 17.46)</td>
<td>0.85 (0.82, 0.88)</td>
</tr>
</tbody>
</table>

* It was not possible to conduct separate sub-group analyses for consultation and chronic physical illness samples due to lack of studies for the Zung and Whooley questions
Comparing validity coefficients for case identification tools in older adults
The impact of old age, and residing in a nursing home on the validity coefficients of the case identification tools reviewed above were assessed through meta-regression. Due to lack of data the PHQ-2, Whooley, Zung, and One-Item measures were unable to be included in the analysis.

The GDS and GDS-15 were almost always used for older adults therefore the validity of these measures in older adults is already accounted for in the previous analysis. However, further analyses were conducted to assess the validity of these measures in nursing home populations.

**Table 9 Meta-regressions assessing the impact of differences within populations of studies**

<table>
<thead>
<tr>
<th>Population and instrument</th>
<th>Beta-Coefficient</th>
<th>$I^2$ (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing over 65s with under 65s</td>
<td>Sensitivity = 1.23 Specificity = 1.84</td>
<td>Joint $I^2$ = 0</td>
<td>0.65 0.73 0.83</td>
</tr>
<tr>
<td>BDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing over 65s and under 65s</td>
<td>Sensitivity = 1.58 Specificity = 0.74</td>
<td>Joint $I^2$ = 0%</td>
<td>0.34 0.79 0.65</td>
</tr>
<tr>
<td>BDI-non somatic items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing over 65s and under 65s</td>
<td>Sensitivity = 1.58 Specificity = 2.12</td>
<td>Joint $I^2$ = 58.64</td>
<td>0.80 0.02 0.09</td>
</tr>
<tr>
<td>CES-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing over 65s with under 65s</td>
<td>Sensitivity = 1.23 Specificity = 1.61</td>
<td>Joint $I^2$ = 43.30</td>
<td>0.09 0.18 0.17</td>
</tr>
<tr>
<td>GDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing nursing home and non-nursing home</td>
<td>Sensitivity = 1.54 Specificity = 1.13</td>
<td>Joint $I^2$ = 0%</td>
<td>0.85 0.65 0.80</td>
</tr>
<tr>
<td>GDS-15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing nursing home and non-nursing home</td>
<td>Sensitivity = 2.14 Specificity = 0.91</td>
<td>Joint $I^2$ = 0%</td>
<td>0.36 0.34 0.44</td>
</tr>
<tr>
<td>GHQ-12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparing over 65s to under 65s</td>
<td>Sensitivity = 0.43 Specificity = 1.45</td>
<td>Joint $I^2$ = 11.28%</td>
<td>0.14 0.33 0.32</td>
</tr>
</tbody>
</table>

**Older adults**

There was some evidence that the BDI versions with no somatic items ($p=0.02$) were associated with improved specificity in older adults compared with people under 65 years of age. There was a trend towards reduction in sensitivity for the CES-D ($p=0.09$) in older adults compared with people under 65 years of age. For all other scales there were no statistically significant differences. However, there was often a lack of power in most studies as only a small number of studies on older adults were found for most scales.
People in nursing homes

Only the GDS and GDS-15 provided sufficient data on people in nursing homes. There appeared to be limited differences in validity when assessing people either in nursing homes or in the community for both scales.

5.2.6 Case identification in black and minority ethnic populations

Culture and ethnicity are known to influence both the prevalence and incidence of mental illnesses, including common mental disorders such as depression (Bhui, 2001). For example Shaw et al (1999) indicated that women from BME groups had an increased incidence of common mental disorders including both depression and anxiety. Such findings cannot wholly be explained by differences in factors such as urbanicity, socioeconomic status and perceptions of disadvantage (Weich et al. 2004; Bhugra and Cochrane, 2001). Furthermore, culture is known to exert an influence on the presentation and subjective experience of illness. What an individual constitutes as an illness, and whom they seek for remedy are all affected by an individual’s culture and ethnicity. With regards to depression, a number of findings have indicated both ethnic and cultural variations in the subjective experience and initial presentation of the illness. For example, Commander et al. (1997) are amongst researchers to suggest that ‘Asians’ which included Indian, Bangladeshi and Pakistani people, are more likely to present to their GP with physical manifestations, and do so more frequently than their White counterparts. However, both Wilson and MacCarthy (1994) and Williams and Hunt (1997) have indicated that despite this increased GP contact and even when a psychological problem is present, GPs are less likely to detect depression and more likely to diagnose ‘Asians’ with a physical disorder.

There is an increasing evidence base to suggest that the reduced identification of depression in different ethnic and cultural groups may be one barrier to receiving appropriate treatment, including both psychological and pharmacological interventions. For example, research has suggested that across mental disorders, particular ethnic groups are often underrepresented in primary care services (Bhui et al. 2003, DH, 2008), whereas a healthcare commission survey highlighted how both Asian and Black/Black British people were less likely to be offered ‘talking therapies’ (DH, 2008).

Despite an increased awareness that different cultural and ethnic factors may influence the presentation of depression, the majority of case identification tools used in routine clinical practice were originally created and validated on White populations (Husain, 2007). Owing to the above evidence indicating ethnic and cultural variations in the presentation and subjective experience of illness, one proposed method to improve the identification of depression in black and minority ethnic participants is to assess the validity of ethnic specific screening tools. Such tools, most of which are still early in their development, aim to incorporate specific cultural idioms and descriptions commonly reported by people from a particular ethnic or cultural group.

Definition and aim of topic of review
The review considered any ethnic specific case identification instruments aimed at detecting depression in black and minority ethnic populations. This included new identification tools designed for different cultural and ethnic groups, and also existing scales modified and tailored towards the specific needs of particular black and minority ethnic groups. Although, the GDG are aware of papers from outside of the UK, and most notably from the US, the decision was taken to only include UK studies. As discussed above, the presentation and subjective experience of depression is known to be influenced by cultural and ethnic factors, therefore it was felt that findings from non-UK ethnic minority populations would not be generalisable due to the differences both ethnically and culturally between the populations studied. The review also assessed the validity of established depression case identification tools for different ethnic minority populations within the UK.

**Databases searched and inclusion/exclusion criteria**

The review team conducted a new systematic search for cross-sectional studies aiming to assess tools for identifying depression. This was undertaken as a joint review for this guideline and the guideline for depression in chronic physical health problems. Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 10.

<table>
<thead>
<tr>
<th>Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological interventions.</th>
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<tr>
<td><strong>Electronic databases</strong></td>
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<td><strong>Date searched</strong></td>
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<td><strong>Study design</strong></td>
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<td><strong>Instruments</strong></td>
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<td><strong>Outcomes</strong></td>
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6 Papers assessing the validity of established scales in UK black and minority ethnic populations were required to have a Gold standard diagnosis defined as DSM-IV or ICD-10 diagnosis of depression.
Studies considered

A total of four studies met the eligibility criteria of the review. All four papers were conducted within the community or primary care. One included study compared the Amritsar Depression Inventory (ADI) to the GHQ-12, whereas two studies assessed the Caribbean Culture-Specific Screen for emotional disorders (CCSS) compared to the GDS. Only one study assessed the validity of an established scale, namely the PHQ-9 in a UK black and minority ethnic population, namely people of Pakistani family origin (see appendix 17 for further details).

In addition, ten studies were excluded from the analysis. The most common reason for exclusion was non-UK based study/population or paper presented no usable evaluation of a screening tool (see appendix 17 for further details).

Evaluating identification tools for depression in BME populations

Due to both the paucity of data on ethnic specific scales in the UK and differences in the populations and instruments investigated, it was not possible to conduct a meta-analysis of the included studies. The findings from the included studies were instead summarised in a narrative review.

Amritsar Depression Inventory (ADI)

The ADI is a culturally specific instrument developed in the Punjab in India and is aimed at detecting depression in the Indian subcontinent Punjabi population (Singh et al. 1974). The 30-item dichotomous (yes/no) questionnaire was developed on the basis of 50 statements commonly used by Punjabi people with depression. The screen development process also utilised frequently used ‘illness statements’ and common descriptions of signs and symptoms of depression prevalent in the psychiatric literature.

Using the ADI and the GHQ-12, Bhui et al. (2000) screened both Punjabi and White English attendees of five primary care practices in South London. Throughout the study, a cultural screen assessing self-affirmed cultural origin was applied to detect both Punjabi and White English participants. To overcome any additional barriers due to language, the screening tools were administered in English, Punjabi or a combination of the two, depending on the preference of the participant. A two-phase screening protocol was applied in which all ‘probable cases’, e.g. those scoring ≥2 on the GHQ or ≥5 on the ADI and one third of ‘probable non-cases’ proceeded to a second interview in which the CIS-R was administered by a bilingual psychiatrist.

Results of the validity coefficients and ROC curve analysis using the standard CIS-R thresholds for depression indicated that whilst the GHQ-12 performed well across both groups, culture had an impact on the validity co-efficient of the ADI. In particular, although performing in line with the GHQ-12 for the White English participants, the ADI performed worse in detecting depression in the Punjabi participants. Results indicated that the ADI was no better than chance in identifying cases of depression,

7 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).
particularly for Punjabis who had been resident in the UK for more than 30 years. One additional finding of interest was that the optimal cut-off for the ADI was higher for the Punjabi compared to their White English counterparts, although this finding was not sustained for the GHQ-12 in which the same cut-off was optimal for both groups. Analysis of the individual items of both the GHQ-12 and the ADI failed to indicate any specific items which were strongly predictive of depression caseness in either cultural group.

Caribbean Culture-Specific Screen for emotional distress (CCSS)

The CCSS (Abas et al. 1996) is a 13-item dichotomous (yes/no) culture-specific screen which was developed through a process of generating locally derived classifications of mental disorders in Caribbean people and gathering commonly used terms for emotional distress. The majority of participants interviewed in the piloting stages of the screen were from Jamaica with a number of participants identifying themselves as from other Caribbean countries including Guyana, Barbados, Trinidad and Grenada.

Two papers assessed the validity of the CCSS screen in older African-Caribbean participants living in two geographical locations in the UK, namely South London and Manchester. Both papers compared the validity of the CCSS to the GDS and utilised the Geriatric Mental State – AGECAT as a gold standard for case identification.

The sample in Abas et al. (1998) consisted of consecutive African-Caribbean primary care users aged over 60, and included both clinic attendees and those receiving home visits from primary care teams. Participants were firstly administered the CCSS, GDS-15 and the Mini-Mental State Exam (MMSE). Responders were categorised as high scorers if they scored ≥4 on either measure, whereas low scorers were those attaining less than 4 on both screens. A random sample of 80% of the high scorers and 20% of the low scorers were selected to attend a further interview. During this second stage interview, the GMS-AGECAT and a culturally specific diagnostic interview, which was informed through a process of consultation with African-Caribbean religious healers / ministers were administered to the selected participants.

Rait et al. (1999) included a community sample of African-Caribbean people aged 60 years and over. Registers for general practices with a high-proportion of African-Caribbeans were used to identify members of the community. In stage one, letters were sent to potential participants, with those who consented to take part in the study subsequently interviewed in their homes. All included participants were interviewed by one of two interviewers of similar cultural background. During this stage, three depression screens were applied, namely the GDS-15, CCSS and the Brief Assessment Schedule depression cards (BASDEC). The second stage of the study involved the home administration of the GMS-AGECAT, used as a diagnostic gold-standard for the detection of depression.

The ROC curve analyses for the papers indicated that both the GDS and the CCSS performed well in the populations, with a high level of sensitivity and specificity when using the GMS-AGECAT as a gold standard for diagnosis. In both papers, the culturally specific CCSS did not outperform the GDS. In the Abas et al. (1998) paper it was demonstrated that at certain cut-off, the GDS appeared to perform better than the CCSS, although the authors note that the small sample size prevents any meaningful test of statistical significant. As it was noted that considerable variation may exist.
amongst people of Caribbean origin from different islands e.g. Jamaica, Trinidad etc., the results of Rait et al. (1999) paper were presented for the sample as a whole and for a sub-group of Jamaican participants who constituted the majority of participants. Although slight variation existed between the two analyses, the results were similar, with the same optimal cut-off occurring in both analyses.

One important feature of the Rait et al (1999) study was that the authors sought advice from a panel of community resident African-Caribbeans regarding the acceptability of the GDS. The content of the screens were deemed acceptable, with no resulting suggestion for changes being made. Rait et al. (1999) argue that the success of case identification measures may be more dependent on the way in which the screen is delivered, for example, the cultural competence of staff and delivering the screen in a culturally sensitive way, instead of the content per se. This conclusion was supported by Abas et al. (1998) who found that a proportion of participants were more likely to discuss and disclose information during the culturally sensitive diagnostic interview, when compared to the standard GMS-AGECAT. Consequently both papers have suggested that routine clinical screens may be appropriate for black and minority ethnic participants, particularly when delivered in a culturally sensitive way.

PHQ-9

Although, a number of studies have assessed the validity of the PHQ in a range of languages and cultural settings (e.g. Han 2008, Henkel 2003), only one UK based study has assessed its validity in a black and minority ethnic group. Husain et al (2007) assessed the validity of the PHQ in Pakistanis, resident in the UK. The authors noted that unlike many screening instruments, the PHQ contains no “difficult culture specific idioms”, thus making translations into other languages possible. In the present study, the PHQ was translated and back translated into Urdu, the main language of immigrants from Pakistan, with group discussion utilised to reach a single consensus.

Consecutive primary care attendees of Pakistani family origin aged 16-64 were included in the sample. Eligible participants were identified through either their name and/or language or via direct questioning. As with the other screening studies, a two stage process was employed. All eligible participants firstly completed the PHQ in either English or Urdu depending on patient preference, with a research psychiatrist administering the screen in the case of illiteracy. In the second stage of the study, all participants were interviewed in either their home or within the primary care practice. A psychiatrist administered the Psychiatric Assessment Schedule, a semi-structured interview resulting in an ICD-10 diagnosis, in either Urdu or English dependent on preference.

Results of the ROC curve analysis indicated that the recommended cut off score of $\geq 7$ produced a sensitivity of 70.4% and a specificity of 89.3%, with a PPV of 82.6 and a NPP of 80.6. The high sensitivity and specificity at the recommended cut-off suggested that the PHQ is able to detect depression in people of Pakistani family origin, when administered in either English or Urdu. Furthermore, the authors noted that participants in this study and in a study conducted in Pakistan (Husain et al. 2000) did not experience any difficulties in understanding and answering the screening questions.
Limitations with the evidence base

It must be noted that a number of potential limitations exist in relation to the above studies. One caveat is the lack of an established gold standard for the diagnosis of depression in people from black and minority ethnic groups. Only one paper (Abas et al. 1998) used a culturally sensitive diagnostic tool as a measure of caseness. The remaining three papers compared the screens to long standing measures, predominantly based on the DSM and ICD-10 classification systems. It is argued (Bhui et al., 2000) that these measures may not be culturally specific and sensitivity to cultural differences, but are instead based on ethnocentric ideas of mental illness. Consequently, any culturally sensitive measure may not be expected to have a high sensitivity and specificity for caseness when compared to these diagnostic measures. Further research into this area is hence required to answer such questions.

A further caveat to consider is that three of the four included studies assessed consecutive primary care attendees, who may or may not be wholly representative of ethnic minorities, particularly those who experience barriers to accessing and engaging with primary care services. However, the one paper in which a community sample was recruited, were consistent with the results of the primary care suggesting the findings may be robust for each particular ethnic group under investigation.

Clinical summary for both reviews

There was very high heterogeneity found for almost all identification tools which is an important limitation of the review. Scales varied a great deal in terms of targeted populations, number of items and scoring systems. Some of the shorter item scales had very high levels of sensitivity (for example, the Whooley) but lower levels of specificity. While other scales with more items (such as the PHQ-9 and GDS-15) were slightly less sensitive but still had acceptable sensitivity and specificity.

There was also planned subgroup analyses conducted for older adults, this included scales specifically targeted at this population (for example, the GDS and GDS-15) but also all other measures reviewed. The GDS-15 appeared to be relatively effective in consultation populations. However, the large number of studies on the 30 item GDS could not be meta-analysed as there was very high heterogeneity. There was less studies on the CES-D but the available data suggested a slightly, but not statistically significant, reduced sensitivity compared with consultation populations as a whole. There were studies that targeted older adults for all of the other scales reviewed however the number of studies was too small to conduct meta-analyses for any of these measures.

There was a paucity of data concerning ethnic specific identification tools, with limited data suggesting that the scales, which may be in their developmental infancy, failing to detect depression in different ethnic and cultural groups. In all studies, validated and well researched measures such as the PHQ and the GHQ-12 outperformed the ethnic specific scales in terms of both sensitivity and specificity and in the case of the PHQ was validated in a particular black and minority ethnic group, namely Pakistanis resident in the UK.

From evidence to recommendations
The GDG noted the different nature of the scales contained in the review and their psychometric properties and the possible benefit of a two stage process of identification and diagnosis.

The first stage of case identification would require using a highly sensitive instrument that could be used in routine clinical practice with limited training and implementation difficulties. The data supported the use of the Whooley questions and given that this measure is already in current use in primary care the GDG concluded that in the first stage of case identification the Whooley questions remained an appropriate tool for depression. However, given the lack of specificity found with the Whooley it was the view of the GDG that people with a positive response would benefit from a more detailed clinical assessment which may include a more detailed instrument possessing better overall psychometric properties. The data on case finding instruments in BME groups did not identify any specific measures that in the opinion of the GDG improved upon the results obtained with the Whooley questions and therefore no specific BME recommendations on case finding tools are made. However, the need for cultural competence of staff in assessments was noted in our review of case finding instruments in BME groups and this is reflected in the recommendations. In addition in performing a more comprehensive mental health assessment, as recommended in the previous version of this guideline, the need to move beyond simple symptom counts was noted and so the recommendation from the first guideline has been amended. Other recommendations from the previous guideline remain essentially the same.

5.2.7 Clinical practice recommendations for case identification

5.2.7.1 Practitioners should be alert to possible depression (particularly in those with a past history of depression or a chronic physical illness with associated functional impairment) and consider asking patients they suspect may have depression two questions, specifically:

- During the last month, have you often been bothered by feeling down, depressed or hopeless?
- During the last month, have you often been bothered by having little interest or pleasure in doing things? [KP]

5.2.7.2 If a person answers ‘yes’ to either of the depression identification questions, a healthcare professional, who is competent in basic mental health assessment, should undertake a mental health assessment. If the healthcare professional is not competent in basic mental health assessment, a referral should be made to an appropriate professional. Where this is not the person’s GP, the GP should be informed of the referral.

5.2.7.3 When undertaking an assessment of someone with suspected depression, practitioners should consider the use of a validated measure (for example, for symptoms, functions and/or disability) in order to inform and evaluate treatment.
5.2.7.4 For people with significant language or communication difficulties, for example those with sensory impairments, practitioners should consider the use of the Distress Thermometer\(^8\) and/or asking a family member or carer about the person’s possible depressive symptoms to identify depression.

5.2.7.5 When assessing a person who may be depressed, practitioners should conduct a comprehensive assessment which takes into account the degree of impairment and/or disability associated with the possible depression, the duration of the episode, and does not rely simply on a symptom count.

5.2.7.6 When assessing need, practitioners should seek to understand how the factors set out below may have affected the development, course and severity of a person’s depression.

- the quality of interpersonal relationships
- the history of depression and other comorbid mental or physical disorders
- the past experience of, and response to, treatments
- the living conditions and degree of social isolation
- a review of any past history of mood elevation to determine if the depression may be part of a bipolar disorder (in which case they should refer to ‘Bipolar Disorder’, NICE clinical guideline 38).

Along with the person’s preferences, this assessment should guide the content of any treatment.

5.2.7.7 Practitioners should be aware that some people with depression find discussion of their problems difficult because of shame or stigma. Care should be taken to ensure that discussion takes place in settings in which confidentiality, privacy and dignity can be respected.

Depression with anxiety

5.2.7.8 When depression is accompanied by symptoms of anxiety, the first priority should usually be to treat the depression. Treatment for depression often reduces anxiety symptoms. When the patient has an anxiety disorder without depression, the NICE guideline for the relevant anxiety disorder should be followed.

Risk assessment and monitoring

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\(^8\) Distress thermometer is a single-item question screen, which will identify distress coming from any source. The patient places a mark on the scale answering: “How distressed have you been during the past week on a scale of 0 to 10?”. Scores of 4 or more indicate a significant level of distress that should be investigated further. (Roth AJ, et al. 1998. Rapid screening for psychological distress in men with prostate carcinoma. *Cancer* 82: 904-1908.)
5.2.7.9 Where a person with depression presents considerable immediate risk to self or others, urgent referral to a specialist mental health service should be arranged.

5.2.7.10 Practitioners should advise patients of the potential for increased agitation, anxiety, suicidal ideation (and for people taking antidepressants, akathisia) in the initial stages of treatment. They should actively seek out these symptoms and ensure that the person with depression knows how to seek help promptly if these are at all distressing. In the event that a patient develops marked and/or prolonged agitation (or akathisia while taking an antidepressant), the treatment should be reviewed.

5.2.7.11 When a person with depression is assessed to be at risk of suicide, practitioners should consider:

- toxicity in overdose where an antidepressant is prescribed and when determining the quantity supplied at any one time; where necessary, implement strategies to limit the amount of drug available
- the use of additional support such as more frequent direct or telephone contacts
- referral to specialist mental health services.

5.2.7.12 Practitioners should always ask a person with depression directly about suicidal ideas and intent. Where the risk of self-harm or suicide is present practitioners should assess whether the person has adequate social support and is aware of sources of help. They should arrange help appropriate to the level of risk and advise the person to seek further help if the situation deteriorates.

5.2.7.13 Practitioners should advise a person with depression and their carers to be vigilant for changes in mood, negativity and hopelessness, and suicidal ideas, particularly during high-risk periods, such as during initiation of, and changes to, any treatment plan and increased personal stress. They should be advised to contact the appropriate healthcare practitioner if concerned.

Active monitoring

In the previous guideline a recommendation was made for watchful waiting. In the process of the development of this guideline, in discussion with stakeholders and with the GDG, considerable concern was expressed about the term itself and the fact that it suggested a passive process rather than the more active process of assessment, advice and support that characterises effective interventions for people with mild depression that may spontaneously remit. In light of this, the GDG switched from the term ‘watchful waiting’ to ‘active monitoring’ and revised the original recommendation accordingly.
5.2.7.14 For people with persistent minor and mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, practitioners should:

- discuss the presenting problem(s) and any concerns that the person may have about them
- provide information about the nature and course of depression
- arrange a further assessment, normally within 2 weeks
- make contact with people who do not attend follow-up appointments.

5.3 Service delivery systems in the treatment and management of depression

5.3.1 Introduction

As indicated above there have been a considerable number of service focused developments since the development of the last guideline. In this guideline we use the overarching term enhanced care to refer to them all. This includes a number of interventions or models that often have some degree of overlap or where individual interventions are contained within large models. For example collaborative care interventions (Gilbody et al, 2006) may included stepped care (Bower and Gilbody, 2005) as a component (Katon et al., 1999; Unutzer et al., 2002)). Some of the more prominent models are listed below:

Graduated access

One way of changing access is to modify service provision at the point at which people want to access services (Rogers, Hassell & Nicolaas, 1999). This may involve ‘graduated access’ to services, including the use of ‘direct health services’ which people can access without having face to face contact with professionals and which maximise the use of new technologies such as the internet.

The consultation-liaison model

This model (e.g. Gask, Sibbald & Creed, 1997; Darling & Tyler, 1990; Creed & Marks, 1989) is a variant of the training and education model (which is outside of the scope of the guideline), in that is seeks to improve the skills of primary care professionals and improve quality of care through improvements in their skills. However, rather than the provision of training interventions which teach skills in dealing with depressed patients in general, in this model specialists enter into an ongoing educational relationship with the primary care team, in order to support them in caring for specific patients who are currently undergoing care. Referral to specialist care is again only expected to be required in a small proportion of cases. A common implementation of this model involves a psychiatrist visiting practices regularly and discussing patients with primary care professionals.
The attached professional model

In this model (e.g. Bower & Sibbald, 2000) a mental health professional takes on direct responsibility for the care of a person (usually in primary care) focusing on the primary treatment of the problem/disorder, be it pharmacological or psychological. The coordination of care remains with the general practitioner/primary care team. Contact is usually limited to treatment and involves little or no follow up beyond that determined by the specific intervention offered (for example, booster sessions in CBT).

Stepped care

Stepped care (e.g. Bower & Gilbody, 2005) is a system for delivering and monitoring treatment with the explicit aim of providing the most effective yet least burdensome treatment first to the patient. Typically stepped care starts by providing low intensive, minimal interventions. In some stepped care systems low intensity care is received by all individuals, although in some systems, patients are stepped up to a higher intensity intervention on immediate contact with the service, for example if they are acutely suicidal.

Stratified (or matched care)

This is a hierarchical model of care (e.g. van Stratten et al., 2006), moving from low to high intensity interventions, where at the patient’s point of first contact with services are matched to the level of need and the consequent treatment is determined by the assessing professional in consultation with the patient.

Case management

This describes a system where an individual health practitioner takes responsibility for the co-ordination of the care of an individual patient (e.g. Genischen et al, 2006), but is not necessarily directly involved in the provision of any intervention; this may also involve the co-ordination of follow-up.

Collaborative care

The collaborative care model (e.g. Katon et al., 2001; Wagner, Austin & von Korff, 1997) emerged from the chronic disease model and has four essential elements, they are:

- the collaborative definition of problems, in which patient defined problems are identified alongside medical problems diagnosed by health care professionals
- a focus on specific problems where targets, goals and plans are jointly developed by the patient and professional to achieve a reasonable set of objectives, in the context of patient preference and readiness
- the creation of a range of self-management training and support services in which patients have access to services that teach the necessary skill to carry out treatment plans, guided behaviour change and promote emotional support
- the provision of active and sustained follow-up in which patients are contacted at specific intervals to monitor health status, identify possible complications and check and reinforce progress in implementing the care plan.
In mental health services collaborative care also typically includes a consultation liaison role with a specialist mental health professional and generic primary care staff. It may also include elements of many of the other interventions described above.

**Current practice and aims of the review**

Over the past 20 years, there has been a growing interest in the development of systems of care for managing depression. This work has been influenced by organisational developments in healthcare in the US, such as managed care and Health Maintenance Organisations (Katon et al., 1999), developments in the treatment of depression, the development of stepped care (Davison, 2000), and influences from physical healthcare, for example chronic disease management (Wagner & Groves, 2002). A significant factor in driving these developments has been the recognition that for many people depression is a chronic and disabling disorder.

The implementation in the NHS of the various developments described in the introduction is very variable. Perhaps the most consistent model adopted has been the stepped care model within the IAPT programme but outside of demonstration sites and experimental studies (Layard, 2006; Van Stratten, 2006) there has been no consistent adoption of any single model. Resource limitations have to an extent been a significant limitation of these developments, but there have also been changes in mental health care policy which have influenced implementation, for example the varying developments of the attached professional role over the past 20 years (Bower & Sibbald, 2000).

One consistent factor that links these together is the lack of a significant evidence base for most if not all of these interventions. Perhaps the most notable exception is the evidence base for collaborative care which has grown considerably in the past 10 years and has led some (e.g. Simon, 2006) to call for the widespread implementation of collaborative care. However, with collaborative care it should be noted that the evidence base is largely from the United States and, as it is a complex intervention, care must be taken when considering its adoption in different health care systems (Campbell et al, 2003).

**Interventions included**

The GDG considered the range of interventions described above and the extent of current practice and decided to focus the reviews for this update on the following interventions: stepped care (including where possible matched care), collaborative care, the attached professional model and medication management. This was because they were the focus of considerable concern in the NHS and in the case of at least one of the models (collaborative care) considerable new evidence has emerged since the publication of the original guideline. No additional studies were found for the attached professional models, so the GDG decided that rather than performing a separate review they would comment on it, particularly in relation to collaborative care. The GDG decided to review medication management as there was evidence of increased use of this intervention in depression but considerable uncertainty as to whether the evidence supported medication management as single, stand alone intervention.

The increasing focus on social inclusion and the role of employment in maintaining good mental health led the GDG to also consider an updated review of employment
but as no new studies were identified in the searches undertaken for this guideline the GDG decided not to update the review undertaken for the 2002 guideline. For the same reasons the reviews of social support systems, crisis resolution and home treatment teams and day hospitals were not updated.

Definitions

The definitions adopted are as given in the introduction above with the exception of medication management, which is given below:

Medication management

Medication management (e.g. Peveler et al., 1999) is an intervention aimed at improving patient adherence to medication. It is usually delivered by a pharmacist or nurse. It usually involves the monitoring of treatment adherence and side effects, patient education about the nature and treatment of depression and the delivery of medication adherence strategies.

5.3.2 Stepped care

Introduction

Stepped care seeks to identify the least restrictive and least costly intervention that will be effective for the problems with which an individual presents (Davison, 2000). The most usual minimal interventions are those that are less dependent on the availability of professional staff and focus on patient-initiated approaches to treatment. These may include self-help materials such as books (Cuijpers, 1997) and computer programmes (Proudfoot et al., 2004). The use of these materials may be entirely patient managed, which is often referred to as pure self-help, or involve some limited input from a professional or para-professional, which is often referred to as guided self-help (Gelanty et al., 2007). Escalating levels of response to the complexity or severity of the disorder are often implicit in the organisation and delivery of many healthcare interventions, but a stepped care system is an explicit attempt to formalise the delivery and monitoring of patient flows through the system. In establishing a stepped care approach, consideration should not only be given to the degree of restrictiveness associated with a treatment and its costs and effectiveness, but the likelihood of its uptake by a patient and the likely impact that an unsuccessful intervention will have on the probability of other interventions being taken up.

Studies considered

The review team conducted a new systematic search for studies of stepped care in depression. This was undertaken as a joint review for this guideline and the guideline for depression in chronic physical health problems (NICE, 2009). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 11. Details of the search strings used are in appendix 7.

<table>
<thead>
<tr>
<th>Table 11 Databases searched and inclusion/exclusion criteria for clinical effectiveness of stepped care</th>
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<tbody>
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<td><strong>Electronic databases</strong></td>
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<td><strong>Date searched</strong></td>
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<tr>
<td><strong>Update searches</strong></td>
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<tr>
<td><strong>Study design</strong></td>
</tr>
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</table>
Population

People with a diagnosis of depression according to DSM, ICD or similar criteria

Treatments

Stepped care

The systematic review identified only one high quality study (VANSTRATEN2006). However, this study included a sample of mixed depression and anxiety disorders and it was therefore decided to conduct a narrative review which is set out below.

Narrative review

In the field of mental health in the UK, stepped care models are currently popular and underpin the organisation and delivery of care in a number of recent NICE mental health guidelines (see for example the guidelines for depression [NICE, 2004a] and anxiety [NICE, 2004b]). However, despite this current enthusiasm, the model is not supported by a strong evidence base. Bower and Gilbody (2005) reviewed the evidence for the use of stepped care in the provision of psychological therapies and were unable to find a significant body of evidence. They set out three assumptions on which they argue a stepped care framework is built and which need to be considered in any evaluation of stepped care. These assumptions concern the equivalence of clinical outcomes (between minimal and more intensive interventions at least for some patients), the efficient use of resources (including healthcare resources outside the immediate provision of stepped care) and the acceptability of minimal interventions (to both patients and professionals). They reviewed the existing evidence for stepped care against these three assumptions and found some limited evidence to suggest that stepped care might be a clinically and cost-effective system for the delivery of psychological therapies but no evidence that strongly supports the overall effectiveness of the model. Some evidence for the equivalence of minimal interventions comes, for example, from work on computerised cognitive behavioural therapy (Proudfoot et al., 2004; Kalenthaler et al., 2008) and the use of written materials (Cuijpers et al, 1997). For the efficiency assumption, evidence is more difficult to identify, although there is some suggestion that computerised cognitive behavioural therapy may be more cost effective than therapist-delivered care (Kalenthaler et al., 2002). Other evidence suggests that individuals in stepped care programmes may seek treatment in addition to the minimal interventions offered in the study and thereby undermine the efficiency assumption (Treasure et al., 1996; Thiel et al., 1998). Further problems emerge when the acceptability assumption is considered; with some suggestion that stepped care models may be associated with lower rates of entry into studies (Marks et al., 2003; Whitfield et al., 2001). Bower and Gilbody (2005) suggest that some of these problems could be addressed by taking into account patient choice (possibly by offering a choice from a range of minimal interventions) and also by adjusting the entry level into the stepped care system to take account of the severity of the disorder. Past experience of treatment or treatment failure may also be a useful indicator of which level a patient should be entered into the stepped care model.

Since the publication of the Bower and Gilbody (2005) review, a study of stepped care for over 720 patients by van Stratten and colleagues (2006) has been published; this compared two forms of stepped care with a “matched care” control. Both forms of stepped care involved assignment to a psychological therapy, brief behaviour therapy (BT) with a strong self-help component and therapist-delivered CBT. The matched care control involved patients being allocated to an appropriate psychological treatment as determined by the responsible clinician, unlike the other two arms of the trial where the type and duration of treatment was determined by the trial protocol. Patients in the
matched control received more treatment sessions but outcomes were no better than for those patients in the other two arms. Although the study lacked power to determine whether the difference was statistically significant (despite including over 700 patients), it is possible that the two stepped care models were more cost effective (Hakkaart-van Roijen et al., 2006). However, both stepped care arms had higher attrition rates and there was some diversion, especially in the BT group, into additional treatments other than those delivered in the study.

Outside of the area of stepped care for psychological therapies for depression, most notably in the area of collaborative care, considerable use has been made of stepped care programmes (for example, Hunkeler et al., 2006) where the stepped care intervention is often integrated into an overall collaborative care programme. A fuller review of the collaborative care literature is contained in the section on collaborative care below. Specifically in relation to collaborative care, few of the collaborative care studies have been built exclusively on a stepped care model with all individuals receiving a lower intensity intervention at first point of contact. In many collaborative care studies the prescription of anti-depressant drugs has been the first intervention offered (Katon et al., 1999; Swindle et al., 2003). The decision whether to step up to another intervention was then based on no or limited response to treatment. A more limited number of studies have offered psychological interventions as the first point of contact (or the option of a pharmacological or psychological first treatment) in a collaborative care programme (Rost et al., 2001; Unutzer et al., 2002) and where benefit has not been obtained have stepped up either to more intensive pharmacological or psychological treatments or a combination of both. As may be apparent from this discussion a number of other factors including the role of case management and other health care interventions may have an influence on the outcome. It is also the case that more complex collaborative care interventions (e.g. greater duration of intervention and follow up and a greater range of available interventions e.g. the IMPACT study [Unutzer, 2002]) tend to be associated with better outcomes but whether this reflects the specific contribution of a stepped care framework is unclear. In addition, meta-regression studies such as those by Bower et al (2006) and Gilbody et al (2006) did not identify the presence of stepped care or specific algorithms of care (which may be taken as a rough equivalent or proxy for stepped care) as being associated with a more positive outcome.

The final evidence for the effectiveness of a stepped care model comes from the report on the two IAPT demonstration sites (e.g. Layard et al, 2008) which provide a stepped psychological care programme. In the demonstration projects there was good evidence for increased patient flows through the system whilst at the same time the outcomes obtained were broadly in line with those reported in randomised controlled trials for depression and anxiety.

In summary there is very limited evidence from direct studies in the support of a stepped care model. Beyond the area of depression in fields such as addiction (Davison, 2000), there is some evidence for the effectiveness of the model. Bower and Gilbody (2005) also provide some limited evidence in favour of the model in psychological therapies, but with the single exception of the van Stratten et al. (2006) study no formal trials of the relative efficiency or effectiveness of a pure stepped care model were identified. There is some suggestion that the integration of stepped care into a more complex model of collaborative care may be associated with better outcomes but no strong evidence that this is the case.
From evidence to recommendations

The 2004 guideline along with other NICE guidelines (e.g. NICE 2004b) recommended the adoption of a stepped care model for the provision of psychological and pharmacological interventions for depression. Since that time there has been further but limited evidence providing direct support for the model (van Stratten et al, 2006; Hakkaart-van Rooijen et al., 2006; Layard et al 2008) along with its increasing use in a number of collaborative care interventions. It has also been adopted by the IAPT programme (DH, 2007) as the framework for the delivery of the service. In the view of the GDG the stepped care model remains the best developed system for ensuring access to cost-effective interventions for a wide range of people suffering from depression, particularly if supported by systems for routine outcome monitoring which ensure that there are systems in place that enable prompt stepping up for those who have not benefited from a low intensity intervention. In light of this the GDG made no changes to any recommendations to the model set out in the 2004 guideline but did make some adjustments to the structure and content of the model which is set out in Figure 1.

Figure 1. The stepped care model

<table>
<thead>
<tr>
<th>Focus of the intervention</th>
<th>Nature of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1</strong>: All known and suspected presentations of depression</td>
<td>Assessment, referral, psychoeducation, active monitoring and support</td>
</tr>
<tr>
<td><strong>STEP 2</strong>: Minor, mild to moderate depression</td>
<td>Low intensity psychological and psychosocial interventions, medication, referral</td>
</tr>
<tr>
<td><strong>STEP 3</strong>: Mild to moderate depression with limited response to initial interventions, moderate and severe depression</td>
<td>Medication, high intensity psychological interventions, combined treatments, referral</td>
</tr>
<tr>
<td><strong>STEP 4</strong>: Severe and complex* depression, risk to life, severe self-neglect</td>
<td>Medication, high intensity psychological interventions, ECT, crisis service, combined treatments, multi-professional and in-patient care.</td>
</tr>
</tbody>
</table>

* Complex includes depression with a poor response to multiple treatments, complicated by psychosis, and/or significant psychiatric comorbidity or psychosocial factors

Current models are in development (e.g. Richards et al, 2009) which will allow service delivery systems to monitor and review the effectiveness of stepped care models.
Further research however is clearly needed to address the issues of efficacy, efficiency and acceptability of stepped care for depression.
5.3.3 Collaborative care

Introduction

The origins of collaborative care lay in concerns about the inadequacy of much current treatment for depression and developments in the field of chronic physical disorders. In many of the earlier studies, mental health professionals provided the enhanced staff input to primary care settings and undertook a care co-ordinator role (Katon et al., 1995; Katon et al., 1996; Unutzer et al., 2002). However, more recently, others including primary care nurses (Hunkeler et al., 2000; Mann et al., 1998; Rost et al., 2000) or graduates without core mental health professional training (Katzelnick et al., 2000; Simon et al., 2000) have taken this role. Most studies have been from the US. In the UK, one study used practice nurses in the care co-ordinator role, and this did not improve either patient antidepressant uptake or outcomes compared with usual GP care (Mann et al., 1998), more recent studies have used mental health professionals or para-professionals (Chew-Graham et al., 2006; Richards et al, 2009, Pilling et al, 2009)

In the UK, there is a concern that there are not sufficient mental health professionals to provide enhanced input and care co-ordination for all primary care patients with depression. Primary care nurses have multiple and increasing demands on their time and many are also uninterested in working with patients with psychological problems (Nolan et al., 1999). Therefore, it is unlikely that practice nurses will take on a significant role in the routine care of patients with depression. A major NHS staffing initiative for primary care mental health was the appointment of new graduate primary care mental health workers (Department of Health, 2000; Department of Health, 2003) who may potentially affect this situation. The advent of these posts has more recently been superseded by the development of the IAPT programme where the role of the low intensity staff (in many cases a development of the primary care mental health worker role) has elements that are common to a number of collaborative care interventions.

A number of recent meta-analyses of collaborative care have supported the statistical and clinical effectiveness of the model for depression (Badamgarav et al., 2003; Neumeyer-Gromen et al., 2004; Gilbody et al., 2006a; Cape et al., 2009) but not necessarily the cost effectiveness (Ofman et al., 2004; Gilbody et al., 2006b). Other related reviews have focused on the use of case management in depression (Gensichen et al., 2006), which they defined as “an intervention for continuity of care including at least the systematic monitoring of symptoms. Further elements were possible such as coordination and assessment of treatment and arrangement of referrals”. Given this rather broad definition, the GDG did not consider that a separate analysis of case management from collaborative care was meaningful, particularly in light of the considerable variation in the duration and complexity of the interventions covered in the meta-analyses described above.

The effect sizes on depressive and related symptoms described by the Badamgarav and colleagues (2003), Neumeyer-Gromen and colleagues (2004), Gilbody and colleagues (2006a) and Cape and colleagues (2009a; 2009b) reviews were generally modest, ranging between 0.25 (95% CI 0.18, 0.32) (Gilbody et al., 2006a) and 0.75 (95% CI 0.70, 0.81) (Neumeyer-Gromen et al., 2004), with most reviews reporting effect sizes at the lower end of the range indicated. The reviews by Cape and colleagues (2009a; 2009b) are the most comprehensive yet, including 29 separate studies of collaborative care from a total of 64 studies of the enhanced care of depression (and including some
studies of dysthymia and anxiety). The reviews are important for a number of reasons: first, they place the work on collaborative care in a wider context and usefully allow for a comparison of the effect of collaborative care with other elements of the enhanced care of depression in primary care, including the effectiveness of the attached professional model (Bower & Sibbald, 2000); secondly, they include a review of the type and intensity of interventions offered in collaborative care; thirdly, they also include a consideration of the impact on the delivery of enhanced care by different professional groups including psychiatrists, depression care specialists and non-professionally qualified staff; and finally, they allow for a consideration of the healthcare system in which the interventions were provided. All of these factors are potentially important in determining the shape and content of an NHS-based model of collaborative care.

**Current practice and aims of the review**

The extent of UK NHS based provision has already been reviewed in the introductory section on service delivery systems and as can be seen from that section the formal provision of collaborative care is not much evident in the NHS although some elements of it are becoming available through the low intensity arm of the IAPT programme, including medication management (Peveler et al, 1999), care management (Gensichen et al., 2006) and signposting (Grayer, 2005).

**Interventions included and definitions**

These are set out in the introduction to the section on service delivery systems.

**Studies considered for review**

The review team conducted a new systematic search for studies of collaborative care of depression. This was undertaken as a joint review for this guideline and the guideline for depression in chronic physical health problems (NICE, 2009). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 12. Details of the search strings used are in appendix 17.

<table>
<thead>
<tr>
<th>Table 12 Databases searched and inclusion/exclusion criteria for clinical effectiveness of collaborative care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electronic databases</strong></td>
</tr>
<tr>
<td><strong>Date searched</strong></td>
</tr>
<tr>
<td><strong>Update searches</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
</tr>
</tbody>
</table>

In total, 48 trials were found from searches of electronic databases. Of these, 28 were included and 20 were excluded. Of the included studies, 11 were from the previous guideline (NICE, 2004) and of the excluded studies, 1 had been included in the previous guideline but was removed for this guideline because only 21% had a diagnosis of depression at baseline. The most common reasons for exclusion were that there was no extractable data or that less than 80% of participants had a diagnosis of depression.
All studies of populations with depression and an identified physical health problem (e.g. Katon 2004) were excluded at the outset. Of the included studies, Unutzer 2002 was removed because the high incidence of chronic health problems reported in the study sample led the GDG to decide that the trial was more appropriately placed in the parallel Depression and Chronic Physical Health Problems guideline (NICE, 2009). Araya 2003 was also removed in a sensitivity analysis, because it was identified as an outlier producing a great deal of heterogeneity (non-response data pre-sensitivity analysis $I^2 = 82.2\%$; post-sensitivity analysis $I^2 = 21.1\%$). The GDG felt that this was a likely consequence of the study setting; based in Chile, it is possible that the usual care arm which was utilised as the control reflected a different healthcare system not relevant to a UK setting. Similarly, the Major Depression subsample from Katon 1996 was removed from mean endpoint analysis because it too introduced an exceptionally large amount of heterogeneity, which was eradicated completely after it was taken out of the analysis (mean endpoint pre-sensitivity analysis $I^2 = 42.8\%$; post-sensitivity analysis $I^2 = 0\%$). Wells 1999 reported follow-up data at 45 months after acute phase, which was not extracted as it was felt that the data could not reliably be converted into intention-to-treat analysis given the high attrition rate at that time point.

A range of self-rated and clinician-rated outcomes were reported in the included studies. These included the SCL-20 and SCL-depression subscale which are both depression specific scales derived from the 90-item Hopkins Symptom Checklist (HSCL; Derogatis, 1974), the BDI (Beck, Ward & Mendelson, 1961), BDI-II (Beck, Steer & Brown, 1996), PHQ-9 (Spitzer, 1999), CES-D (Radloff, 1977) and HRSD (Hamilton, 1960). One study reported follow-up relapse prevention data. Data were only extracted where a comparison to usual care was available.

The studies which were found by the search and included in this review varied considerably in terms of the complexity of the care protocols implemented. In addition to this, the inclusion of both UK and non-UK based trials resulted in inevitable variation in the nature of the usual care used as a comparator. There was also variation in participant diagnoses; studies including patients presenting with an antidepressant prescription were included along with those reporting a more formal diagnosis. Previous meta-regression had identified a number of factors such as mental health background of the care coordinator, antidepressant use, and the provision of supervision as associated with better outcomes. The presence of such elements raise question about the complexity or comprehensiveness of the intervention in particular when assessed against the criteria originally developed by Wagner and von Korff (1997). With this in mind a simple checklist to assess the complexity of the intervention provided was developed to see if this may help in more reliably characterising the interventions and whether or not this may relate to the outcome of the intervention. This checklist is included in Appendix 10.

In order to reduce the possible confounding crossover effects in which the implementation of collaborative care changes the standard care for all patients in the practice, a number of trials employed a cluster randomised design. In these trials the

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9 Here and throughout the rest of this chapter the study IDs for studies which were in the previous guideline are in lower case whereas those for new studies are capitalised.
unit of randomisation was the individual physician, clinic, healthcare firm or geographical area (DATTO2003, DIETRICH2004, DOBSCHA2006, ROST20001a, Rost2001b, Wells1999, and SWINDLE2003). A design effect10 was applied to the analysis of studies that had not accounted for the clustering in their analysis. Where papers reported the intracluster correlation coefficient (ICC) this was used in the calculations, with the empirically derived value of 0.02 used where the ICC was not reported. A sensitivity analysis was conducted to compare the results of the meta-analysis with and without the application of the design effect. The results indicated that applying the transformation had little to no impact on any of the results reported, thus strengthening the robustness of the original analysis.

Summary study characteristics of the included studies are in Table 13 with full details in Appendix 17 which also includes details of excluded studies.

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Collaborative care v usual care</th>
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</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
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<tr>
<td></td>
<td>(1) ADLER2004</td>
</tr>
<tr>
<td></td>
<td>(2) Araya2003</td>
</tr>
<tr>
<td></td>
<td>(3) Blanchard1995</td>
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<tr>
<td></td>
<td>(4) CHEWGRAHAM2007</td>
</tr>
<tr>
<td></td>
<td>(5) DATTO2003</td>
</tr>
<tr>
<td></td>
<td>(6) DIETRICH2004</td>
</tr>
<tr>
<td></td>
<td>(7) DOBSCHA2006</td>
</tr>
<tr>
<td></td>
<td>(8) FINLEY2003</td>
</tr>
<tr>
<td></td>
<td>(9) Hunkeler2000*</td>
</tr>
<tr>
<td></td>
<td>(11) Katon1996</td>
</tr>
<tr>
<td></td>
<td>(12) Katon1999</td>
</tr>
<tr>
<td></td>
<td>(13) Katon2001***</td>
</tr>
<tr>
<td></td>
<td>(14) LUDMAN2007**</td>
</tr>
<tr>
<td></td>
<td>(15) Mann1998b</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 364/72</td>
</tr>
<tr>
<td></td>
<td>(2) 240/100</td>
</tr>
<tr>
<td></td>
<td>(3) 82/85</td>
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<td></td>
<td>(13) 286/74</td>
</tr>
<tr>
<td></td>
<td>(14) 74/71</td>
</tr>
</tbody>
</table>

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10 \( N \) (effective) = \( k \times m \) / (1 + (m - 1) * ICC), where \( k \) indicates the number of clusters, \( m \) the number of observations per cluster and ICC the intracluster correlation coefficient.
### Mean age

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<td>16</td>
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<td>29</td>
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### Diagnosis

<table>
<thead>
<tr>
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<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MDD, Dysthymia or Double Depression (DSM-IV)</td>
</tr>
<tr>
<td>2</td>
<td>MDD (DSM-IV)</td>
</tr>
<tr>
<td>3</td>
<td>Probable Pervasive Depression (Short-CARE)</td>
</tr>
<tr>
<td>4</td>
<td>unclear</td>
</tr>
<tr>
<td>5</td>
<td>MDD (MINI) or referred with depressive symptoms</td>
</tr>
<tr>
<td>6</td>
<td>MDD, Dysthymia or Double Depression (DSM-IV)</td>
</tr>
<tr>
<td>7</td>
<td>Minor Depression, Dysthymia (DSM-IV) or unclear</td>
</tr>
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<td>8</td>
<td>unclear: clinical judgment</td>
</tr>
<tr>
<td>9</td>
<td>MDD or Dysthymia (DSM-IV)</td>
</tr>
<tr>
<td>10</td>
<td>MDD or Minor Depression (DSM-III-R)</td>
</tr>
<tr>
<td>11</td>
<td>MDD or Minor Depression (DSM-III-R)</td>
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<td>12</td>
<td>Recurrent Depression or Dysthymia (DSM-IV)</td>
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<tr>
<td>13</td>
<td>Recovered but high risk of relapse</td>
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<td>14</td>
<td>Minor Depression or Dysthymia (treatment resistant; DSM-IV)</td>
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<td>15</td>
<td>MDD (DSM-III)</td>
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<td>Depressive illness (ICD-10)</td>
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<td>MDD (DSM-IV)</td>
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<td>18</td>
<td>clinical diagnosis established by GP (unclear)</td>
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<td>19</td>
<td>MDD (DSM-IV)</td>
</tr>
<tr>
<td>20</td>
<td>unclear: antidepressant prescription</td>
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<td>MDD (DSM-III-R)</td>
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<td>22</td>
<td>MDD (DSM-III-R)</td>
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<td>23</td>
<td>unclear: antidepressant prescription</td>
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<td>24</td>
<td>unclear: beginning antidepressant treatment</td>
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<td>25</td>
<td>Depressive Disorder (unclear)</td>
</tr>
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<td>MDD (DSM-IV)</td>
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<tr>
<td>27</td>
<td>MDD, Dysthymia, partially remitted MDD or Double Depression (PRIME-MD)</td>
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<td>28</td>
<td>MDD, Dysthymia or Double Depression (DSM-IV)</td>
</tr>
<tr>
<td>29</td>
<td>MDD, Dysthymic Disorder, Double Depression or Subthreshold Depression (CIDI)</td>
</tr>
</tbody>
</table>

### Setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>USA</td>
</tr>
<tr>
<td>2</td>
<td>Chile</td>
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<tr>
<td>16</td>
<td>UK</td>
</tr>
<tr>
<td>17</td>
<td>Europe</td>
</tr>
</tbody>
</table>
### Evidence profile

On all outcome measures of efficacy collaborative care was more effective than standard care, although the effect sizes were very small. See Table 14 for the summary evidence profile (and Appendix 15 for the full profile).

#### Table 14 Summary evidence profile for collaborative care versus standard care (acute-phase efficacy data)

<table>
<thead>
<tr>
<th></th>
<th>Self-rated</th>
<th>Clinician-rated</th>
<th>DSM criteria</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>RR 0.83 (0.75 to 0.92) (49.7% vs 59.9%)</td>
<td>RR 0.86 (0.69 to 1.06) (44.2% vs 48.7%)</td>
<td>N/R</td>
<td>N/R</td>
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<tr>
<td>Quality</td>
<td>High</td>
<td>Moderate</td>
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<td></td>
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<tr>
<td>Number of studies; participants</td>
<td>K=7; n=1820</td>
<td>K=2; n=1264</td>
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</tr>
<tr>
<td>Forest plot</td>
<td>Service c-care 05.01</td>
<td>Service c-care 05.01</td>
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</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.92 (0.86 to 0.98) (70% vs 76%)</td>
<td>RR 0.98 (0.88 to 1.09) (56.4% vs 57.5%)</td>
<td>RR 0.88 (0.72 to 1.07) (29.5% vs 29.3%)</td>
<td>12 months</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Receiving collaborative care appeared to make little difference to the number of people leaving treatment early. However, it improved the number adhering to medication. See Table 14 for the summary evidence profile, with the full profile in Appendix 15.

One study, Katon2001, looked at relapse prevention in people who had achieved remission. There was no difference between the number relapsing who had received collaborative care and the number relapsing who had received standard care.

**Collaborative care: implications of data on the attached professional role**

As part of the collaborative care review, the GDG were concerned to understand the potential impact of collaborative care for depression in the UK healthcare system. This arose from a concern that a significant proportion of the data for the effectiveness of collaborative care was drawn from studies conducted in North America. Given the development of the attached professional role in primary care services in the UK (Bower and Sibbald, 2000) it was decided to explore the potential effect sizes of the attached professional role versus usual GP care or waitlist control, and therefore provide a comparator for collaborative care. In order to estimate the potential effect of the attached professional role, we therefore reviewed all trials for high intensity psychological interventions that were included in the guideline. We did consider the inclusion of pharmacological trials based in primary care, but these were very few in number and also as collaborative care as a minimum often involves antidepressant treatment, it was not felt to be a useful comparator. The following studies were identified, and the study characteristics for these can be found in Chapter 6: Schulberg1996, Scott1992, Scott1997, Simpson2003 and Ward2000.

The effect sizes for depressive symptoms obtained in our review for the attached professional role were: BDI, SMD -0.28 (95% CI -0.66, 0.10); HAMD, SMD -0.35 (95% CI -0.58, -0.11). These effect sizes were similar to that obtained in a more extensive review, albeit one with somewhat different inclusion criteria, by Cape et al. (2009a). The effect size for depressive symptomatology in that study was -0.26 (SMD, 95% CI -0.35, -0.16). The effect size for collaborative care in our review was: self-rated outcome, SMD 0.15 (95% CI -0.24, -0.06). Given the similarity of effect sizes and the closely overlapping confidence intervals it seems reasonable to conclude, at least initially in the absence of any direct comparisons, that there may be little difference in outcomes between these

<table>
<thead>
<tr>
<th>Number of studies; participants</th>
<th>K=3; n=1480</th>
<th>K=1; n=962</th>
<th>K=7; n=1440</th>
<th>K=1; n=863</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forest plot</td>
<td>Service c-care 05.02</td>
<td>Service c-care 05.02</td>
<td>Service c-care 05.02</td>
<td>Service c-care 05.03</td>
</tr>
<tr>
<td>Mean depression scores at endpoint</td>
<td>SMD -0.15 (-0.24 to -0.06)</td>
<td>SMD -0.05 (-0.64 to 0.53)</td>
<td>N/R</td>
<td>3-4 months SMD -0.36 (-0.63 to -0.09)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=11; 1894</td>
<td>K=1; n=43</td>
<td>K=3; n=214</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service c-care 05.05</td>
<td>Service c-care 05.05</td>
<td>Service c-care 05.06</td>
<td></td>
</tr>
<tr>
<td>Mean depression change scores at endpoint</td>
<td>N/R</td>
<td>SMD -0.02 (-0.15 to 0.11)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
</tbody>
</table>

N/R = not reported
two modes of delivery of care. When attempting to understand these results a number of factors need to be considered. These include the considerable variation in the nature of the collaborative care provided; in some cases it involved case managers taking on the long-term care of people with depression (for example, Simon et al., 2004), in others it involved little more than advice and consultation with a psychiatrist (for example, Katon et al., 1995); differences in the nature of the intervention provided; for example, within the attached professional model the professionals more consistently provided specific psychological interventions (for example, Scott et al., 1997) and this may have an impact on the effectiveness of the intervention; the populations included in the trials may be different; and finally the comparators and the nature of the healthcare system in which the interventions were delivered may also be different. For example in the Cape et al (2009a) review, the majority of the attached professional studies were based in the UK (26 out of 30) and most of the collaborative care studies were based in the US (24 out of 29).

Clinical summary for collaborative care

The studies of collaborative care reviewed here were limited to those individuals without an accompanying chronic physical health problem. A review of collaborative care for these individuals, including studies in populations of older people with a high incidence of physical health problems (Unutzer 2001) is contained in the related guideline (NICE, 2009). The evidence profiles developed for this guideline show that when the review of collaborative care is restricted to the groups with depression and no significant chronic physical health problems, then the effects of the intervention are of limited clinical importance (see, for example the effect sizes for remission and response) and there is a small effect on endpoint continuous data. It should also be noted that the endpoint continuous data effect sizes were similar to those obtained from an analysis of the attached professional role. The small size of the data set included here prevented any more detailed analysis, for example a meta-regression. There was considerable variation between studies with some, for example Katon1996MAJOR, reporting a large effect on continuous data: SMD = -1.11 (95% CI -1.64, -0.59) but inclusion of this study in the meta-analysis resulted in considerable heterogeneity which entirely disappeared when the study was removed in the sensitivity analysis. It is also worth noting that when response data are reviewed, there is a noticeable decline in effect size from the early studies for example Katon1996MAJOR RR = 0.49 (95% CI 0.27, 0.92) and Katon1996MINOR RR= 0.68 (95% CI 0.41, 1.15), to more recent studies such as SIMON2006 RR = 0.97 (95% CI 0.79, 1.18).

Health Economic Evidence and Considerations

The systematic search of the economic literature undertaken for the guideline update identified one eligible study on service level interventions for people with depression set in the UK.

This study by Kendrick et al (2006) compared the cost and benefits of usual GP care, generic community mental health nurse care and problem-solving treatment (PST) provided by specially trained Community Mental Health Nurses (CMHN). The population included in the analysis of patients with new episode of anxiety, depression or reaction to life difficulties of between 4 wks and 6 month duration and a score of =>3 GHQ-12.
An incremental cost-effectiveness analysis was performed, comparing PST-CMHN care with GP care, and generic CMHN care with GP care. In both cases, care provided by nurses was dominated by GP care. The authors explicitly recommended that patients with common mental disorders should not be referred to CMHTs and should be managed by GPs, since there are no additional benefits, and the referral generates greater costs and greater workload to CMHN teams. They also suggested that further research is required to explore factors that affect the chronicity of common mental disorders in order to allow provision of specific treatment to patients who are likely to make progress in the short term in usual GP care.

This study has high internal validity and expressed benefits in terms of QALYS, thus enabling the results to be compared with other health care technologies and programmes. Although the cost data were derived from official national sources, they were treated deterministically and no sensitivity analysis of the costs was conducted; this may limit the interpretation of the findings. Given that PST provided by trained nurses could not be monitored for all cases, there may be uncertainty around the faithfulness of the method of treatment provision. The GPs involved in the study did not refer all eligible patients for the trial and this might have introduced referral bias. Bias might also have been introduced to the results on account of the lower follow-up rates in the GP care group, as the course of disease could be monitored for those who dropped out. However, the sensitivity analysis demonstrated the robustness of the results.

This data was considered to be insufficient to inform the development of recommendations in this area. As a result this evidence was considered but more emphasis was placed on clinical effectiveness evidence.

No UK based studies evaluating the cost effectiveness of collaborative care were identified in the literature search. The collaborative care meta-analysis conducted for the update points to a small effect size of collaborative care when compared to usual care. A collective decision was reached by the GDG not to recommend collaborative care interventions in the depressed population. The effect sizes were considered too small to warrant a formal economic evaluation. Collaborative care studies included in the meta-analysis point to a resource use that is more intensive than usual care, e.g. the additional input of a case manager in the co-ordination of care for depressed patients and associated liaison time with GPs and specialist psychiatrists. From this one can assume that collaborative care may be more costly than usual care. However this does not exclude the possibility of collaborative care being cost effective when compared to usual care as even small differences in effects and costs could potentially result in a cost effective intervention. A significant portion of the effectiveness data was based on studies conducted in the United States of America. There are usually no contra-indications to using such data for a model set in the UK, furthermore sensitivity analysis can be conducted to test the inputs/assumptions made. However, Collaborative care is a service level intervention with effects that largely reflect the nature of the health care setting in which it is set. More studies conducted in the UK health care setting may provide more UK specific effects and resource use estimates.

**Evidence to recommendations for collaborative care**

The evidence, both clinical and cost data, reviewed in this guideline for collaborative care in depression or for medication management alone was not viewed as being
sufficiently strong to generate any recommendations. The GDG did recognize that co-ordinated care with long term follow-up is an important element of effective care for people with severe and complex depression. For example, it is acknowledged in the guideline on depression and chronic physical health problems (NICE, 2009), collaborative care can play an important role. In addition, co-ordinated multiprofessional interventions are key elements of the care provided in specialist mental health services in Step 4 of this guideline. In view of this, the GDG thought it appropriate in a recommendation to draw attention to the role of collaborative care for people with chronic physical health problems in depression and of co-ordinated multi-professional care in specialist mental health services for those with severe and complex depression.

5.3.4 Clinical practice recommendations

5.3.4.1 For people with severe depression and those with moderate depression and complex problems practitioners should consider:
- referral to specialist mental health services for a programme of co-ordinated multi-professional care
- the provision of collaborative care where the depression is in the context of a chronic physical health problems with associated functional impairment

5.3.4.2 Teams working with people with complex and severe depression should develop comprehensive multidisciplinary care plans in collaboration with the person with depression (and their family or carer, where agreed with the person). The care plan should:
- identify clearly the roles and responsibilities of all health and social care professionals involved
- develop a crisis plan that identifies potential triggers that could lead to a crisis
- be shared with the GP and the person with depression and other relevant people involved in the person’s care.

5.3.5 Medication management

Introduction
The effectiveness of antidepressants in the treatment of depression has long been recognised, has as the problem of poor compliance d inevitably has led to the interest in developing strategies to promote and support adherence to antidepressant medication.
If the potential benefits of longer-term treatment are to be realised, two conditions need to hold. First, that the drugs are prescribed at an adequate dose and secondly that the regime of treatment is adhered to. Dunn and colleagues (1999), in a study of over 16,000 primary care patients prescribed either TCAs or SSRIs, reported that while 33% of those prescribed an SSRI were judged to have completed an adequate period of treatment (that is, prescriptions covering at least 120 days’ treatment within the first 6

11 See the DCHP guideline for the evidence base for this
months after diagnosis) only 6% of those prescribed a TCA did. Of course this study does not account for the possibility that some patients may have switched medication and may have done so to their long-term benefit. However, evidence from studies of prescribing patterns in primary care suggests that if patients discontinue one form of antidepressant medication they often do not take another medication. For example, Isacsson and colleagues (1999), in a study of nearly 1000 patients, report that only 35% ever received one prescription and only a minority received further prescriptions. This presents a potentially worrying picture; the effects of antidepressants seem modest and adherence to treatment regimes is also limited. For example, Lingam and Scott (2002), in a systematic review report non-adherence rates between 10% and 60% for antidepressants, with an average around 40%. They were also able to identify only a few well-conducted studies designed to improve antidepressant adherence, with at best modest effects. Isacsson and colleagues (1999), in a study of nearly 1000 patients, report that only 35% ever received one prescription and only a minority received further prescriptions.

This view of increased adherence to antidepressants in collaborative care was also supported by the meta-regression study of Bower and colleagues (2006), which suggests that collaborative care was associated with increased medication adherence and by the review conducted for this guideline of outcomes for collaborative care which suggested a potentially positive impact on medication adherence (RR 0.70; 95% CI 0.46, 1.08).

Beyond depression and mental health, the problem of poor medication adherence has been the subject of considerable research and debate. Most recently, NICE (2009b) have produced guidance on promoting medication adherence, which has general applicability for promoting adherence across all fields of medical care. However, the GDG were specifically concerned with the effectiveness of medication adherence (medication management programs) in depression.

**Studies considered for review**

The review team conducted a new systematic search for studies of medication management. This was undertaken as a joint review for this guideline and the guideline for depression in chronic physical health problems (NICE, 2009). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 15. Details of the search strings used are in appendix 8.

<table>
<thead>
<tr>
<th>Table 15 Databases searched and inclusion/exclusion criteria for clinical effectiveness of medication management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electronic databases</strong></td>
</tr>
<tr>
<td><strong>Date searched</strong></td>
</tr>
<tr>
<td><strong>Update searches</strong></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
</tr>
</tbody>
</table>

In this update four trials with potential relevance to medication management for depression were found from searches of electronic databases. Of these three were
included and one was excluded because it did not report any outcomes relevant to the scope. The GDG that two studies identified in the collaborative care review were relevant to medication management so these were also included. None of the studies were included in the 2004 guideline.

Of the included studies, CROCKETT2006 was a cluster randomised trial but the outcomes could not be adjusted because the number of clusters was not reported in the paper. It is therefore reported separately. PEVELER1999 reported both overall outcomes for all participants and an analysis of a sub-sample of more severely depressed patients. In order to be consistent with the other studies, the overall outcomes were extracted for this review, but it should be noted that the authors reported a significant effect for patients who met criteria for major depression at the outset and received medication doses above 75mg.

Summary study characteristics of the included studies are in Table 16 with full details in Appendix 17 which also includes details of excluded studies.

### Table 16 Summary study characteristics of medication management versus usual care

<table>
<thead>
<tr>
<th>No. trials (Total participants)</th>
<th>Medication management v usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 RCTs (963)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study IDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) ADLER2004*</td>
</tr>
<tr>
<td>(2) CROCKETT2006</td>
</tr>
<tr>
<td>(3) PEVELER1999**</td>
</tr>
<tr>
<td>(4) RICKLES2005*</td>
</tr>
<tr>
<td>(5) WILKINSON1993</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N/% female</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 364/72</td>
</tr>
<tr>
<td>(2) 84/71</td>
</tr>
<tr>
<td>(3) 157/74</td>
</tr>
<tr>
<td>(4) 53/84</td>
</tr>
<tr>
<td>(5) 45/74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 42</td>
</tr>
<tr>
<td>(2) 46</td>
</tr>
<tr>
<td>(3) 45</td>
</tr>
<tr>
<td>(4) 38</td>
</tr>
<tr>
<td>(5) 49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) MDD; dysthymia, double depression (DSM-IV)</td>
</tr>
<tr>
<td>(2) Antidepressant prescription (unclear)</td>
</tr>
<tr>
<td>(3) Depressive illness (unclear; clinical diagnosis)</td>
</tr>
<tr>
<td>(4) Antidepressant prescription (unclear)</td>
</tr>
<tr>
<td>(5) Depressive disorder (unclear)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) US</td>
</tr>
<tr>
<td>(2) Australia</td>
</tr>
<tr>
<td>(3) UK</td>
</tr>
<tr>
<td>(4) US</td>
</tr>
<tr>
<td>(5) UK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 180</td>
</tr>
<tr>
<td>(2) 60</td>
</tr>
<tr>
<td>(3) 84</td>
</tr>
<tr>
<td>(4) 90</td>
</tr>
<tr>
<td>(5) 56</td>
</tr>
</tbody>
</table>

* From collaborative care review **
Evidence profile

There was no evidence that medication management helped to reduce depression symptoms, although it had some effect on medication adherence and appeared acceptable to participants. See Table 17 for the summary evidence profile (and Appendix 15 for the full profile).

Table 17 Summary evidence profile for medication management v usual care

<table>
<thead>
<tr>
<th></th>
<th>Self-rated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>RR 0.94 (0.47 to 1.89)</td>
</tr>
<tr>
<td></td>
<td>(32.2% vs 34.4%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=63</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service med-man 01.01</td>
</tr>
<tr>
<td>Mean depression scores at endpoint</td>
<td>SMD -0.14 (-0.31 to 0.02)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=604</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service med-man 01.02</td>
</tr>
<tr>
<td>Adherence</td>
<td>RR 0.7 (0.51 to 0.96)</td>
</tr>
<tr>
<td></td>
<td>(32.8% vs 40.9%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=340</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service med-man 01.03</td>
</tr>
<tr>
<td>Leaving treatment early for any reason (including lost to follow-up)</td>
<td>RR 0.81 (0.63 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>(25.5% vs 31.4%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=594</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service med-man 02.01</td>
</tr>
</tbody>
</table>

N/R = not reported

Clinical summary
A total of five studies, focusing specifically on medication management in depression, were reviewed. Overall, the quality of the evidence from these five studies was limited, and it did not prove possible to perform a single meta-analysis of all the studies, focusing on depression outcomes. Where possible data from studies was combined, but even allowing for this, no consistent picture of a clinically important benefit of medication management alone emerged from the data. This is consistent with other reviews in the areas (e.g. Vergouwen et al., 2003). In light of this, the GDG did not feel able to make any recommendations for medication management alone in the treatment of depression. However, it is recognised that the recommendations set out in the NICE guideline on medication adherence (NICE 2009b) are potentially important in improving adherence. Where there are specific concerns about potential problems with adherence (for example increased side effects with tricyclic antidepressants, the delay in onset of antidepressant effects or the possibility of discontinuation symptoms) specific attention is drawn to these within the recommendations on pharmacological interventions (Chapters 7, 8 and 9).

Evidence into recommendations
The evidence reviewed in this guideline for medication management alone was not viewed as being sufficiently strong to generate any positive recommendations.

5.3.6 Clinical practice recommendation

5.3.6.1 Medication management as a discrete intervention for people with depression should not be routinely provided by services. It is likely to be effective only when provided as part of a more complex intervention.

5.3.7 Crisis resolution and home treatment teams

Introduction
Traditionally, a depressive episode marked by serious risk to self (most often suicidal ideation and intent) or very severe deterioration to care for the self is managed by admission to an acute inpatient unit. However, in recent years there has been growing interest in attempting to manage such episodes in the community. If this could be done safely, it might avoid the stigma and costs associated with hospital admission, thus providing benefits to both patients and service providers. Crisis resolution and home treatment teams (CRHTTs) are a form of service that aims to offer intensive home-based support in order to provide the best care for someone with depression where this is the most appropriate setting.

Definition
The GDG adopted the definition of crisis resolution developed by the Cochrane review of crisis intervention for people with serious mental health problems (Joy et al., 2003). Crisis intervention and the comparator treatment

Crisis resolution is any type of crisis-oriented 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 suffering from acute psychiatric episodes in the area concerned; this involved hospital-based treatment for all studies included.

**Studies considered for review**

The GDG chose to use the Cochrane review of CRHTTs (Joy et al., 2003), which included five RCTs (FENTON1979, HOULT1981, MUIJEN21992, PASAMANICK1964, STEIN1975), as the starting point for this section. A further search identified no new RCTs suitable for inclusion. Of the five RCTs included in the Cochrane review, only STEIN1975 met the inclusion criteria set by the GDG (all the other studies had a very significant or exclusive focus on schizophrenia), providing data for 130 participants. For the purposes of the guideline, the focus of this section is to examine the effects of CRHTT care for people with serious mental illness (where the majority of the sample was diagnosed with non-psychotic disorders) experiencing an acute episode compared with the standard care they would normally receive. Studies were excluded if they were largely restricted to people who were under 18 years or over 65 years old, or to those with a primary diagnosis of substance misuse or organic brain disorder.

**Clinical evidence statements**

**Crisis resolution and home treatment teams versus standard care**

**Effect of treatment on death (suicide or death in suspicious circumstances)**

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of death due to any cause taking place during the study (N = 1; n = 130; RR = 1.00; 95% CI, 0.06 to 15.65).

**Effect of treatment on acceptability**

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of patients leaving the study early by six or 12 months (N = 1; n = 130; RR = 0.60; 95% CI, 0.15 to 2.41) or by 20 months (N = 1; n = 130; RR = 1.17; 95% CI, 0.41 to 3.28).

**Effect of treatment on burden to family life**

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of a patient’s family reporting disruption to their daily routine due to the patient’s illness by three months (N = 1; n = 130; RR = 0.88; 95% CI, 0.70 to 1.10).

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of a patient’s family reporting significant disruption to their social life due to the patient’s illness by three months (N = 1; n = 130; RR = 0.83; 95% CI, 0.67 to 1.02).

There is evidence suggesting that there is a statistically significant difference favouring CRHTTs over ‘standard care’ on reducing the likelihood of a patient’s family reporting physical illness due to the patient’s illness by three months but the size of this difference is unlikely to be of clinical significance (N = 1; n = 130; RR = 0.84; 95% CI, 0.73 to 0.96).
There is some evidence suggesting a clinically significant difference favouring CRHTTs over ‘standard care’ on reducing the likelihood of a patient’s family reporting physical illness due to the patient’s illness by six months (N = 1; n = 130; RR = 0.79; 95% CI, 0.66 to 0.95).

Effect of treatment on burden to community

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of patients being arrested (N = 1; n = 130; RR = 0.76; 95% CI, 0.51 to 1.12).

There is insufficient evidence to determine whether there is a clinically significant difference between CRHTTs and ‘standard care’ on reducing the likelihood of patients using emergency services (N = 1; n = 130; RR = 0.86; 95% CI, 0.51 to 1.45).

Clinical summary

The very large majority of patients with depression are never admitted to hospital (in contrast to schizophrenia where 60% to 70% are admitted to hospital at first presentation; McGorry & Jackson, 1999). Therefore, it is unsurprising that much of the evidence base is drawn from the treatment of schizophrenia and this means that there is currently insufficient evidence from RCTs to determine the value of CRHTTs for people with depression. Nevertheless, CRHTTs may have value for that small group of patients with depression that require a higher level of care than can be provided by standard community services.

5.3.8 Clinical practice recommendations

(These are the same as the previous guideline but edited to fit NICE update style)

5.3.8.1 Crisis resolution and home treatment teams should be used as a means of managing crises for people with severe depression who are assessed as presenting significant risk, and as a means of delivering high-quality acute care. In this context, teams should pay particular attention to risk monitoring as a high-priority routine activity in a way that allows people to continue their normal lives without disruption.12

5.3.8.2 Crisis resolution and home treatment teams should be considered for people with depression who might benefit from early discharge from hospital after a period of inpatient care.12

5.3.8.3 Inpatient treatment should be considered for people with depression who are at significant risk of suicide, self-harm or self neglect.12

12 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
5.3.8.4 The full range of high intensity psychological therapies should normally be offered in inpatient settings. However, consideration should be given to increasing the intensity and duration of the treatments and ensuring that they can be provided effectively and efficiently on discharge.

5.4 Day hospitals

5.4.1 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 (Dick et al., 1985; Creed et al., 1990).

Definition

Acute psychiatric day hospitals were defined for the purposes of the guideline as units that provided ‘diagnostic and treatment services for acutely ill individuals who would otherwise be treated in traditional psychiatric inpatient units’. Thus, trials would be eligible for inclusion only if they compared admission to an acute day hospital with admission to an inpatient unit. Participants were people with acute psychiatric disorders (where the majority of the sample were diagnosed with non-psychotic disorders) who would have been admitted to inpatient care had the acute day hospital not been available. Studies were excluded if they were largely restricted to people who were under 18 years or over 65 years old, or to those with a primary diagnosis of substance misuse or organic brain disorder.

Studies considered for review

The GDG selected a Health Technology Assessment (Marshall et al., 2001) as the basis for this section. Marshall et al. (2001) focused on adults up to the age of 65 and reviewed nine trials of acute day hospital treatment published between 1966 and 2000. A further search identified no new RCTs suitable for inclusion. Of the nine studies included in the existing review, only three (DICK1985, SCHENE1993, SLEDGE1996) met the inclusion criteria set by the GDG, providing data for 510 participants.

Clinical evidence statements

The studies included in this review examined the use of acute day hospitals as an alternative to acute admission to an inpatient unit. The individuals involved in the studies were a diagnostically mixed group, including between 50 and 62% of people with a diagnosis of mood or anxiety disorder. Moreover, acute day hospitals are not suitable for people subject to compulsory treatment, and some studies explicitly excluded people with families unable to provide effective support at home. Clearly, the findings from this review, and the recommendations based upon them, cannot be generalised to all people with depression who present for acute admission.

Effect of treatment on efficacy

There is insufficient evidence to determine whether there is a clinically significant difference between acute day hospitals and inpatient care on reducing the likelihood of readmission to hospital after discharge from treatment (N = 2; n = 288; RR = 1.02; 95% CI, 0.74 to 1.43).

Effect of treatment on inpatient days per month
There is some evidence suggesting that there is a clinically significant difference favouring acute day hospitals over inpatient care on inpatient days per month ($N = 1; n = 197; WMD = -2.11; 95\% CI, -3.46 to -0.76$).

**Effect of treatment on acceptability**

There is insufficient evidence to determine whether there is a clinically significant difference between acute day hospitals and inpatient care on reducing the likelihood of patients leaving the study early for any reason ($N = 2; n = 288; RR = 0.86; 95\% CI, 0.29$ to $2.59$).

### 5.4.2 Non-acute day hospital care

**Introduction**

Although the earliest use of day hospitals in mental health care was to provide an alternative to inpatient care (Cameron, 1947), non-acute day hospitals have also been used for people with refractory mental health problems unresponsive to treatment in outpatient clinics. Two broad groups of people have been referred for non-acute day hospital care: those with anxiety and depressive disorders who have residual or persistent symptoms, and those with more severe and enduring mental disorders such as schizophrenia.

Given the need for services for people with severe and enduring mental health problems that are refractory to other forms of treatment, the review team undertook a review of the evidence comparing the efficacy of non-acute day hospitals with that of traditional outpatient treatment programmes.

**Definition**

For this section, the GDG agreed the following definition for non-acute day hospitals, in so far as they apply to people with serious mental health problems: Psychiatric day hospitals offering continuing care to people with severe mental disorders.

Studies were excluded if the participants were predominantly either over 65 years or under 18 years of age.

**Studies considered for review**

The GDG chose to use the Cochrane systematic review (Marshall et al., 2003) that compared day treatment programmes with outpatient care for people with non-psychotic disorders, as the starting point for the present section. Of the four studies included in the Cochrane review (BATEMAN1999, DICK1991, PIPER1993, TYRER1979), BATEMAN1999 was excluded from the current section because the sample were patients diagnosed with borderline personality disorder.

Therefore, three studies (DICK1991, PIPER1993, TYRER1979) were included providing data on 428 participants.

**Clinical evidence statements**

**Effect of treatment on death (all causes)**

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on reducing the likelihood of death during the study ($N = 1; n = 106; RR = 2.42; 95\% CI,$
Effect of treatment on efficacy

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on reducing the likelihood of admission to hospital during the study at six to eight months (N = 2; n = 202; RR = 1.48; 95% CI, 0.38 to 5.76) and at 24 months (N = 1; n = 106; RR = 1.81; 95% CI, 0.54 to 6.05).

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on improving the patient’s mental state (change from baseline on the PSE) at four months (N = 1; n = 89; WMD = –3.72; 95% CI, –8.69 to 1.25) and at eight months (N = 1; n = 88; WMD = –3.39; 95% CI, –8.96 to 2.18).

Effect of treatment on social functioning

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on improving the patient’s social functioning (change from baseline on the SFS) at four months (N = 1; n = 89; WMD = –3.24; 95% CI, –8.07 to 1.59) and at eight months (N = 1; n = 89; WMD = –4.38; 95% CI, –9.95 to 1.19).

Effect of treatment on acceptability

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on reducing the likelihood of patients reporting that they were not satisfied with care (assuming that people who left early were dissatisfied; N = 2; n = 200; RR = 0.97; 95% CI, 0.68 to 1.39).

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on reducing the number of people lost to follow-up at six to eight months (N = 2; n = 202; RR = 1.08; 95% CI, 0.49 to 2.38), at about 12 months (N = 1; n = 226; RR = 1.35; 95% CI, 0.94 to 1.94) and at 24 months (N = 1; n = 106; RR = 1.61; 95% CI, 0.85 to 3.07).

Clinical summary

There is currently insufficient evidence to determine whether acute day hospital care differs from inpatient care in terms of readmission to hospital after discharge. With regard to treatment acceptability, the evidence is inconclusive although there is a trend favouring day hospitals.

There is currently insufficient evidence to determine whether non-acute day hospital care differs from outpatient care in terms of admission to hospital, mental state, death, social functioning or acceptability of treatment.

5.5 Non-statutory support

5.5.1 Introduction

It is widely accepted that social support can play an important part in a person’s propensity to develop depression and his or her ability to recover from it. Despite this and the considerable amount of work that has described the importance of social
support, few formal studies of the potential therapeutic benefits of different forms of social support have been undertaken.

There is evidence from a series of studies that providing social support in the sense of befriending (women with depression) confers benefits (Brown & Harris, 1978). There is also evidence to suggest that supported engagement with a range of non-statutory sector services is beneficial, but this study was not limited to patients with depression and so was excluded from the review (Grant et al., 2000). Given that social isolation is associated with poor outcome and chronicity in depression, this is regrettable. Several descriptive reports suggest that the provision of social support (e.g. Newpin; Mills & Pound, 1996) in a variety of non-healthcare settings may confer some benefit and it is hoped that such projects are the subject of more formal evaluation.

There are many organisations offering local group peer support to people with depression, including Depression Alliance and Mind. Although such self-help groups are likely to be beneficial, we were unable to find any research evidence for their effectiveness.

**Definition of non statutory support**

A range of community-based interventions often not provided by healthcare professionals, which provide support, activities and social contact in order to improve the outcome of depression.

**Studies considered for review**

The review team found one RCT (HARRIS1999) of befriending compared with wait list control in people with depression.

**5.5.2 Clinical evidence statements**

**Befriending versus wait list control**

One RCT of befriending (HARRIS1999) was identified, so a descriptive review of the data is presented here. In this trial befriending was defined as ‘meeting and talking with a depressed woman for a minimum of one hour each week and acting as a friend to her, listening and “being there for her”’. The trained volunteer female befrienders were also encouraged to accompany their ‘befriendee’ on trips, to broaden their range of activities, to offer practical support with ongoing difficulties and to help create ‘fresh-start’ experiences often found to precede remission in previous work. ‘Befriendees’ were women with chronic depression in inner London who were interested in being befriended. Women were allowed to be on other treatments such as antidepressants and contact with other healthcare professionals. On an intention-to-treat analysis a clinically significant effect upon remission was found at one year:

There is some evidence suggesting that there is a clinically significant difference favouring befriending over wait list control on increasing the likelihood of patients achieving remission (defined as patients not meeting ‘caseness’ for depression23) (N = 1, n = 86, RR = 0.58; 95% CI, 0.36 to 0.93).

Other treatments monitored naturalistically did not relate to remission nor did initial duration of chronic episode or comorbidity. Although remission tended to be higher among those completing the full 12 months of befriending, as opposed to two to six months, this did not reach statistical significance. This suggests that the benefits of befriending may be obtained by a shorter intervention.
Additional trials with less restricted intake conditions and in more naturalistic general practice settings might confirm volunteer befriending as a useful adjunct to current treatments.

5.5.3 Clinical summary
There is some evidence that befriending given to women with chronic depression as an adjunct to drug or psychological treatment may increase the likelihood of remission.

5.5.4 Clinical practice recommendation
(these are the same as the previous guideline but edited to fit NICE update style)

5.5.4.1 For people with long-standing moderate or severe depression who would benefit from additional social or vocational support consideration should be given to:
- befriending as an adjunct to pharmacological or psychological treatments. Befriending should be by trained volunteers providing, typically, at least weekly contact for between 2 and 6 months
- a rehabilitation programme where a person’s depression has resulted in loss of work or disengagement from other social activities over a longer term.

6 Psychosocial treatments

6.1 Introduction
A range of psychological and related psychosocial treatments for depression have been shown to relieve the symptoms of depression and there is growing evidence that psychosocial therapies can help people recover from depression in the longer-term (NICE, 2004). However, not everyone responds and of those people who do respond not everyone remains free of depression longer-term. Thus, there is a need to offer a range of psychosocial therapies and for further clinical innovation focussed on improving treatment outcomes.

People suffering depression typically prefer psychological and psychosocial treatments to medication (Prins et al., 2008) and value outcomes beyond symptom reduction that include positive mental health and a return to usual functioning (Zimmerman et al., 2006). Significant national initiatives are beginning to explore how to maximise the accessibility, acceptability and cost-effectiveness of psychosocial treatments. This chapter sets out how these therapies have emerged as evidence-based approaches and some of the contextual issues that are important in translating recommendations based
6.1.1 Recommending for psychosocial treatments

NICE’s remit is to consider cost-effective treatments that should be provided in the NHS. This means that treatments need to have been shown to work against robust criteria that support evidence based practice (See Chapter 3) and which are likely to be cost-effective. Since the last guideline there has been significant therapeutic innovation and research effort but in comparison to the research on pharmacological interventions the extent of the development is limited. However, there are sufficient developments to require a significant review of the literature with consequent refinements to existing recommendations. The recommendations in this guideline are pre-dominantly based on the available controlled. It is important to note the limitations of this available data for making recommendations about treatments (see Pilling, 2008 for a fuller discussion of these issues).

First recommendations are made where there are data to support the effectiveness of treatments. While there are a broad array of psychosocial and alternative therapies that people access to help themselves with depression, for many established therapies and promising new developments there will be insufficient data to recommend them. However, absence of evidence does not mean evidence of absence. Just because an approach is not recommended here does not mean that it is not effective or that it should never be provided, rather that the question of efficacy has not yet been satisfactorily addressed. Where established therapies are not recommended, this should not be taken to justify the withdrawal of provision but rather to suggest the need for research to establish their effectiveness or otherwise.

Second, the majority of available trials of psychosocial interventions have focused on the acute treatment of depression, usually of mild to moderate severity and usually of relatively recent onset. Several of the approaches considered below have shown greater efficacy than control conditions in such trials. However, with even the most effective treatments for depression, a substantial minority of patients do not respond adequately to treatment (both pharmacological and psychological) and of those that do a substantial proportion relapse. This means that less than half of treated patients will achieve full remission and sustain it over a period of two years following treatment (e.g. Hollon et al., 2005). Unfortunately, there is a paucity of data on treatment interventions for these many patients with depressive symptoms that have persisted despite first line treatments. As such we recommend that therapists monitor therapy outcomes carefully so that alternative treatments can be offered where patients do not respond or respond only partially to initial treatments.

It is also important to note that such patients with relapsing and persistent problems constitute a significant proportion of the work of psychological treatment services. In the absence of recommendations that can be made on the basis of research evidence, services would do well to maintain a broad base of therapeutic expertise, and a sufficient range of potentially effective treatment options pending further research into which approaches are most effective. In the research recommendations (Section 6.10) we suggest priorities for further research to establish more definitively what therapies
work for what people, especially in enabling people’s longer term recovery, a pressing concern for many people who suffer recurrent depression.

6.1.2 How do psychosocial interventions become evidence-based?

For a therapy to become evidence-based it typically passes through several phases of treatment development (Rounsaville et al., 2001; Medical Research Council, 2008). There is ongoing debate among researchers, therapists and policy makers in psychological therapies about what constitutes evidence and how evidence should be used (Kazdin, 2008) and it would be unrealistic to assume there is consensus. However, the process and methodology that matches the process used by NICE around psychosocial therapies has been described by Salkovskis as an hourglass and we use this metaphor here as an illustration, which applies well to some of the therapies we recommend (Figure 1).

Figure 1

Error! Objects cannot be created from editing field codes.

In the first phase of treatment development a theoretical model and therapeutic approach are articulated. As in most clinical sciences these are normally guided by astute clinical observations and theoretical ideas about processes involved in depression and followed by interventions designed to target these processes. For example, in cognitive therapy negative distortions in thinking were identified as key in maintaining depression and therapy therefore aims to help clients identify and respond to these distortions. Through a process of trial and error clinical innovators find ways to develop a treatment approach, sometimes in the form of a treatment manual. For example a treatment manual for cognitive therapy of depression sets out how to engage people, help people become more active and test out and change their cognitive distortions and underlying beliefs (Beck et al., 1979).

Often in this initial phase of treatment development case reports, single case studies and expert opinion provide preliminary evidence that is used to refine the treatment approach. If the treatment appears promising an uncontrolled open trial enables preliminary research into the potential efficacy of a treatment. This sort of exploratory trial also lays the groundwork for a more definitive trial.

The neck of the hourglass represents the stage where a more definitive randomised controlled trial to establish efficacy is conducted (RCT). In medical research the RCT is generally considered the gold standard for establishing a treatment’s efficacy due to its ability to distinguish between treatment outcomes and outcomes for the group which did not receive treatment. Thus, the new treatment is compared with a meaningful comparison group. Ideally the comparison is another active treatment, and, if ethically justifiable, a further comparison with some kind of control such as a placebo, an attentional control or no treatment. This enables the researchers to conclude that the new treatment is better than no active treatment and as good as or superior as another established treatment. It is beyond the scope of this chapter to discuss the RCT and its role in evaluating psychosocial treatments. RCTs are explored and critiqued in detail elsewhere (Stirman et al., 2005; Westen et al., 2004; De Los Reyes & Kazdin, 2008; Kazdin, 2008).
The final phase of treatment development is depicted in the bottom of the hour glass. Having established that the therapy works, this phase of treatment development asks:

Is the treatment exportable to real world settings where therapist competence may be more variable, treatment delivery less adherent, treatment contexts more varied etc.? In short when the high internal validity expected in an RCT is traded for external validity do the outcomes hold up? Is the treatment cost-effective? Is the treatment acceptable and accessible? Can therapists be readily trained, is the therapy appropriate for NHS settings, is it acceptable to clients, potential therapists and service commissioners? Other research designs, and routinely collected outcomes data, are well suited to answering important questions at this stage. Finally, as the evidence base accumulates systematic literature reviews, meta-analyses and mega-analyses can make sense of larger bodies of data, making inferences about what factors might moderate or mediate treatment effects. These studies also drive the next incremental phases of clinical research.

Recent Systematic Reviews of Psychosocial Treatments for Depression

As part of the development of this guideline we reviewed not only relevant RCTs but we also considered recent meta-analyses that had been published since the last NICE Guideline (NICE, 2004) to inform both our reviews and to provide a better understanding of the context in the updated guidance was being developed. As will be apparent from the summary below while meta-analysis is a powerful tool for synthesizing the results of several studies, it is not without problems. The most frequent challenges are the studies selected for inclusion, the approach to synthesizing the data and the way the results are interpreted.

Of the recent meta-analyses identified during the development of this guideline seven were considered of particular relevance and they are briefly summarised below. All the meta-analyses were assessed for quality and the included studies references were checked to verify we had considered them for the reviews in this guideline.

One meta-analysis compared the efficacy between psychological and pharmacological interventions in the treatment of adult depressive disorders (Cuijpers et al., 2008a). Three meta-analyses analysed the efficacy of psychodynamic psychotherapy in several mental health disorders (Liechsenring et al., 2004; 2008 and Abbass et al., 2008). A further meta-analysis looked at different types of psychological treatments and analysed their effectiveness in the treatment of depression (Cuijpers et al., 2008b). Ekers et al. (2008) reviewed the effectiveness of behaviour activation in the treatment of depression. Finally, a Cochrane review (Mead et al., 2008) evaluated the effectiveness of exercise for the treatment of depression.

Cuijpers et al. (2008a) conclude that pharmacological and psychological interventions may be equivalent in major depression but that pharmacological interventions are more effective for dysthymia than psychological interventions (see Chapter 10 for a review of sub-threshold disorders). This is largely supported by the available data, but that the finding may reflect the fact that the dataset for pharmacological interventions is stronger (more high quality studies, less heterogeneity) than that for psychological interventions, rather than due to a large number of high quality head-to-head studies. Cuijpers et al. (2008b) concluded that there were no large differences in efficacy between any psychological treatments for mild to moderate depression including cognitive behavioural therapy, interpersonal therapy, problem solving, behavioural
activation, short-term psychodynamic therapy, social skills training and non-directive supportive therapy. A more accurate summary would be that they had failed to find such differences rather than they had established that no differences exist and that the reason that they had failed to do so rested on two main issues. First, that they trials they reviewed were designed to test differences in efficacy not establish equivalence (see Piaggio et al, (2006) for fuller discussion of this issue). Secondly, the nature of the disorders reviewed (patient populations included those with physical health problems, dementia and post-natal depression which are not covered by this guideline) and the nature of the interventions compared (they grouped high and low intensity interventions together) seriously limited the data’s ability to support the conclusions they drew.

Both Leichsenring et al. (2004; 2008) and Abbass et al. (2008) conclude that psychodynamic psychotherapy is effective in the treatment of a broad range mental health disorders (and by implication depression). Leichsenring et al., 2008 looked at long-term psychodynamic psychotherapy when compared to other shorter forms of psychotherapy. Leichsenring et al. (2004) and Abbass et al., 2008 evaluated the effectiveness of short-term psychodynamic psychotherapy versus control groups ranging from medical management to psychotherapeutic support. However, it should be noted that these reviews contained very few studies of depression (3) which are considered in the review of psychodynamic psychotherapy in this guideline. The fact that so few studies were concerned with depression limits the validity of their conclusions in relation to this guideline.

Ekers et al.’s (2008) review concludes that behaviour activation is an effective treatment for depression, with outcomes superior to those of supportive counselling and brief psychotherapy. However, it is difficult to agree with their conclusion a number of trials which for sub-threshold disorders, were not peer-reviewed and did not meet the quality criteria established for this guideline. (Note below we consider high and low intensity interventions separately, in Ekers et al as in a number of the other reviews these interventions are combined in the meta-analyses.)

Mead et al (2008) conclude that physical activity should be recommended to people with depressive symptoms and those who fulfil the diagnostic criteria for depression but note that the effects are less convincing for those with an established diagnosis. They do not specify details about particular forms (i.e. aerobic, anaerobic, mixed, etc.), whether group or individual or duration of exercise because of lack of consistent evidence. They state that because discontinuation from exercise can be substantial it is better to recommend a physical activity that the person will enjoy.

The phases of treatment development illustrated in the hourglass take considerable resource and time and this may explain why of the many psychosocial treatments developed to date only a subset have passed through all three phases. This means that many promising therapies have not been subjected to a full test of their efficacy. To take the example of CBT, the development work took place in the 1960’s and 1970’s, the manual was published in 1979 (Beck et al., 1979), the first RCTs were published in the late 1970’s and early 1980’s (Rush et al., 1977; Kovacs et al., 1981; Rush et al., 1981), the first meta-analysis in 1990 (Robinson et al., 1990) and the effectiveness and cost-effectiveness studies have only started to emerge in the last decade (Bower et al., 2000; Scott et al., 2003; Byford et al., 2003).
In summary, over the last 100 years there has been an explosion of theories and therapies for depression. However, only a relatively small number of therapies have travelled the empirical road and demonstrated that they are efficacious, and can be cost-effective treatment options for the NHS.

Increasing the availability of psychosocial therapies in health care settings?

The 2004 NICE Guideline (NICE, 2004) has been influential in reshaping the sorts of psychosocial depression treatments available to people suffering depression. Most notably there has been a recent increase in the accessibility of evidence-based therapies, mainly for patients with less complex or enduring disorders at the level of primary care. Alongside the NICE Guideline and evidence base a number of factors determine whether a psychosocial therapy becomes accessible in the NHS. First, public demand and expectation influences service commissioners. User groups have long advocated the need for psychosocial approaches and this has influenced commissioning at a national and regional level. The high direct and indirect costs associated with depression, and the tremendous human suffering for people who experience depression and their friends and families have also been drivers. Psychosocial therapies, particularly high intensity therapies that involve one-to-one therapy over longer periods of time, are resource intensive. The NHS has limited resources and there are therefore drivers to find therapies that are as cost-effective as possible. This has been one of the drivers for the development of less intensive therapies as well as innovative delivery formats such as group based work. Finally, there is greater understanding of how depression presents in the NHS and models of care and service delivery have been shaped accordingly (See Chapter 5).

6.1.3 Improving Access to Psychological Therapies (IAPTS) initiative as an example of increasing the accessibility of established evidence-based therapies

The Improving Access to Psychological Therapies (IAPT) (DH, 2007) programme seeks to support Primary Care Trusts in England in implementing NICE guidelines for people suffering from depression and anxiety disorders. (Similar programmes are underway in Scotland and Northern Ireland.) The goal is to alleviate depression and anxiety using NICE recommended treatments and help people return to full social and occupational functioning. The development of IAPT was driven by an acknowledgement that the treatments NICE recommended were not as accessible as they should be and sought to redress this imbalance through a large investment of new training monies and service monies in the NHS.

The IAPT programme began in 2006 with demonstration sites in Doncaster and Newham focusing on improving access to psychological therapies services for adults of working age. In 2007, 11 IAPT Pathfinders began to explore the specific benefits of services to vulnerable groups. A national rollout of IAPT delivery sites is now underway and is scheduled to complete in 2013. It is expected that it will lead to large increases in the accessibility of evidence-based psychosocial treatments. The intention is to provide £340 million of additional funding to train 3,500 therapists and treat a further 45,000 patients per year. The initial focus of the programme is on high and low intensity psychological CBT based interventions focused on new presentations to services and including the opportunity for self-referral. Many of those presenting to services will of course have chronic disorders and will, in the case of depression
require not just the treatment of the acute problems but also help with the prevention of relapse. In 2009 it is expected that other intervention such as IPT will form part of the treatments offered by IAPT.

Another essential element, in addition to CBT, of the NICE 2004 guideline that was introduced by IAPT is the stepped care framework (see Chapter 5 for further details) which is the organising principle for the provision of IAPT services. A key element of the organisation of psychological therapies in the IAPT programme is between high intensity psychological interventions (that is formal psychological therapies provided by a trained therapist such as CBT, IPT or couples therapy) and low intensity interventions such as guided self-help, computerised cognitive behavioural therapy and exercise where a para-professional acts to facilitate or support the use of self-help materials and not as a provider of therapy per se. This distinction between high and low intensity is adopted in this guideline and is the basis on which sections 6a and 6b of this chapter are organised.

6.1.4 Contextual factors that impact on clinical practice

Clinical guideline recommendations are based on syntheses of reasonably sized trials comprising groups of patients with depression; inevitably they make recommendations about average patients. Of course this approach is consistent with the approach taken in all clinical guidelines and set out in Chapter 1 of this guideline; that is clinical guidelines are a guide for clinicians and not a substitute for clinical judgement which often involves tailoring the recommendation to the needs of the individual. Unfortunately the relationship of factors which may influence the tailoring of clinical practice recommendations and in particular the relationship to outcomes, is poorly understood in psychological interventions (and pharmacological interventions (see Chapters 7, 8 and 9). In the same way that RCTs can be critiqued, so too some of the assumptions typically made in clinical practice can be critiqued (Kazdin, 2008). There is an increasingly sophisticated research literature addressing factors that can affect treatment choices and outcomes but the research has as yet produced little that directly relates to the outcome of psychosocial treatments for depression. It is beyond the scope of this chapter to review these in depth, but some of the key factors that may influence treatment decisions are discussed below. Interested readers are referred to one of several key texts for a comprehensive review (e.g., Kreamer et al, 2002; Lambert, 2004; Roth and Pilling, 2009)

Client factors

A broad array of client factors that could potentially affect treatment choices have been considered, including demographics, marital status, social factors and culture, nature of depression, stage of change, expectations and preferences and experiences of previous treatment. In the main, few factors consistently predict treatment outcomes except chronicity and severity of depression which predict compromised treatment outcomes across treatment modalities (e.g. Sotsky et al, 1991).

Therapist factors

Several therapist factors that could potentially affect treatment have been considered, including therapist demographics, professional background, training, use of
supervision and competence. Two aspects of this are dealt with in some detail below: the therapeutic alliance and therapist competence.

The therapeutic alliance

There are various definitions of the therapeutic alliance, but essentially it is viewed as a constructive relationship between therapist and client, characterised by a positive and mutually respectful stance in which both parties work on the joint enterprise of change. Bordin, (1979) conceptualised the alliance as having three elements comprising the relationship between therapist and patient, agreement on the relevance of the tasks (or techniques) employed in therapy, and agreement about the goals or outcomes the therapy aims to achieve.

There has been considerable debate over the importance of the alliance as a factor in promoting change with some arguing that technique is inappropriately privileged over the alliance, a position reflected in many humanistic models, where the therapeutic relationship itself is seen as integral to the change process, with technique relegated to a secondary role (e.g. Rogers 1951). The failure of some comparative trials to demonstrate differences in outcome between active psychological therapies (e.g. Elkin et al, 1994) is often cited in support of this line of argument and is usually referred to as the dodo-bird hypothesis (Luborsky et al 1975). However, apart from the fact that dodo-bird findings may not be as ubiquitous as is sometimes claimed this does not logically imply that therapy technique is irrelevant to outcome. Identifying and interpreting equivalence of benefit across therapies remains a live debate (e.g. Ahn and Wampold 2001, Stiles et al. 2006) but should also include a consideration of cost-effectiveness as well as clinical efficacy (NICE, 2007).

Meta-analytic reviews report consistent evidence of a positive association of the alliance with better outcomes with a correlation of around 0.25 (e.g. Horvath and Symonds, 1991, Martin et al., 2000), a finding which applies across a heterogeneous group of trials (in terms of variables such as type of therapy, client presentation, type of measures applied, and the stage of therapy at which measures are applied). However, it is the consistency, rather than the size of this correlation, which is most striking, since it accounts for only 6% of the variance in the known outcome. Therefore it seem reasonable to debate the extent to which a good alliance is necessary to outcome, but clearly it unlikely to be sufficient.

Therapist Competence

Studies of the relationship between therapists and outcomes suggest that all therapists have variable outcomes, although some therapists will produce consistently better outcomes across clients (e.g., Okiishi et al., 2003).

There is evidence that more competent therapists produce better outcomes (Barber et al., 1996; Barber et al., 2006; Kuyken & Tsivrikos, 2009;). A number of studies have also sought to examine more precisely therapist competence and its relation to outcomes; that is what it is that therapists do in order to achieve good outcomes. A number of studies are briefly reviewed here; this section, which focuses mainly on CBT and depression, draws on a more extensive review of the area by Roth and Pilling (2009). In an early study Shaw et al. (1999) examined competence in the treatment of 36
patients treated by 8 therapists offering CBT as part of the NIMH trial of depression (Elkin et al. 1986). Ratings of competence were made the Cognitive Therapy Scale (CTS). Although simple correlation of the CTS with outcome suggested that it contributed little to outcome variance, regression analyses indicated a more specific set of associations. Specifically, when controlling for pre-therapy depression scores, adherence and the alliance the overall CTS score accounted for 15% of the variance in outcome. However, a subset of items on the CTS account for most of this association. Some understanding of what may account for this association emerges from three studies by Rob DeRubeis’s research group ((DeRubeis and Feeley (1990), Feeley et al., (1999), Brotman et al. (in preparation)). All the studies made use of the Collaborative Study Psychotherapy Rating Scale (CSPRS: Hollon et al.1988), subscales of which contained items specific to CBT. On the basis of factor analysis the CBT items were separated into two subscales, labelled ‘Cognitive therapy – Concrete’ and ‘Cognitive therapy – Abstract’. (Concrete techniques can be thought of as pragmatic aspects of therapy (such as establishing the session agenda, setting homework tasks, or helping clients identify and modify negative automatic thoughts). Both DeRubeis and Feeley (1990) and Feeley et al. (1999) found some evidence for a significant association between the use of ‘concrete’ CBT techniques and better outcomes.

Trepka et al. (2004) examined the impact of competence through analysis of outcomes in Cahill et al. (2003). Six clinical psychologists (with between 1 and 6 years post-qualification experience) treated 30 depressed clients using CBT, with ratings of competence made on the CTRS. In a completer sample (N=21) better outcomes were associated with overall competence on the CTRS (r= 0.47); in the full sample this association was only found with the “specific CBT skills” subscale of the CTRS. Using a stringent measure of recovery (a BDI score no more than one SD from the non-distressed mean) nine of the 10 completer patients treated by the more competent therapists recovered, contrasted to four of the 11 clients treated by the less competent therapists. These results remained robust even when analysis controlled for levels of the therapeutic alliance.

Agreeing and monitoring homework is one of the set of ‘concrete’ CBT skills identified by researchers reviewed above. All forms of CBT place an emphasis on the role of homework because it provides a powerful opportunity for clients to test-out their expectations. A small number of studies have explored whether compliance with homework is related to better outcomes, though rather fewer have examined the therapist behaviours associated with better client “compliance” with homework itself. Kazantzis et al. (2000) report a meta-analysis of 27 trials of cognitive or behavioural interventions which contained data relevant to the link between homework assignment, compliance and outcome. In 19 trials clients were being treated for depression or anxiety; the remainder were seen for a range of other problems. Of these 11 reported on the effects of assigning homework in therapy, and 16 on the impact of compliance. The type of homework varied, as did the way in which compliance was monitored, though this was usually by therapist report. Overall there was a significant, though modest, association between outcome and assigning homework tasks (r = 0.36), and between outcome and homework compliance (r = 0.22). While Kazantzis et al. indicate that homework has greater impact for clients with depression than anxiety disorders, the number of trials on which this comparison is made is small.

Bryant et al. (1999) examined factors leading to homework compliance in 26 depressed clients receiving CBT from 4 therapists. As in other studies, greater compliance with
homework was associated with better outcome. In terms of therapist behaviours, it was not so much therapists’ CBT-specific skills (such as skilfully assigning homework or providing a rationale for homework) which were associated with compliance, but ratings of their general therapeutic skills, and particularly whether they explicitly reviewed the homework assigned in the previous session. There was also some evidence that compliance was increased if therapists checked how the client felt about the task being set, and identified potential difficulties in carrying it out.

The focus of the research on both the alliance and therapist competence has been on high intensity interventions but it is the view of the GDG that they are potentially of equal importance in the effective delivery of low intensity interventions.

### 6.1.5 Databases searched and inclusion/exclusion criteria for clinical evidence

For the guideline update, a new systematic search was carried out looking at both published and unpublished randomised controlled trials (RCTs). The electronic databases searched for published trials are given in Table 18 (further information about the search strategy can be found at appendix 17).

**Table 18: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological treatments**

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria, or depressive symptoms as indicated by depression scale score for subthreshold and other groups</td>
</tr>
<tr>
<td>Treatments</td>
<td>Behaviour activation</td>
</tr>
<tr>
<td></td>
<td>Cognitive behavioural therapies</td>
</tr>
<tr>
<td></td>
<td>Computerised cognitive behaviour therapy</td>
</tr>
<tr>
<td></td>
<td>Counselling</td>
</tr>
<tr>
<td></td>
<td>Couples-focused therapy</td>
</tr>
<tr>
<td></td>
<td>Guided self-help</td>
</tr>
<tr>
<td></td>
<td>Interpersonal therapy</td>
</tr>
<tr>
<td></td>
<td>Problem solving</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
</tr>
<tr>
<td></td>
<td>Psychodynamic psychotherapy</td>
</tr>
<tr>
<td></td>
<td>Rational emotive behaviour therapy</td>
</tr>
</tbody>
</table>

Studies considered in the systematic review of clinical evidence

A total of 127 trials relating to clinical evidence met the eligibility criteria set by the GDG, providing data on 13,531 participants. All trials were published in peer-reviewed journals between 1979 and 2009. In addition, 51 studies found in the search for this guideline update were excluded from the analysis. Two studies included in the previous guideline were excluded from this update guideline (see section 1.1.24 Clinical evidence for guided self-help). Further information about both included and excluded studies can be found in Appendix 17.
6.2 Low intensity Psychosocial Interventions:

6.2.1 Computerised Cognitive Behaviour Therapy

Introduction

The use of information technology to deliver psychological treatments has been explored, for example: self-help delivered by telephone (Osgood-Hynes et al., 1998), over the internet (Christensen et al., 2002), or by computer (Proudfoot et al., 2004). Cognitive behavioural therapy (CBT) may lend itself readily to computerisation and to date CBT is the main psychological treatment approach that has been developed in this manner.

Computerised cognitive behaviour therapy (CCBT) is a form of CBT, which is delivered using a computer (including CD-ROM and the internet). It can be used as the primary treatment intervention, with minimal therapist involvement or as augmentation to a therapist-delivered programme where the introduction of CCBT supplements the work of the therapist; this review is essentially concerned with its use as a primary treatment.

Essentially these programmes engage the patient in a structured programme of care, the content of which is similar to and based on the same principles to that of therapy provided by a therapist following a standard CBT programme. Direct staff input is usually limited to introducing the programme, brief monitoring and being available for consultation. Most of the programmes have been developed to treat a range of depressive and/or anxiety disorders, often explicitly as part of a stepped care programme. The programmes vary considerably in style, degree of complexity and content.

Early studies suggested that patients find computer-based treatment acceptable and they manifest degrees of clinical recovery of similar magnitude to those with face-to-face therapy (Selmi et al., 1990). The technology more recently available has led to the development of a more sophisticated range of computer-based or internet-based CBT programmes. These have been the subject of a technology appraisal by (NICE, 2005) which covers both depression and anxiety. However, this review in this guideline will supersede that aspect of the technology appraisal concerned with depression.

Clinical evidence

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 19. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

Table 19 Summary study characteristics of CCBT studies

<table>
<thead>
<tr>
<th></th>
<th>CCBT versus control</th>
<th>CCBT versus active control</th>
<th>Therapist augmented CCBT versus control</th>
<th>Therapist augmented CCBT versus active control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total)</td>
<td>6 RCTs (1376)</td>
<td>2 RCTs (548)</td>
<td>1 RCT (30)</td>
<td>1 RCT (30)</td>
</tr>
<tr>
<td>Study IDs</td>
<td>N / % female</td>
<td>Mean age</td>
<td>Diagnosis</td>
<td>CCBT program</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>----------</td>
<td>-----------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| (1) ANDERSSON2005A  
(2) CHRISTENSEN2004A*  
(3) CLARKE2002  
(4) CLARKE2005*  
(5) PROUDFOOT2004A  
(6) SPEK2007* | (1) 117/74  
(2) 360/71  
(3) 223/75  
(4) 200/77  
(5) 274/74  
(6) 202/63 | (1) 36  
(2) 36  
(3) 44  
(4) 47  
(5) 44  
(6) 55 | (1) major depression  
(2) >=12 KPDS  
(3) depression  
(4) depression  
(5) mixed depression & anxiety  
(6) <12 EDS | (1) not reported  
(2) MoodGYM  
(3) Overcoming Depression on the Internet  
(4) Overcoming Depression on the Internet  
(5) Beating the Blues  
(6) Coping with Depression | (1) email feedback from therapist  
(2) phone to direct website use by lay interviewer  
(3) email reminders  
(4) phone/postcard reminders  
(5) nurse facilitating use at clinic  
(6) no support | (1) Online discussion group  
(2) Weekly phone discussion  
(3) Health information webpage  
(4) Health information webpage  
(5) TAU  
(6) Waitlist | (1) 10 wks  
(2) 6 wks | (1) 10 wks  
(2) 6 wks | (1) 6 wks  
(2) not reported | (1) 8 wks | (1) 8 wks |
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>CCBT vs. waitlist control</th>
<th>CCBT vs. TAU control</th>
<th>CCBT vs. discussion control</th>
<th>CCBT vs. information control</th>
<th>CCBT vs. any control</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 6 months</td>
<td>RR 0.82 (0.57 to 1.16) (34.3% vs. 42%)</td>
<td>RR 1.35 (0.95 to 1.93) (37% vs. 27.3%)</td>
<td>RR 2.24 (1.52 to 3.31) (28% vs. 12.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) 6 &amp; 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) 2, 3, 5, 8 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*3-armed trial

**Table 20 Summary evidence profile for CCBT versus control**

<table>
<thead>
<tr>
<th>Leaving study early for any reason</th>
<th>CCBT vs. waitlist control</th>
<th>CCBT vs. TAU control</th>
<th>CCBT vs. discussion control</th>
<th>CCBT vs. information control</th>
<th>CCBT vs. any control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=202</td>
<td>K=1; n=274</td>
<td>K=2; n=477</td>
<td>K=1; n=195</td>
<td>K=2; n=380</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -0.27 (-0.54 to 0.01)</td>
<td>SMD -0.62 (-0.91 to -0.33)</td>
<td>SMD -0.61 (-1.22 to 0)</td>
<td>SMD -0.23 (-0.43 to -0.02)</td>
<td>SMD -0.4 (-0.58 to -0.22)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=202</td>
<td>K=1; n=195</td>
<td>K=2; n=380</td>
<td>K=2; n=369</td>
<td>K=6; n=1146</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Forest plot**

<table>
<thead>
<tr>
<th>3m follow-up</th>
<th>5m follow-up</th>
<th>6m follow-up</th>
<th>8m follow-up</th>
<th>12m follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression self-report measures at follow-up</td>
<td>SMD -0.4 (-0.7 to -0.11)</td>
<td>SMD -0.42 (-0.73 to -0.11)</td>
<td>SMD -0.2 (-0.46 to 0.06)</td>
<td>SMD -0.56 (-0.85 to -0.27)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=178</td>
<td>K=1; n=164</td>
<td>K=1; n=237</td>
<td>K=1; n=186</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 21 Summary evidence profile for CCBT versus active control

<table>
<thead>
<tr>
<th></th>
<th>CCBT vs. psychoeducation control</th>
<th>CCBT vs. group CBT control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early for any reason</td>
<td>RR 1.67 (1.08 to 2.59) (25.3% vs. 15.2%)</td>
<td>RR 0.79 (0.56 to 1.12) (34.3% vs. 43.4%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=347</td>
<td>K=1; n=201</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -0.03 (-0.27 to 0.2)</td>
<td>SMD 0.06 (-0.22 to 0.34)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=276</td>
<td>K=1; n=201</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 6m follow-up

| Depression self-report measures at follow-up                     | SMD 0.05 (-0.21 to 0.31)         | SMD -0.02 (-0.22 to 0.17)   |
| Quality                                                         | Moderate                         | Moderate                   |
| Number of studies; participants                                 | K=1; n=221                       | K=2; n=402                  |
| Forest plot                                                     |                                  |                            |

### Table 22 Summary evidence profile for therapist augmented CCBT versus waitlist control

<table>
<thead>
<tr>
<th></th>
<th>Therapist augmented CCBT vs. waitlist control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early for any reason</td>
<td>RR 2 (0.2 to 19.78) (13.3% vs. 6.7%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -1.28 (-2.07 to -0.48)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
</tr>
</tbody>
</table>

### Table 23 Summary evidence profile for therapist augmented CCBT versus therapist CBT control

<table>
<thead>
<tr>
<th>Therapist augmented CCBT vs. CBT control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early</td>
</tr>
</tbody>
</table>

Depression in adults (update): full guideline DRAFT (February 2009)
for any reason

<table>
<thead>
<tr>
<th>Quality</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Forest plot</th>
<th>Depression self-report measures at endpoint</th>
<th>Depression self-report measures at 3m follow-up</th>
<th>Depression self-report measures at 6m follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
<td>K=1; n=30</td>
<td>K=1; n=30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Forest plot</th>
<th>Depression clinician-report measures at endpoint</th>
<th>Depression clinician-report measures at 3m follow-up</th>
<th>Depression clinician-report measures at 3m follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
<td>K=1; n=30</td>
<td>K=1; n=30</td>
</tr>
</tbody>
</table>

Clinical summary for CCBT

From the six studies that compared CCBT with a control group, one study (PROUDFOOT2004A) indicated that CCBT had a significant medium effect (SMD -0.40) in reducing self-reported depression scores when compared to wait list control at 3 month follow-up; a significant medium sized effect (SMD -0.42) when compared to treatment as usual at 5 month follow-up; a significant small to medium effect when compared to information control at endpoint (SMD -0.23) and 8 month follow-up (SMD -0.56); and a significant small effect (SMD -0.23) when compared to any control at 24 month follow-up. When CCBT was compared to active controls (psychoeducation and group CBT) no clinically important difference were identified. In the one small study (WRIGHT2005A) looked at therapist augmented CCBT and compared it to both therapist only CBT and a wait list control, there was a large effect of therapist augmented CCBT in decreasing self-reported depression scores compared to waitlist (SMD -1.28) and a small to modest advantage of CCBT augmented therapy over CBT alone.

Health Economic Evidence review and considerations

The previous guideline made reference to an unpublished paper on CCBT by McCrone et al. (2003) and the economic review for the technology appraisal by Kaltenhaler et al. (2002). The first paper was subsequently published and the Kaltenhaler et al. paper was updated in 2006. The paper by McCrone is one of the earliest economic evaluations of CCBT and apart from the technology appraisal it is the only published economic evaluation available. It compares the Beating the Blues (BtB) software...
package and treatment as usual in the care of people with anxiety and/or depression treated in primary care. This study was based on a well conducted RCT by Proudfoot et al (2004) . BtB was found to be ‘clinically superior to treatment as usual, at negligible additional cost’. It was also thought to have a higher probability of being cost-effective from the perspective of the health service. The results were reported in terms of QALYs, thereby allowing comparisons to be made with other economic studies. However, the issue of the generalisability of the study results was not touched upon. This study was reviewed during the technology appraisal and they pointed out weakness in the method of the study which they addressed in the model developed for the technology appraisal . The indirect method in which QALYs were estimated (from a range of published sources) was replaced by a more direct approach of mapping BDI scores onto utility values. They also highlighted a weakness in the costing for the intervention: the throughput levels used to estimate the cost per patient using the program was based on unrealistic assumptions about the number of patients likely to be picked up from a general practice.

The economic analysis for the technology appraisal by Kaltenhaler et al. aimed to evaluate a range of CCBT packages for the treatment of depression and other mental health disorders. The software packages considered for depression included BtB, Overcoming Depression and Cope. The study included a review of the evidence submitted by sponsors for each of the products and of published literature.  . BtB achieved the lowest cost per QALY. Variation in cost effectiveness by severity of depression was also explored with a subgroup analysis and no differences were found. However, the findings were subject to considerable uncertainties. Strong assumptions were made in the face of absent data e.g. relapse rates. There were also significant uncertainties around the costs of the licence per patient owing to a lack of clarity around the ‘organisational level for purchasing these products and the likely throughput’ of people receiving CCBT.

Summary of Health Economic Evidence

Despite the uncertainties BtB was recommended by NICE (2005) as suitable treatment for patients with depression.

All CCBT economic evaluations based on RCTs to date are those based on BtB and Proudfoot2004. To date no new BtB RCT data has become available and there have been no new published economic evaluations in the UK related to BtB or other CCBT packages. Therefore the BtB effectiveness data has remained the same. The problem of paucity of data mentioned in the HTA remains, with no new RCT evidence the assumptions regarding compliance, relapse rates and costings made in the previous economic evaluations cannot be challenged with new evidence and changed.

The clinical effectiveness data reviewed for this guideline suggests that other CCBT packages (internet/web based) may be as effective as BtB. The results are based on indirect evidence as no head-to-head trials were identified. Advancements in the field of economic evaluations have allowed for the development of indirect treatment comparison models. Using such techniques different CCBTs (as presented in the CCBT clinical evidence) could be compared using the indirect trial evidence in the absence of head-to-head trials. However, indirect comparisons can only be made providing they are compared to controls that are uniform. Unfortunately the studies highlighted in the review have very different controls and different measures are used as outcome measures. The dichotomous nature of the outcomes of the meta-analysis highlights a
further obstacle to economic analysis. As the measure of benefit could not be reported as cost per QALY but as the cost per SMD (standard mean difference). This is essentially meaningless as to our knowledge, SMDs cannot be mapped on to QALYs.

The CCBT packages reviewed are considered to be as effective as BtB, they are also cheaper as they are available free of charge. Therefore they should be cost effective given the ICERs reported in both the McCrone and HTA evaluations were judged to be so in the technology appraisal.

6.2.2 Guided Self-Help

Introduction

Guided self-help is defined as a self-administered intervention designed to treat depression, which makes use of a range of books or other self-help manuals based on an evidence-based intervention and designed specifically for the purpose. A healthcare professional (or para-professional) facilitates the use of this material by introducing, monitoring and reviewing the outcome of such treatment. This intervention would have no other therapeutic goal, and would be limited in nature, usually no less than three contacts and no more than six.

Guided self-help is generally accepted as being more than simply giving patients literature to read (this simpler alternative is usually referred to as pure self-help), and often is based on a cognitive or behavioural psychological approach. Contact with professionals is limited and tends to be of a supportive or facilitative nature. It is potentially more cost-effective for patients with milder disorders, and could lead to more effective targeting of professional resources. Most of the early literature on guided self-help came from the US. In the US, there are over 2000 self-help manuals of different sorts published each year, and it is not within the scope of this guideline to make recommendations on specific self-help manuals, but rather the principle and practice of guided self-help in the NHS and related services.

Guided self-help has some obvious limitations, particularly with written materials, such as a requirement of a certain reading ability, and understanding of the language used. For example, 22% of the US population is functionally illiterate, and 44% will not read a book in any year (NCES, 1997). On the other hand, many patients are not keen on using medication, because of antidepressant intolerance, drug interactions, pregnancy, breast feeding or personal preference, and many patients are understandably worried about having a formal diagnosis of depression recorded in their medical records. For those people, guided self-help can be a more accessible and acceptable form of therapy. Carers and family members can also be involved in understanding the nature and course of depression through the material made available. The majority of guided self-help programmes are in book form and this review is limited to these studies.

Clinical evidence for guided self-help

The review undertaken for the original guideline was updated with new studies. Since there had been only 9 included studies in the original review, and 20 new studies were found, the review was substantially re-formed. Note that 2 of the studies included in
The included studies were grouped based on the nature of support offered to patients. Data were available to examine the following strategies compared with waitlist or treatment as usual:

- Individual guided self-help
- Group psychoeducation/group guided self-help
- Bibliotherapy/telephone guided self-help
- Pure self-help/contact by mail only.

Data were also available to make the following comparisons:

- Individual versus group
- Individual versus telephone contact only
- Group guided self-help versus telephone contact only
- Guided self-help versus psychotherapy.

It was possible to undertake the following sub-analyses:

- Depression diagnosis – formal diagnosis, no formal diagnosis
- Use of medication – all patients on medication, some patients on medication.

Summary study characteristics of the included studies are in Table 24 in full details in Appendix 17 which also includes details of excluded studies.

Table 24 Summary study characteristics of studies of guided self-help

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Individual guided self-help</th>
<th>Group psychoeducation/group guided self-help</th>
<th>Telephone guided self-help</th>
<th>Self-help with support by mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/ % female/ mean age</td>
<td>(1) 30/55/37 (2) 59/73/38 (3) 22/86/42 (4) 281/68/41</td>
<td>(1) 120/93/NA (2) 319/73/44 (3) 56/86/42</td>
<td>(1) 76/70/47 (2) 30/55/37 (3) 46/76/68 (4) 80/84/40 (5) 23/87/40 (6) 56/86/42 (7) 29/79/70 (8) 67/85/68 (9) 216/66/41</td>
<td>(1) 177/70/19 (2) 96/80/40 (3) 95/70/18</td>
</tr>
</tbody>
</table>
### Diagnosis

|   | (1) MDD  
|   | (2) GP diagnosis + BDI > 14  
|   | (3) BDI >= 10  
<table>
<thead>
<tr>
<th></th>
<th>(4) BDI &gt;= 14</th>
</tr>
</thead>
</table>
|   | (1) MDD  
|   | (2) Depression  
<table>
<thead>
<tr>
<th></th>
<th>(3) BDI &gt;= 10</th>
</tr>
</thead>
</table>
|   | (1) MDD  
|   | (2) MDD/minor depression/intermittent depressive disorder  
|   | (3) MDD  
|   | (4) MDD  
|   | (5) MDD/minor depression  
|   | (6) BDI > 10  
|   | (7) HAMD >= 10  
|   | (8) HAMD >= 10  
|   | (9) subthreshold depression |

###Treatment

|   | (1) CWD with individual support  
|   | (2) Individual guided-self help  
|   | (3) Individual self-help  
<table>
<thead>
<tr>
<th></th>
<th>(4) Guided self-help</th>
</tr>
</thead>
</table>
|   | (1) Psycheducation workshop  
|   | (2) Psychoeducation Contactus  
<table>
<thead>
<tr>
<th></th>
<th>(3) Self-help group (large)</th>
</tr>
</thead>
</table>
|   | (1) self-directed therapy  
|   | (2) CWD  
|   | (3) bibliotherapy (Feeling Good)  
|   | (4) bibliotherapy (Feeling Good)  
|   | (5) bibliotherapy (Feeling Good)  
|   | (6) bibliotherapy (self-help manual)  
|   | (7) bibliotherapy (Feeling Good)  
|   | (8) bibliotherapy (Feeling Good)  
<table>
<thead>
<tr>
<th></th>
<th>(9) minimum contact therapy (based on CWD course)</th>
</tr>
</thead>
</table>
|   | (1) Personalised feedback and brochure with coping strategies by mail  
|   | (2) Tailored workbook  
|   | (3) bibliotherapy (Feeling Good) |

###Control

|   | (1) Waitlist  
|   | (2) TAU  
|   | (3) Waitlist  
<table>
<thead>
<tr>
<th></th>
<th>(4) TAU</th>
</tr>
</thead>
</table>
|   | (1) Waitlist  
|   | (2) TAU  
<table>
<thead>
<tr>
<th></th>
<th>(3) Waitlist</th>
</tr>
</thead>
</table>
|   | (1) Group CBT/focused expressive psychotherapy  
|   | (2) Waitlist  
|   | (3) Waitlist  
|   | (4) Waitlist  
|   | (5) Waitlist  
|   | (6) Waitlist  
|   | (7) Waitlist  
|   | (8) Waitlist  
<table>
<thead>
<tr>
<th></th>
<th>(9) TAU</th>
</tr>
</thead>
</table>
|   | (1) list of community resources  
|   | (2) Waitlist  
|   | (3) TAU |

* 4-armed trial; 3-armed trial; *** cluster randomised trial analysed separately
CWD = Coping With Depression course; MDD = Major Depressive Disorder (or equivalent based on recognised diagnostic system); TAU = treatment as usual; NA = not available

### 6.2.3 Clinical evidence summary

When compared to wait list controls or treatment as usual, the evidence indicates that guided self-help has a significant effect in reducing self-reported depression scores at endpoint (WMD -6.89) and at 12 month follow-up (WMD -5.31). More specifically, the
use of books with phone support (WMD -6.71) and phone guided self with initial face to face contact (WMD -9.72) also had a significant effect in reducing BDI scores at endpoint. The use of facilitated self-help books also showed to have a beneficial effect in reducing clinician-rated depression scores (WMD -8.55) at endpoint.

Pure self-help mail contact only when compared to treatment as usual also had an effect in reducing self-report depression scores at endpoint (one study STICE2007; WMD -4.22). However, this effect was not maintained at 1 month or 3 month follow-up in STICE2007 but other studies at 6 month follow-up two studies suggested that this intervention may have a potentially clinically important effect (WMD -3.42).

Group guided self-help when compared to wait list control or treatment as usual also indicates having an effect in reducing self-reported depression scores at endpoint (WMD -2.55) and at 6 month follow-up (WMD -3.83) (this last comparison was based on only one study DALGARD2006). Based on the results of one medium-sized study (WILLIAMS2008), the evidence indicates that individual guided self-help also had a significant effect in reducing BDI scores at 6 month follow-up (WMD -5.31) when compared to treatment as usual.

6.2.4 Health economic considerations

No evidence on the cost-effectiveness of individual or group-based guided self-help programmes for people with persistent minor and mild to moderate depression was identified by the systematic search of the health economics literature.

The clinical evidence in the guideline systematic literature review described interventions consisting of 3-10 sessions over a 9-12 week period. The intervention would be delivered by a mental health professional with each session lasting 15-30 minutes.

Individual guided self-help is likely to be delivered by a low intensity therapy worker on the Agenda for Change Band 5 salary scale. The unit cost of a low intensity therapy worker is not currently available. However, the salary scale for a community mental health nurse at AfC Band 5 is and so this was used. The unit cost of an AfC Band 5 community mental health nurse is £51 per hour of patient contact in 2007/08 prices (Curtis, 2009). This cost includes salary, salary on-costs, overheads and capital overheads plus any qualification costs. In addition, as part of their treatment each person receives a written self-help manual; the booklet ‘A Recovery Programme for Depression’, K. Lovell and D. Richards which currently costs £4 was used as an example for costing purposes.

Based on the estimated staff time associated with delivering an individual guided self-help programme as described above and the cost of an AfC Band 5 post (using the community mental health nurse costing) the average cost of the programme would range between £42 to £259 per person in 2007/08 prices.

Using the lower cost-effectiveness threshold of £20,000 per QALY set by NICE (NICE, 2008), a simple threshold analysis suggests that an individual guided self-help programme would be cost-effective if they improve Health-Related Quality of Life (HRQoL) of people with persistent minor and mild to moderate depression by 0.002-
0.013 per year, on a scale 0 (death) – 1 (perfect health). Using the upper cost-effectiveness threshold of £30,000 per QALY, the improvement in HRQoL required for physical activity programmes to be considered cost-effective fell to 0.001-0.009 per year. Both of these seem achievable given the clinical effectiveness of the interventions.

6.2.5  Physical activity

Introduction
The effect of physical activity on mental health has been the subject of research for several decades. There is a growing body of literature primarily from the US examining the effects of physical activity in the management of depression. In the past decade ‘exercise on prescription’ schemes have become popular in primary care in the UK (Biddle et al., 1994), many of which include depression as a referral criterion.

For the purposes of the guideline, physical activity was defined as a structured, achievable physical activity with a recommended frequency, intensity and duration when used as a treatment for depression. It can be undertaken individually or in a group. Physical activity may be divided into aerobic forms (training of cardiorespiratory capacity) and anaerobic forms (training of muscular strength/endurance and flexibility/co-ordination/relaxation) (American College of Sports Medicine, 1980). The aerobic forms of physical activity, especially jogging or running, have been most frequently investigated. In addition to the type of physical activity, the frequency, duration and intensity should be described.

Guidelines for physical activity referral schemes have been laid down by the Department of Health (2001b) (Mead et al., 2008). Several plausible mechanisms for how physical activity affects depression have been proposed. In the developed world, regular physical activity is seen as a virtue; the depressed patient who takes regular physical activity may, as a result, get positive feedback from other people and an increased sense of self-worth. Physical activity may act as a diversion from negative thoughts, and the mastery of a new skill may be important (Lepore, 1997; Mynors-Wallis et al., 2000). Social contact may be an important benefit, and physical activity may have physiological effects such as changes in endorphin and monoamine concentrations (Leith, 1994; Thoren et al., 1990).

Studies considered for review
For the guideline update, a new systematic search was carried out looking at both published and unpublished randomised controlled trials (RCTs). The electronic databases searched for published trials are given in Table 25 (further information about the search strategy can be found at appendix 8).

---

13 Note in the 2004 guideline the term exercise was used.
Table 25 Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008; January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>Exercise /Physical activity</td>
</tr>
</tbody>
</table>

In total, fifty-nine RCTs were found, of which twenty-five were included and thirty-two were excluded. Principal reasons for exclusion included trials not being RCTs, trials not involving a physical activity intervention, papers not reporting outcome data, or trials not including participants with depression.

Twenty-five studies were included in the review. Of these, nine (BOSSCHER1993, FREMONT1987, GREIST1979, HERMAN2002, KLEIN1985, MCCANN1984, MCNEIL1991, SINGH1997, VEALE1992) were included in the previous guideline.

Data were available to compare physical activity with non-physical activity control, waitlist or pill placebo, psychotherapy, and pharmacotherapy, various combination treatments, and different kinds of physical activity. Since there was a wide range of types of physical activity in the included studies, the GDG divided these into aerobic (for example, running) and non-aerobic (for example, resistance training). Combined data are reported here since there was little difference between aerobic and non-aerobic physical activity. There were insufficient studies to look at specific types of activity separately. The GDG considered supervision to be an important factor in the success of physical activity programmes, and so this factor was also included in the analysis. Since there were a large number of data to report, dichotomous efficacy outcomes were not extracted since these were reported by a relatively small number of studies, whereas continuous outcomes were more widely reported. Since so much of the data are inconclusive, the following comparisons are not reported here but the forest plots can be seen in Appendix 19: physical activity compared with other types of exercise, and some combination strategies (including physical activity plus light therapy) compared with no-physical activity control or physical activity alone.

Physical activity versus no-physical activity control, pill placebo and waitlist
Seventeen studies compared exercise with no-exercise control. See Table 26.

Table 26 Summary of study characteristics of RCTs of physical activity compared with no physical activity control, placebo and waitlist

<table>
<thead>
<tr>
<th>No. RCTs</th>
<th>Supervised aerobic</th>
<th>Supervised non-aerobic</th>
<th>Unsupervised aerobic</th>
<th>Unsupervised non-aerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Study ID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) BERLIN2003*</td>
<td></td>
<td>(1) Butler2008*</td>
<td>(1) BLUMENTHAL2007**</td>
<td></td>
</tr>
<tr>
<td>(2) bLUMENTHAL2007**</td>
<td></td>
<td>(2) Mather2002</td>
<td>(2) Hoffman2008**</td>
<td></td>
</tr>
<tr>
<td>(3) Dunn2005</td>
<td></td>
<td>(3) Singh1997</td>
<td>(3) Singh1997A</td>
<td></td>
</tr>
<tr>
<td>(1) Sims2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/% female/mean age</td>
<td>(1) 55/55/40</td>
<td>(2) 202/76/52</td>
<td>(3) 80/75/36</td>
<td>(4) 20/65/69</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) BDI &gt;= 14</td>
<td>(2) MDD/minor depression/dysthymia</td>
<td>(3) Moderate depressive episode</td>
<td>(4) HRSD &gt;= 10</td>
</tr>
<tr>
<td></td>
<td>(1) Dysthymia/depression/minor depression/dysthymia/mild depressive episode</td>
<td>(2) Mood disorder</td>
<td>(3) MDD/minor depression/dysthymia</td>
<td>(4) Major depression/minor depression/dysthymia</td>
</tr>
<tr>
<td>Exercise</td>
<td>(1) Water aerobics</td>
<td>(2) Walking/jogging</td>
<td>(3) Treadmill/biking at different intensities/frequency</td>
<td>(4) Ballroom dancing</td>
</tr>
<tr>
<td></td>
<td>(1) Yoga</td>
<td>(2) Resistance training</td>
<td>(3) Resistance training</td>
<td>(4) Resistance training</td>
</tr>
<tr>
<td>Control</td>
<td>(1) No treatment</td>
<td>(2) Placebo pill</td>
<td>(3) Stretching</td>
<td>(4) Wait-list</td>
</tr>
<tr>
<td></td>
<td>(1) Health education</td>
<td>(2) Health education</td>
<td>(3) Health education</td>
<td>(4) Health education</td>
</tr>
</tbody>
</table>

Physical activity was more effective in reducing depression symptoms than no-physical activity control, although the effect was reduced at follow-up, see Table 27

Table 27 Summary evidence profile for physical activity versus no-physical activity control

<table>
<thead>
<tr>
<th>Clinician-rated mean depression scores at endpoint</th>
<th>Supervised</th>
<th>Follow-up</th>
<th>Unsupervised</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMD -1.26 (-2.12 to -0.41)</td>
<td>24 weeks: SMD 0.15 (-0.67 to 0.97)</td>
<td>34-36 weeks: SMD -0.38 (-0.75 to -0.01)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
</tbody>
</table>
Quality | Moderate | 24 weeks: low 34-36 weeks: high
--- | --- | ---
Number of studies; participants | K=5; n=2113 | 24 weeks: K=1; n=23 34-36 weeks: k=2; n=113
Forest plot | Psych ex 10.01 | Psych ex 10.02
Self-rated mean depression change scores at endpoint | SMD -0.83 (-1.31 to -0.34) | 4 weeks: SMD -1.58 (-2.09 to -1.08) 8 weeks: SMD -1.06 (-1.53 to -0.59) 34 weeks: SMD -0.24 (-0.67 to 0.18) | SMD 0.42 (-0.37 to 1.21) | SMD 0.1 (-0.6 to 0.8)
Quality | Moderate | 4 weeks: moderate 8 weeks: moderate 34 weeks: low | Low | Low
Number of studies; participants | K=7; n=82 | 4 weeks: K=1;n=82 8 weeks: K=1;n=82 34 weeks: K=1;n=86 | K=1; n=26 | K=1; n=32
Forest plot | Psych ex 10.03 | Psych ex 10.05 | Psych ex 10.06 | Psych ex 10.06
Leaving treatment early for any reason | RR 1.32 (0.62 to 2.82) (17.9% vs 12.7%) | | N/R | 
Quality | Low | 
Number of studies; participants | K=3; n=155 | 
Forest plot | Psych ex 10.07 | 
N/R = not reported

Table 28 Summary evidence profile for physical activity versus pill placebo

<table>
<thead>
<tr>
<th></th>
<th>Supervised physical activity versus pill placebo</th>
<th>Unsupervised physical activity versus pill placebo</th>
<th>Supervised physical activity versus waitlist</th>
<th>Supervised physical activity versus waitlist at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician-rated mean depression scores at endpoint</td>
<td>WMD -1.8 (-4.38 to 0.78)</td>
<td>WMD -0.8 (-3.46 to 1.86)</td>
<td>WMD -3.2 (-8.38 to 1.98)</td>
<td>WMD -2.1 (-7.42 to 3.22)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=100</td>
<td>K=1; n=102</td>
<td>K=1; n =22</td>
<td>K=1; n=19</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 11.01</td>
<td>Service ex 11.02</td>
<td>Service ex 12.01</td>
<td>Service ex 12.01</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR = 0.64 (0.33 to 1.23)</td>
<td>RR = 0.2 (0.06 to 0.65)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=170</td>
<td>K=1; n=102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 11.05</td>
<td>Service ex 11.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Physical activity versus antidepressants

Three studies compared physical activity with an antidepressant (all used sertraline). See Table 29.

Table 29 Summary study characteristics for physical activity versus antidepressants

<table>
<thead>
<tr>
<th>Supervised aerobic</th>
<th>Unsupervised aerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. RCTs</td>
<td>3</td>
</tr>
<tr>
<td>Study ID</td>
<td></td>
</tr>
<tr>
<td>(1) Blumenthal2007**</td>
<td>(1) Blumenthal2007**</td>
</tr>
<tr>
<td>(2) Herman2002</td>
<td>(2) Hoffman2008**</td>
</tr>
<tr>
<td>(3) Hoffman2008**</td>
<td></td>
</tr>
<tr>
<td>N/ % female/ mean age</td>
<td></td>
</tr>
<tr>
<td>(1) 202/76/52</td>
<td>(1) 202/76/52</td>
</tr>
<tr>
<td>(2) 156/73/57</td>
<td>(2) 202/76/52</td>
</tr>
<tr>
<td>(3) 202/76/52</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>(1) MDD/minor depression/dysthymia</td>
<td>(1) MDD/minor depression/dysthymia</td>
</tr>
<tr>
<td>(2) MDD/minor depression/dysthymia</td>
<td>(2) MDD/minor depression/dysthymia</td>
</tr>
<tr>
<td>(3) MDD/minor depression/dysthymia</td>
<td>(3) MDD/minor depression/dysthymia</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>(1) Walking/jogging</td>
<td>(1) Walking/jogging</td>
</tr>
<tr>
<td>(2) Walking/jogging</td>
<td>(2) Aerobics</td>
</tr>
<tr>
<td>(3) Aerobics</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>(1) Sertraline</td>
<td>(1) Sertraline</td>
</tr>
<tr>
<td>(2) Sertraline</td>
<td>(2) Sertraline</td>
</tr>
<tr>
<td>(3) Sertraline</td>
<td></td>
</tr>
</tbody>
</table>

* 3-armed trial, ** 4-armed trial; MDD = major depressive disorder

The data comparing physical activity with antidepressants (sertraline) were largely inconclusive, although there was some evidence that unsupervised physical activity was more effective than antidepressants. People taking antidepressants were more likely to leave treatment early because of side effects. See Table 30.

Table 30 Summary evidence profile for physical activity compared with antidepressants

<table>
<thead>
<tr>
<th>Supervised aerobic</th>
<th>Unsupervised aerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician-rated mean depression scores at endpoint</td>
<td>WMD -3.8 (-9.78 to 2.18)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=201</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 13.01</td>
</tr>
<tr>
<td>Self-rated mean depression scores at endpoint</td>
<td>WMD -1.4 (-4.33 to 1.53)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=101</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 13.03</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 1.59 (0.87 to 2.9)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Number of studies; participants  
K=2; n=201  
K=1; n=102

Forest plot  
Service ex 13.06  
Service ex 13.06

Leaving treatment early due to side effects  
RR 7.41 (1.4 to 39.23)  
(19.2% vs 6.2%)  
RR 2.77 (0.3 to 25.78)

Quality  
Moderate  
Low

Physical activity versus psychosocial and psychological interventions

Four studies compared physical activity with a psychosocial or psychological intervention. See Table 31.

Table 31 Summary study characteristics for physical activity versus psychosocial and psychological interventions

<table>
<thead>
<tr>
<th>No. RCTs</th>
<th>Supervised aerobic</th>
<th>Supervised non-aerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Study ID | (1) FREMONT1987  
(2) KLEIN1985  
(3) MCNEIL1991  
(1) Butler2008*  |
| N/% female/ mean age | (1) 61/74/unclear  
(2) 74/72/30  
(3) 30/-73  
(1) 46/74/50 |
| Diagnosis | (1) BDI = 9-30  
(2) Major/minor depression  
(3) BDI >=12 and <=24  
(1) Dysthymia/depression/minor depression/dysthymia/mild depressive episode |
| Physical activity | (1) Running  
(2) Running  
(3) Walking  
(1) Yoga |
| Control | (1) Cognitive techniques  
(2) Group therapy  
(3) Social contact  
(1) Hypnosis |

The data for physical activity compared with psychosocial and psychological interventions were inconclusive. See Table 32.

Table 32 Summary evidence profile for physical activity versus psychosocial and psychological interventions

<table>
<thead>
<tr>
<th></th>
<th>Supervised aerobic</th>
<th>Follow-up</th>
<th>Supervised non-aerobic</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician-rated mean depression scores at endpoint</td>
<td>N/R</td>
<td>N/R</td>
<td>WMD 6.11 (0.2 to 12.02)</td>
<td>36 weeks: WMD -1 (-5.4 to 3.4)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=24</td>
<td>K=1; n=26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 14.01</td>
<td>Service ex 14.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Self-rated mean depression scores at endpoint | SMD -0.23 (-0.68 to 0.21) | 8 weeks: WMD -0.6 (-5.4 to 4.2)  
16 weeks: WMD -3.1 (-8.79 to 2.59)  
34 weeks: WMD -N/R | N/R | N/R |
Physical activity + antidepressants versus antidepressants

Two studies compared physical activity antidepressants versus antidepressants. See Table 33.

Table 33 Summary study characteristics for physical activity antidepressants versus antidepressants

<table>
<thead>
<tr>
<th>Supervised aerobic physical activity + antidepressants versus antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. RCTs</td>
</tr>
</tbody>
</table>
| Study ID | (1) HERMAN2002  
(2) PILU2007 |
| N/× female/ mean age | (1) 156/73/57  
(2) 30/100/unclear |
| Diagnosis | (1) Major depressive disorder  
(2) MDD/minor depression/dysthymia |
| Physical activity | (1) Running + sertraline  
(2) Running + antidepressant (range of drugs used) |
| Control | (1) Sertraline  
(2) Combination antidepressants (range of drugs used) |

Physical activity plus an antidepressant more effectively reduced depression scores than a combination of 2 antidepressants. There appeared to be no difference between combination treatment versus a single antidepressant. There was only one study in each comparison. See Table 34.

Table 34 Summary evidence profile for physical activity antidepressants versus antidepressants

<table>
<thead>
<tr>
<th>Supervised aerobic physical activity + antidepressant versus combination antidepressants</th>
<th>Supervised aerobic physical activity + antidepressant versus antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=79</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 14.02</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=16</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 14.04</td>
</tr>
</tbody>
</table>

Leaving treatment early for any reason

RR 1.2 (0.14 to 10.58)  
(20% vs 16.7%)
### Clinician-rated mean depression scores at endpoint

<table>
<thead>
<tr>
<th>Quality</th>
<th>Moderate</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=30</td>
<td>K=1; n=103</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 18.01</td>
<td>Service ex 18.01</td>
</tr>
<tr>
<td>Self-rated mean depression scores at endpoint</td>
<td>N/R</td>
<td>WMD 0.6 (-2.24 to 3.44)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=103</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 18.02</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 1.2 (0.14 to 10.58) (20% vs 16.7%)</td>
<td>RR 1.37 (0.58 to 3.26) (20% vs 14.6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=16</td>
<td>K=1; n=103</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 18.03</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 0.87 (0.27 to 2.83) (9.1% vs 10.4%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=103</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Service ex 18.04</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical evidence summary for physical activity

The evidence is a relatively large data set of 25 trails and over 2,000 participants but it is difficult to interpret. This stems from a number of factors including the considerable variation in the populations which included mixed groups of patients with major depression, dysthymia and minor depression. In addition the nature of the physical activity interventions was also very varied as indeed were the comparators. Some comparators were also potentially problematic with one study having combined antidepressants as the comparator in a population which include those with a diagnosis of dysthymia and minor depression (PILU2007).

Despite these cautions the date suggest that physical activity was more effective in reducing depression symptoms than a no-physical activity control (SMD -1.2), although the effect was reduced at follow-up (SMD -0.38). The effect sizes for physical activity compared with pill placebo (WMD -1.8) and waitlist (WMD -3.20) were largely inconclusive and as they came from low quality studies hard to interpret. The data comparing physical activity with antidepressants suggested that there may be no differences in outcomes for the populations studies but the confidence intervals were wide (WMD -3.8 (-9.78 to 2.18). However, it should be noted that people taking antidepressants were more likely to leave treatment early (RR 1.59 (0.87 to 2.9)) The data for physical activity compared with psychosocial and psychological interventions...
did not suggest any important differences but again were difficult to interpret given the width of the confidence intervals (SMD -0.23 (-0.68 to 0.21)).

Taken together these studies suggest a benefit for physical activity in the treatment of minor and mild to moderate depression. Physical activity also has the advantage of bringing other health gains beyond just improvement in depression. In the absence of any clear indication from the data of benefits for a particular kind of physical activity or mode of delivery (group or individual) the GDG took the view that patients’ preference should be a significant factor in determining the choice of physical activity.

**Health economic considerations**

No evidence on the cost effectiveness of structured physical activity programmes for people with minor and mild to moderate depression was identified by the systematic search of the health economics literature.

The clinical evidence in the literature review described interventions delivered either individually or in structured groups under the supervision of a competent practitioner or physical activity facilitator. The programme would typically involve 2 to 3 sessions per week of 45 minutes to 1 hour duration over a 10 to 14 week period.

It is likely that the sessions would be supervised by an physical activity facilitator (an NHS professional or para-professional with expertise in the area) who would be a recent graduate from an undergraduate or masters’ level course. The unit cost of an physical activity facilitator is not currently available. Therefore, it is assumed that such workers would be on Agenda for Change (AfC) salary scales 4 or 5 which would likely to be comparable to the salary scales of a community mental health nurse. The unit cost of an AfC Band 5 community mental health nurse is £51 per hour of patient contact in 2007/08 prices (Curtis, 2009). This cost includes salary, salary on-costs, overheads and capital overheads plus any qualification costs.

Based on the estimated staff time associated with delivering and supervising a physical activity programme as described above and the cost of a community mental health nurse, the average cost of a physical activity programme when delivered at an individual level would range between £765 to £2,142 per person in 2007/08 prices. If a physical activity programme was delivered in structured groups, it is unclear from the literature what the optimal number of patients per group would be. Obviously, if the number and duration of sessions as well as the number of staff delivering the service remained the same, the total costs per person would be expected to decrease significantly.

Using the lower cost-effectiveness threshold of £20,000 per QALY set by NICE (NICE, 2008), a simple threshold analysis suggests that physical activity programmes would be cost-effective if they improve Health-Related Quality of Life (HRQoL) of people with persistent minor and mild to moderate depression by 0.038-0.107 per year, on a scale 0 (death) – 1 (perfect health). Using the upper cost-effectiveness threshold of £30,000 per QALY, the improvement in HRQoL required for physical activity programmes to be considered cost-effective fell to 0.026-0.071 per year.

**Evidence into Recommendations**

A range of low intensity interventions (guided self-help, physical activity and computerised cognitive behavioural therapy) have been identified has being effective
for minor and mild to moderate depression. There are few trials which allow for the
direct comparison of any of the interventions and the health economic review was not
able to identify any differences in cost effectiveness. As a result the GDG took the view
that the decision as to which intervention to offer should in significant part be guided
by service user preference and this is reflected in the recommendations. The data also
did not support the view that any particular mode of delivery (e.g. group v individual
physical activity, web v. desktop based CCBT) for any low intensity intervention had
any specific advantage over another; save for the fact that both guided self-help and
CCBT should be based on cognitive behavioural principles. All though did seem to
require some form of support to supervision to be fully effective. The GDG were also
concerned that the effective delivery of the interventions may be compromised by
differences in the style and content of delivery of the intervention and so have drawn
on existing trial data to offer specific recommendations on the content of the
interventions.

## 6.3 Clinical practice recommendations

### Low intensity psychosocial interventions

#### 6.3.1.1

For people with persistent minor and mild to moderate depression practitioners should consider:
- a structured physical activity programme
- individual guided self-help based on cognitive behavioural therapy principles
- computerised cognitive behavioural therapy (CCBT).

The choice of intervention should guided by the person’s preference

#### Delivery of low intensity psychosocial interventions

#### 6.3.1.2

Individual guided self-help programmes based on cognitive behavioural principles for people with persistent minor and mild to moderate depression should consist of:
- the provision of appropriate written materials (or alternative media to support access)
- support from a trained practitioner, who typically facilitates the self-help programme and reviews progress and outcome
- treatment sessions normally taking place over 9 to 12 weeks, including follow up.

#### 6.3.1.3

Physical activity programmes for people with persistent minor and mild to moderate depression should normally:
- be delivered individually or in structured groups (according to patient preference) with the support of a competent practitioner
• provide an average of 3 sessions per week of moderate duration (45 minutes to 1 hour) over 10 to 14 weeks (average 12 weeks) tailored to the individual to maximise adherence

6.3.1.4 For people with persistent minor and mild to moderate depression, CCBT based on cognitive behavioural therapy (CBT) should be provided via a stand-alone computer or a web-based programme. Programmes should run for 9 to 12 weeks, including follow-up and should:
• Include an explanation of the CBT model, encourage tasks between sessions, use thought challenging, active monitoring of behaviour, thought patterns and outcomes
• be supported by an appropriately trained practitioner, who typically provides limited facilitation of the programme and reviews progress and outcome:

6.3.1.5 Patients with depression may benefit from advice on sleep hygiene including:
• establishing regular sleep and wake times
• avoiding excess eating, smoking or drinking before sleep
• creating a proper environment for sleep

14 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
6.4 High Intensity Psychological Interventions

This section covers the high intensity interventions that were identified in the searches and groups them according to the definitions developed for the previous guideline (NICE, 2004). Although cognitive behavioural therapies, behavioural activation, problem solving therapy and couples therapy (5 out of 6 of the included studies were based on a behavioural model) share to some degrees a common theoretical base they are reviewed separately.

6.4.1 Cognitive and behavioural therapies

Introduction

Cognitive behavioural therapy for depression was developed by Beck during the 1950s and was formalised into a treatment in the late 1970s (Beck et al., 1979). Its original focus was on the styles of conscious thinking and reasoning of depressed people, which Beck posited was the result of the operation of underlying cognitive schemas or beliefs. The cognitive model describes how, when depressed, people focus on negative views of themselves, the world and the future. The therapy takes an educative approach where, through collaboration and guided discovery, the depressed person learns to recognise his or her negative thinking patterns and to re-evaluate his or her thinking. This approach also requires people to practise re-evaluating their thoughts and new behaviours (called homework). The approach does not focus on unconscious conflicts, transference or offer interpretation as in psychodynamic therapy. As with any psychological treatment, cognitive behavioural therapy is not static and has been evolving and changing. There have been important elaborations of on the techniques of therapy (Beck, 1995) to address underlying beliefs more directly, which have been applied to particular presentations such as persistent residual depressive symptoms that leave people vulnerable to relapse (Moore & Garland, 2003; Paykel et al., 1999; Scott et al., 2000). The guideline refers to ‘cognitive behavioural therapies’ to indicate the evolution of CBT for depression over several decades.

For the purpose of this review cognitive behavioural therapies were defined as discrete, time limited, structured psychological interventions, derived from the cognitive behavioural model of affective disorders and where the patient:

- Works collaboratively with the therapist to identify the types and effects of thoughts, beliefs and interpretations on current symptoms, feelings states and/or problem areas
- Develops skills to identify, monitor and then counteract problematic thoughts, beliefs and interpretations related to the target symptoms/problems
- Learns a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas.

In most individual trials of CBT the manual that was used was Beck’s 1979 “Cognitive therapy of depression” which advocates 16-20 sessions for treatment and relapse prevention work.
**Group Cognitive Behavioural Therapy**

We have also included trials based looking at group CBT which pre-dominantly use the “Coping With Depression” manual (Kuehner, 2004; Lewinsohn et al., 1989). This approach has a strong psycho-educational component focused on teaching people techniques and strategies to cope with the problems that are assumed to be related to their depression. These strategies include improving social skills, addressing negative thinking, increasing pleasant activities, and relaxation training. It consists of 12 two-hour sessions over 8 weeks with groups held twice weekly for the first four weeks. The groups are highly structured (Antonuccio, Steinmetz-Breckenridge, & Teri, 1984; Lewinsohn, Munoz, Youngren, & Zeiss, 1986) and typically consist of six to ten adults, with two group leaders. One- and six-month follow-up sessions are also held and booster sessions can be used to help prevent relapse.

**Mindfulness-Cognitive behaviour therapy**

Mindfulness-based Cognitive Therapy (MBCT) was developed with a specific focus on preventing relapse/recurrence of depression (Segal et al., 2002). MBCT is a relatively brief 8-week group programme with each session lasting two hours, and four follow-up sessions in the year after the end of therapy. With 8-15 patients per group, MBCT has the potential to help a large number of people.

MBCT is a manualised, group-based skills training program designed to enable patients to learn skills that prevent the recurrence of depression (Segal et al., 2002). It is derived from mindfulness-based stress reduction, a program with proven efficacy in ameliorating distress in people suffering chronic disease (Baer, 2003; Kabat-Zinn, 1990) and cognitive behavioral therapy for acute depression (Beck et al., 1979) that has demonstrated efficacy in preventing depressive relapse/recurrence (Hollon et al., 2005). MBCT is intended to enable people to learn to become more aware of the bodily sensations, thoughts and feelings associated with depressive relapse and to relate constructively to these experiences. It is based on theoretical and empirical work demonstrating that depressive relapse is associated with the reinstatement of automatic modes of thinking, feeling and behaving that are counter-productive in contributing to and maintaining depressive relapse and recurrence (e.g., self-critical thinking and avoidance) (Lau et al., 2004). Participants learn to recognize these “automatic pilot” modes, step out of these modes and respond in healthier ways by intentionally moving into a mode in which they de-center from negative thoughts/feelings (e.g., by learning that “thoughts are not facts”), accept difficulties using a stance of self-compassion and use bodily awareness to ground and transform experience. In the latter stages of the course patients develop an “action plan” that sets out strategies for responding when they become aware of early warning signs of relapse/recurrence (See: Williams et al., 2007).

**Clinical evidence for cognitive and behavioural therapies**

In total, 66 RCTs were included; 22 studies were found in the update search and 22 were also reported in the previous guideline. Furthermore, 22 trials were excluded in this update search. The main reasons for exclusion were: trials included populations that were not diagnosed with depression; authors replaced drop-outs, or more than 50% of participants dropping out of the study.
Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 35. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

**Table 35: Summary study characteristics of cognitive behavioural therapies**

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>No. trials (Total participants)</th>
<th>N/% female</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBT vs. control (249)</td>
<td>(1) 45/100</td>
<td>(1) 35</td>
</tr>
<tr>
<td></td>
<td>CBT vs. control (216)</td>
<td>(2) 168/70</td>
<td>(2) 37</td>
</tr>
<tr>
<td></td>
<td>CBT vs. BA (302)</td>
<td>(3) 115/66</td>
<td>(3) 37</td>
</tr>
<tr>
<td></td>
<td>CBT vs. BA (302)</td>
<td>(4) 23/64</td>
<td>(4) 28</td>
</tr>
<tr>
<td></td>
<td>CBT vs. IPT (403)</td>
<td>(1) 60/70</td>
<td>(1) 35</td>
</tr>
<tr>
<td></td>
<td>CBT vs. non-directive psychotherapies (202)</td>
<td>(2) 70/69</td>
<td>(2) 35</td>
</tr>
<tr>
<td></td>
<td>CBT (primary care) vs GP care (1793)</td>
<td>(3) 10/63</td>
<td>(3) 47</td>
</tr>
<tr>
<td></td>
<td>CBT vs ADs (unextractable)</td>
<td>(4) 61/52</td>
<td>(4) 41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>CBT vs. control (180)</th>
<th>CBT vs. REBT (180)</th>
<th>CBT vs. BA (180)</th>
<th>CBT vs. IPT (180)</th>
<th>CBT vs. non-directive psychotherapies (180)</th>
<th>CBT (primary care) vs GP care (180)</th>
<th>CBT vs ADs (180)</th>
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<tr>
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<td>4 RCTs (249)</td>
<td>1 RCT (180)</td>
<td>3 RCTs (216)</td>
<td>3 RCTs (302)</td>
<td>4 RCTs (403)</td>
<td>3 RCTs (202)</td>
<td>15 RCTs (1793)</td>
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<tr>
<td>Elkin1989</td>
<td>1 RCT (180)</td>
<td>1 RCT (180)</td>
<td>3 RCTs (216)</td>
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<td>4 RCTs (403)</td>
<td>3 RCTs (202)</td>
<td>15 RCTs (1793)</td>
</tr>
<tr>
<td>Jarrett1999</td>
<td>3 RCTs (216)</td>
<td>1 RCT (180)</td>
<td>3 RCTs (216)</td>
<td>3 RCTs (302)</td>
<td>4 RCTs (403)</td>
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<td>15 RCTs (1793)</td>
</tr>
<tr>
<td>Selmi1990</td>
<td>3 RCTs (216)</td>
<td>1 RCT (180)</td>
<td>3 RCTs (216)</td>
<td>3 RCTs (302)</td>
<td>4 RCTs (403)</td>
<td>3 RCTs (202)</td>
<td>15 RCTs (1793)</td>
</tr>
</tbody>
</table>

## Diagnosis

1. 91% depressive episode, 9% dysthymia.
2. 100% MDD
3. 100% MDD
4. 100% major, minor, or intermittent depression

## Comparator

1. (1) waitlist (2) ADs (3) placebo (4) waitlist
2. (1) BA (2) BA (3) BA
3. (1) IPT (2) IPT (3) IPT
4. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) IPT
5. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
6. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
7. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
8. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
9. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
10. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
11. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
12. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
13. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
14. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP
15. (1) Psychodynamic psychotherapy (2) Psychodynamic psychotherapy (3) GP

## Length of treatment

1. (1) 15 weeks (2) 16 weeks (3) 10 weeks (4) 6 weeks
2. (1) 14 weeks (2) 12 weeks (3) 20 sessions (4) 8 weeks
3. (1) 16 weeks (2) 16 weeks (3) 16 weeks (4) 8 or 16 weeks
4. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
5. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
6. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
7. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
8. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
9. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
10. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
11. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
12. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
13. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
14. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
15. (1) 16 weeks (2) up to 16 weeks (3) 6 weeks (4) 8 or 16 weeks
Follow-up
(1) 12 months
(2) 18 months
(3) not reported
(4) 2 months
(1) 6 months
(2) not reported
(3) 6 months
(4) not reported
(1) 12 months
(2) not reported
(3) 6 months
(4) not reported
(1) 18 months
(2) not reported
(3) not reported
(4) not reported
(1) 12 months
(2) not reported
(3) not reported
(4) not reported
(1) 5 months
(2) not reported
(3) 6 months
(4) 24 months
(5) not reported
(6) not reported
(7) 18 months
(8) 12 months
(9) 12 months
(10) not reported
(11) not reported
(12) not reported
(13) not reported
(14) 12 months
(15) No follow up

Table 36: Summary study characteristics of cognitive behavioural therapies (continued)

| Study IDs | No. trials (Total participants) | CBT +ADs vs ADs | CBT +ADs vs CBT | CBT for the elderly CBT vs ADs CBT +ADs vs ADs Group CBT vs. waitlist control |
|-----------|---------------------------------|-----------------|-----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| No. trials | 9 RCTs (850)                    | 6 RCT (731)     | 2 RCTs (104)    | 1 RCTs (69)                    | 1 RCT (45)                      |                                |                                |                                |                                |                                |                                |                                |                                |
| N/ % female | (1) Unextractable (2) 24/60 (3) 113/63 (4) 113/63 (5) 445/65 (6) 34/74 (7) 52/74 (8) 32/67 (9) 47/67 | (1) Unextractable (2) 113/63 (3) 113/63 (4) 445/65 (5) 52/74 (6) 47/69 | | (1) 29/73 (2) 67/67 (1) 67/67 (1) 28/62 |                                |                                |                                |                                |                                |                                |                                |                                |
| Mean age   | (1) 43 (2) 47 (3) 40 (4) 40 (5) 44 (6) 37 (7) 33 (8) 41 (9) 62 | (1) 43 (2) 40 (3) 40 (4) 43 (5) 33 (6) 67 | | (1) 76 (2) 67 (1) 67 (1) 74 |                                |                                |                                |                                |                                |                                |                                |                                |
| Diagnosis  | (1) 100% MDD (2) Remission after previous treatment (3) 80% MDD, 20% | (1) 100% MDD (2) 80% MDD, 20% dysthymia (3) 80% MDD, 20% | | (1) 100% MDD (2) 100% MDD (1) 100% MDD (1) Remission from depressive |                                |                                |                                |                                |                                |                                |                                |                                |
### Table 37: Summary study characteristics of cognitive behavioural therapies

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Group CBT vs. other group therapies</th>
<th>Group CBT vs wait list</th>
<th>Relapse prevention studies</th>
<th>CBT vs control</th>
<th>CBT vs ADs</th>
<th>CBT + ADs vs ADs</th>
<th>CBT (mindfulness) vs ADs</th>
<th>Group CBT (mindfulness) vs control</th>
</tr>
</thead>
<tbody>
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<td>Beutler1991 (1)</td>
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<td>5 RCTs (451)</td>
<td>3 RCTs (345)</td>
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<td>1 RCT (132)</td>
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<td>4 RCT (288)</td>
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<td>Bright1999 (2)</td>
<td>ALLARTVAN2003 (1)</td>
<td>BROWN1984 (2)</td>
<td>DALKARD2006 (3)</td>
<td>HARGINSMA2006 (4)</td>
<td>BOCKTING2005 (1)</td>
<td>HOL2005 (1)</td>
<td>PERLIS2002 (1)</td>
<td>KRYKEN2008 (1)</td>
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<tr>
<td>Covi1987 (3)</td>
<td></td>
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<td></td>
<td></td>
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<td>CRAN2008 (1)</td>
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Depression in adults (update): full guideline DRAFT (February 2009)
<table>
<thead>
<tr>
<th></th>
<th>(5) WONG2008</th>
<th>PAYKEL2005</th>
<th>Teasdale2000</th>
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<tbody>
<tr>
<td><strong>N/ % female</strong></td>
<td>(1) 40/63</td>
<td>(1) 65/57</td>
<td>(1) No info</td>
</tr>
<tr>
<td></td>
<td>(2) 70/71</td>
<td>(2) 44/55</td>
<td>(1) 72/55</td>
</tr>
<tr>
<td></td>
<td>(3) 42/60</td>
<td>(3) 118/176</td>
<td>(2) 57/76</td>
</tr>
<tr>
<td></td>
<td>(4) 76/55</td>
<td>(4) 78/49</td>
<td>(3) 110/76</td>
</tr>
<tr>
<td></td>
<td>(5) 75/78</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>(1) 47</td>
<td>(1) 44</td>
<td>(1) 40</td>
</tr>
<tr>
<td></td>
<td>(2) 46</td>
<td>(2) 44</td>
<td>(1) 45</td>
</tr>
<tr>
<td></td>
<td>(3) 44</td>
<td>(3) 43</td>
<td>(2) 44</td>
</tr>
<tr>
<td></td>
<td>(4) 64</td>
<td></td>
<td>(3) 43</td>
</tr>
<tr>
<td></td>
<td>(5) 37</td>
<td></td>
<td></td>
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<tr>
<td><strong>Diagnoses</strong></td>
<td>(1) 100% MDD</td>
<td>(1) Remission</td>
<td>(1) Remission</td>
</tr>
<tr>
<td></td>
<td>(2) 100% MDD or</td>
<td>from depression</td>
<td>from depression</td>
</tr>
<tr>
<td></td>
<td>dysthymia</td>
<td>&gt;10 weeks</td>
<td>(2) Remission</td>
</tr>
<tr>
<td></td>
<td>(3) 100% MDD</td>
<td>(2) Remission</td>
<td>after previous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Remission</td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4) &gt;8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) 5% dysthymia,</td>
<td>(1) Remission</td>
<td>(1) Remission</td>
</tr>
<tr>
<td></td>
<td>95% no diagnosis but BDI ≥10</td>
<td>from major depression</td>
<td>from depression</td>
</tr>
<tr>
<td></td>
<td>(2) 44% MDD RDC, 44% intermittent depressive disorder RDC, 11% minor depressive disorder RDC</td>
<td>&gt;10 weeks</td>
<td>(2) Remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Remission</td>
<td>after previous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Remission</td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4) &gt;8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>(1) TAU – free to seek</td>
<td>(1) TAU</td>
<td>(1) TAU</td>
</tr>
<tr>
<td></td>
<td>(2) wait list</td>
<td>(2) Range of ADs</td>
<td>(2) Range of</td>
</tr>
<tr>
<td></td>
<td>(3) TAU</td>
<td>(3) Clinical management</td>
<td>ADs</td>
</tr>
<tr>
<td></td>
<td>(4) wait list</td>
<td>(4) Paroxetine (mean 38mg/day)</td>
<td>(4) Fluoxetine (40mg/day) + Clinical management</td>
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<td></td>
<td>(5) wait-list</td>
<td></td>
<td>(1) Ads (no details)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1) Wait-list</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) TAU</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) TAU</td>
</tr>
<tr>
<td><strong>Length of treatment</strong></td>
<td>(1) 12 weeks</td>
<td>(1) 8 weeks</td>
<td>(1) 12 weeks</td>
</tr>
<tr>
<td></td>
<td>(2) 8 weeks</td>
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<td>(1) 28 weeks</td>
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<td>(3) 8 weeks</td>
<td>(3) 20 weeks + 14 weeks</td>
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<td>(4) 10 weeks</td>
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<td>(3) 8 weeks</td>
</tr>
<tr>
<td></td>
<td>(5) 10 weeks</td>
<td></td>
<td></td>
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<td><strong>Follow-up</strong></td>
<td>(1) 12 months</td>
<td>(1) 24 months</td>
<td>(1) Not reported</td>
</tr>
<tr>
<td></td>
<td>(2) 6 months</td>
<td>(2) 24 months</td>
<td>(1) 15 months</td>
</tr>
<tr>
<td></td>
<td>(3) 6 months</td>
<td>(3) 6 years</td>
<td>(2) 12 months</td>
</tr>
<tr>
<td></td>
<td>(4) not reported</td>
<td></td>
<td>(3) 12 months</td>
</tr>
<tr>
<td></td>
<td>(5) not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Depression in adults (update): full guideline DRAFT (February 2009)
### Table 38: Summary evidence profile for cognitive and behavioural therapies

<table>
<thead>
<tr>
<th>Comparator</th>
<th>CBT vs wait list</th>
<th>CBT vs placebo</th>
<th>CBT vs therapies designed for depression</th>
<th>CBT vs non-directive psychotherapies</th>
<th>CBT (primary care) vs GP care</th>
<th>CBT vs ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early for any reason</td>
<td>RR 0.44 (0.12 to 1.61)</td>
<td>RR 1.23 (0.89 to 1.71)</td>
<td>RR 0.46 (0.17 to 1.23)</td>
<td>RR 1.54 (0.97 to 2.46)</td>
<td>RR 0.75 (0.63 to 0.91)</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>K=2, n=193</td>
<td>K=6, n=560</td>
<td>K=1, n=66</td>
<td>K=3, n=208</td>
<td>K=13, n=1480</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -0.89 (-1.45 to -0.33)</td>
<td>SMD -0.15 (-0.51 to 0.21)</td>
<td>SMD 0.14 (-0.03 to 0.32)</td>
<td>SMD -0.19 (-0.86 to 0.49)</td>
<td>SMD 0.01 (-0.83 to 0.85)</td>
<td>SMD -0.06 (-0.24 to 0.12)</td>
</tr>
<tr>
<td>Quality</td>
<td>K=2, n=54</td>
<td>K=1, n=124</td>
<td>K=5, n=518</td>
<td>K=2, n=120</td>
<td>K=8, n=480</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression clinician-report measures at endpoint</td>
<td>HRSD&gt;6: RR 0.45 (0.23 to 0.91)</td>
<td>SMD -0.32 (-0.68 to 0.04)</td>
<td>SMD 0.10 (-0.07 to 0.27)</td>
<td>SMD -0.33 (-0.74 to 0.08)</td>
<td>SMD 0.05 (-0.06 to 0.15)</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>K=1, n=24</td>
<td>K=1, n=124</td>
<td>K=5, n=543</td>
<td>K=2, n=92</td>
<td>K=14, n=15 83</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 39: Summary evidence profile for cognitive and behavioural therapies (continued)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>CBT +ADs vs ADs</th>
<th>CBT +ADs vs CBT</th>
<th>CBT for the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBT vs ADs</td>
</tr>
<tr>
<td>Leaving study early for any reason</td>
<td>RR 0.81 (0.65 to 1.01)</td>
<td>RR 1.00 (0.77 to 1.30)</td>
<td>RR 0.57 (0.27 to 1.21)</td>
</tr>
<tr>
<td>Quality</td>
<td>K=8, n=831</td>
<td>K=5, n=710</td>
<td>K=2, n=108</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -0.38 (-0.62 to -0.14)</td>
<td>SMD -0.17 (-0.44 to 0.10)</td>
<td>SMD -0.31 (-0.69 to 0.07)</td>
</tr>
<tr>
<td>Quality</td>
<td>K=6, n=277</td>
<td>K=4, 219</td>
<td>K=2, n=108</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Depression clinician-report measures at endpoint

<table>
<thead>
<tr>
<th></th>
<th>SMD -0.46 (-0.61 to -0.31)</th>
<th>SMD -0.05 (-0.31 to 0.22)</th>
<th>SMD -0.41 (-0.79 to -0.03)</th>
<th>SMD -0.45 (-0.93 to 0.03)</th>
<th>at 6 months: MADRS≥10: RR 0.26 (0.03 to 2.14)</th>
</tr>
</thead>
</table>

**Quality**

Number of studies; participants

|                      | K=7, 724                   | K=4, n=220                | K=2, n=108                  | K=1, n=69                  |

Forest plot

---

### Table 40: Summary evidence profile for cognitive and behavioural therapies (continued)

<table>
<thead>
<tr>
<th></th>
<th>Group CBT vs. other group therapies</th>
<th>Group CBT vs wait list</th>
<th>Relapse prevention studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBT vs control</td>
<td>CBT vs ADs</td>
<td>CBT + ADs vs ADs</td>
</tr>
</tbody>
</table>

#### Leaving study early for any reason

|                      | RR 0.94 (0.57 to 1.53) | RR 1.61 (0.76 to 3.42) | RR 2.47 (1.01 to 6.05) | RR 1.20 (0.30 to 4.85) | RR 0.96 (0.61 to 1.52) | RR 0.34 (0.07 to 1.61) |

**Quality**

Number of studies; participants

|                      | K=3, n=158                     | K=1, n=187             | K=1, n=180               | K=1, n=132              | K=1, 123 |

Forest plot

#### Depression self-report measures at endpoint

|                      | SMD -0.17 (-0.61 to 0.26) | SMD -0.73 (-1.01 to -0.45) |

**Quality**

Number of studies; participants

|                      | K=2, n=83                     |

Forest plot

#### Depression clinician-report measures at endpoint

|                      | SMD -0.12 (-0.55 to 0.31) | Pts with ≥5 previous episodes: SMD -0.08 (-0.54 to 0.39) | SMD -0.18 (-0.52 to 0.16) |

**Quality**

Number of studies; participants

|                      | K=1, n=172                   |

Forest plot
Clinical evidence summary

Cognitive and behavioural therapies (CBT) vs. wait list control

There were two low quality studies (reported in the previous guideline: Beach1992 & Selmi1990) which compared the efficacy of cognitive behavioural therapies versus wait list control. The effectiveness of CBT for the treatment of depression was large (SMD -0.89) in self-reports and looked to be of clinical importance in clinician-reported depression scores (RR 0.45).

Cognitive and behavioural therapies vs. placebo

There was little evidence of the increased effectiveness of CBT when compared to placebo from two studies (also reported in the previous guideline: Elkin1989 & Jarrett1999). There was some indication of higher drop out rates in the placebo groups but the effect (RR 0.44, 95% CI 0.12, 1.61) was not significant and therefore it is inconclusive. There is a very small effect on reducing depression scores at endpoint (self-rated SMD -0.15, 95% CI -0.51, 0.21 and clinician-rated SMD -0.32, 95% CI -0.68, 0.04) when compared to placebo. However, the results are not significant and the confidence intervals are fairly wide so the evidence remains inconclusive.

Cognitive and behavioural therapies vs. other therapies

There were three studies that compared cognitive and behavioural therapies with behavioural activation in the treatment of depression (DIMIDJIAN2006, Gallhagher1982; JACOBSON1996). There were no clinically important differences identified between CBT and BA (BDI at endpoint 0.34; 95% CI -0.26, 0.95; HRSD at endpoint -0.03; 95% CI -0.62, 0.57).

Three studies included a comparison of CBT versus interpersonal therapies (Elkin1989; Freeman2002; MARSHALL2008). Again, there were no. In contrast to BA, there is a more substantial evidence for the efficacy of IPT in the treatment of depression (see table X).

Cognitive and behavioural therapies vs. non-directive psychotherapies

There were four studies that looked at the effectiveness of CBT when compared to non-directive psychotherapies (psychodynamic psychotherapy, Gestalt psychotherapy and interpersonal psychodynamic psychotherapy). One study (LUTY2007) was found in the search for the guideline update and three (Gallagher-Th1994, Rosner1999, Shapiro1994) were in the previous guideline. The evidence indicates no clinically significant differences (BDI at endpoint SMD -0.04; 95% CI -0.50, 0.42; HRSD at endpoint SMD 0.22, 95% CI -0.18, 0.51).

Cognitive and behavioural therapies (primary care) vs. GP care

Three trials reported in the previous guideline included a comparison between CBT in primary care versus usual GP care. In terms of leaving the study early due to any reason, the evidence suggests that there is a higher risk for discontinuation in those in the CBT (primary care) group (RR 1.54). The results for depression scores were not significantly different.

Cognitive and behavioural therapies vs. antidepressants (ADs)
Fifteen trials reported the effectiveness of CBT when compared to antidepressants. Five of those studies were found in the search of the guideline update and ten were reported in the previous guideline. Results for depression scores at post treatment (BDI: SMD -0.06; CI -0.24 to 0.12; HRSD: SMD 0.05; CI -0.06 to 0.15) and at 1 month follow-up (BDI: SMD -0.02; CI -0.68 to 0.65; HRSD: 0.08; CI -0.59 to 0.74) were not significantly different and this along with the relatively tight confidence intervals suggest broad equivalence between CBT and antidepressants. However, by 12 months follow-up the evidence indicates that CBT has a significant medium effect (BDI: -0.41; HRSD: SMD -0.50) over antidepressants. In terms of leaving the study early, there was a higher risk of discontinuation (RR 0.75) in the antidepressant group.

Combination (CBT + ADs) vs. ADs

Nine studies included a comparison between combined treatment of CBT plus ADs and ADs alone. Only one of those studies (FAVA1998) was found in the search for this guideline update. The combination treatment of CBT and antidepressants had a lower risk of discontinuation when compared to antidepressants (RR0.81). There is evidence that the combined treatment has a significant medium effect in the reduction of self-rated (SMD -0.38) and clinician-rated (SMD -0.46) depression scores. At 6- and 24-month follow-ups, however, there was very limited data which introduced some uncertainty about the relative long-term effectiveness of these two treatments.

Combination (CBT + ADs) vs. CBT

Six studies reported in the previous guideline included a comparison of combination treatment and CBT alone. In contrast to the dataset on the combination of CBT and ADs versus ADs, it was not possible to identify a benefit for the combined treatment (BDI at post treatment SMD -0.17, 95% -0.44, 0.10; BDI at 1 month follow-up SMD -0.29, 95% CI -0.94, 0.36; HRSD at 1 month follow-up SMD -0.08, 95% CI -0.72, 0.57). This would suggest that although the CBT and ADs dataset supports combined treatment benefit could still be derived from CBT alone.

Cognitive and behavioural therapies for the elderly

Three studies looked at the effectiveness of CBT in the treatment of depression in elderly populations. LAIDLAW2008 and Thompson2001 compared CBT with antidepressants. Thompson2001 also included a comparison of the combination of CBT with ADs with ADs alone. WILKINSON2009 looked at the effectiveness of group CBT when compared to wait list control.

The evidence was inconclusive regarding leaving study early. In clinician-rated depression scores, there was a significant medium effect favouring CBT (SMD -0.41). The results were not significant for follow-up data.

In the combined treatment of CBT plus ADs versus ADs alone, there was little to no difference in risk for discontinuation amongst the two groups (RR 0.92). In depression scores, there were medium effects for both self-rated (SMD -0.36; CI -0.84 to 0.12) and clinician-rated (SMD -0.45; CI -0.93 to 0.03). Note that the confidence intervals for both effects cross the line of no effect slightly, so these results should be interpreted with caution.
The evidence of group CBT in the treatment of depression for the elderly is not significant. There was only one study in this category reflecting the paucity of the data.

**Cognitive and behavioural therapies – relapse prevention**

Seven studies found in the search for the guideline update examined relapse prevention in people who had been administered CBT. The evidence indicates a higher risk for discontinuation in those administered CBT than treatment as usual (RR 2.47; 95% CI 1.01, 6.05). There were no significant differences between the two groups in terms of relapse or remission rates at 68 weeks.

When the combination treatment of CBT plus ADs was compared to ADs alone it is important to note that there were no significant differences in terms of risk for discontinuation (RR 0.96; 95% CI 0.61, 1.52) or relapse (RR 0.80; 95% CI 0.22, 2.85).

Four studies (CRANE2008; KUYKEN2008; MA2004; Teasdale2000) evaluated the effectiveness of a CBT-mindfulness group treatment in relapse prevention. Two studies (MA2004; Teasdale2000) compared the combined treatment of group CBT-mindfulness with GP care versus GP care alone. The evidence indicates a higher risk for discontinuation in the combined treatment (RR 19.11, 95% CI 2.58, 141.35) but a significantly lower risk for relapse (RR 0.74, 95% CI 0.57, 0.96). When group CBT-mindfulness was compared to antidepressants the evidence indicates a small to medium effect of group CBT-mindfulness in lowering depression scores at 1 month (BDI: SMD -0.37, 95% CI -0.72, -0.01; HRSD: SMD -0.31, 95% CI -0.66, 0.05) and at 15 month (BDI: SMD -0.34, 95% CI -0.69, 0.02; HRSD: SMD -0.23, 95% -0.59, 0.12) follow-ups.

**Group cognitive behavioural therapies**

Three studies reported in the previous guideline looked at the effectiveness of group CBT when compared to other psychotherapies (Bright1999; Covi1987; Klein1984). The results show no significant difference in risk for discontinuation (RR 0.94, 95% CI 0.57, 1.53) or depression scores at post treatment (BDI: SMD -0.17, 95% CI -0.61, 0.26; HRSD: SMD -0.12, 95% CI -0.55, 0.31). However, when self-rated depression scores were analysed by a cut off of BDI>9, there was a significant difference favouring group CBT (RR 0.60, 95% CI 0.46, 0.79).

A further analysis was carried out looking at group CBT compared to waitlist control or treatment as usual. Four studies entailed Coping with Depression (ALLARTVAN2003; BROWN1984; DALGARD2006; HARINGSMA2006). The evidence indicates no clinically significant difference in risk for discontinuation (RR 1.34, 95% CI 0.44, 4.11). There is a significant medium effect of group CBT in lowering depression scores at endpoint (SMD -0.60, 95% CI -0.84, -0.35) and at 6 month follow-up (SMD -0.40, 95% CI -0.83, 0.02. So, for people with mild depression group CBT (especially CDW) is an effective treatment for depression.

### 6.4.2 Behavioural activation

**Introduction**
Behavioural activation for depression evolved from learning theory that posits two types of learning: operant or instrumental learning and classical conditioning. Although classical conditioning theories for depression have been put forward (e.g., Wolpe, 1971; Ferster, 1973) with treatment recommendations (Wolpe, 1979) there have been no treatment trials of this approach. Operant or instrumental learning posits that depressive behaviours are learned through the contingencies around those behaviours. In behavioural therapies depression is seen as the result of a low rate of positive reinforcement and is maintained through negative reinforcement. Most commonly, patients use avoidance to minimise negative emotions and situations they worry will be unpleasant. Behavioural therapies focus on behavioural activation aimed at encouraging the patient to develop more rewarding and task-focused behaviours as well as stepping out of patterns of negative reinforcement. The approach was developed by Lewinsohn (1975). In recent years there has been renewed interest in behavioural activation, as it is now known, as a therapy in its own right (e.g., Hopko et al., 2003; Martell et al., 2001).

Behavioural activation/therapies were defined as a discrete, time limited, structured psychological interventions, derived from the behavioural model of affective disorders and where the therapist and patient:

- Work collaboratively to identify the effects of behaviours on current symptoms, feelings states and/or problem areas.
- Seek to reduce symptoms and problematic behaviours through behavioural tasks related to: reducing avoidance, graded exposure, activity scheduling, reducing avoidance and initiating positively reinforced behaviours.

Clinical evidence for behaviour activation

There were six studies involving a comparison of behaviour activation. Of these, three studies were found in the update and two from the previous guideline. Comparisons between BA and cognitive and behavioural therapies can be found in the previous section (see section 1.1). Two studies (HOPKO2003; McLean1979) entailed a comparison with non-directive psychotherapies. A further study, DIMIDJIAN2006, entailed a comparison between BA and antidepressants.

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 41. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

<table>
<thead>
<tr>
<th>Table 41: Summary study characteristics of behaviour activation studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. trials (Total participants)</strong></td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>2 RCTs (136)</td>
</tr>
<tr>
<td><strong>Study IDs</strong></td>
</tr>
<tr>
<td><strong>N/% female</strong></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
</tbody>
</table>
Clinical evidence summary

### Behaviour activation (BA) vs. non-directive psychotherapies

Only two studies looked at the effectiveness of BA when compared to non-directive psychotherapies. The evidence indicates that BA has a significantly lower risk for discontinuation than people in the psychodynamic psychotherapy group (RR 0.17; 95% CI 0.04 to 0.71). However, it should be noted that this evidence is based on one study (McLean1979) and the confidence intervals are wide.

### BA vs. antidepressants

There is limited evidence of one study (DIMIDJIAM2006) of the effect of behaviour activation in the treatment of depression when compared to antidepressants. The limited evidence shows that there is a risk of discontinuation of antidepressants when compared with behaviour activation (RR 0.31). However, there was a negative to very small effect in reducing depression self-reported scores (SMD 0.15) or clinician-reported scores (moderate severity: SMD 0.14 and moderate severe SMD -0.04) when compared to antidepressants. There seems to be little to no difference between BA and antidepressants in terms of relapse rates at 1 (RR 1.04). There is some difference favouring BA at 2 years (RR 0.47) but this result is not significant so remains inconclusive.

### 6.4.3 Problem Solving

#### Introduction

It has long been recognised that depression is associated with social problem-solving difficulties (Nezu, 1987). The reasons for this may be various, relating to the effects of depressed state, lack of knowledge, and rumination. As a consequence, helping patients solve problems and develop problem-solving skills has been a focus for therapeutic intervention and development of therapy (Nezu et al., 1989). There has been recent interest in developing problem-solving therapies for use in primary care (Barrett et al., 1999; Dowrick et al, 2000).

Problem-solving therapy is a discrete, time limited, structured psychological intervention, which focuses on learning to cope with specific problems areas and where therapist and patient work collaboratively to identify and prioritise key problem...
areas, to break problems down into specific, manageable tasks, problem solve, and develop appropriate coping behaviours for problems.

Clinical evidence for problem solving

There were no new studies found in the search for the guideline update that were included. Two studies were found and excluded on the basis of one study not reporting the outcome data and one study having a sample size <10. Three studies that were reported in the previous guideline are included (Dowrick2000; Mynors-Wallis1995; Mynors-Wallis2000).

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 42. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

Table 42: Summary study characteristics of problem solving

<table>
<thead>
<tr>
<th>Problem solving (PS) vs Placebo</th>
<th>PS vs ADs</th>
<th>PS + ADs vs ADs</th>
<th>PS (GP) vs PS (Nurse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>2 RCTs (377)</td>
<td>2 RCTs (135)</td>
<td>1 RCT (74)</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 277/65 (2) 70/77</td>
<td>(1) 70/77 (2) 116/77</td>
<td>(1) 116/77</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) unextractable (2) 37</td>
<td>(1) 37 (2) 35</td>
<td>(1) 35</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) 52% single episode, 19% recurrent, 16% dysthymia, 4% adjustment disorder (2) 100% RDC MDD</td>
<td>(1) 100% RDC MDD (2) 100% depression</td>
<td>(1) 100% depression</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) Control (no intervention) (2) placebo</td>
<td>(1) Amitriptyline (150mg/day) (2) Fluvoxamine / paroxetine</td>
<td>(1) Fluvoxamine / Paroxetine</td>
</tr>
<tr>
<td>Length of treatment</td>
<td>(1) 6 weeks (2) 12 weeks</td>
<td>(1) 12 weeks (2) 12 weeks</td>
<td>(1) 12 weeks</td>
</tr>
<tr>
<td>Follow-up</td>
<td>(1) 12 months (2) Not reported</td>
<td>(1) Not reported (2) 12 months</td>
<td>(1) 12 months</td>
</tr>
</tbody>
</table>
Table 43: Summary evidence profile for problem solving

<table>
<thead>
<tr>
<th>Problem Solving (PS) vs Placebo</th>
<th>PS vs ADs</th>
<th>PS + ADs vs ADs</th>
<th>PS (GP) vs PS (Nurse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early for any reason</td>
<td>RR 0.11 (0.03 to 0.44)</td>
<td>RR 0.88 (0.18 to 4.20)</td>
<td>RR 1.03 (0.37 to 2.89)</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1, n=60</td>
<td>K=2, n=177</td>
<td>K=1, n=71</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-report measures at endpoint</td>
<td>SMD -0.69 (-1.24 to -0.14)</td>
<td>SMD -0.11 (-0.46 to 0.25)</td>
<td>SMD 0.18 (-0.30 to 0.67)</td>
</tr>
<tr>
<td>RR 0.62 (0.39 to 0.99)</td>
<td>RR 0.67 (0.41 to 1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1, n=60</td>
<td>K=2, n=124</td>
<td>K=1, n=65</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression clinician-report measures at endpoint</td>
<td>SMD -0.66 (-1.21 to -0.12)</td>
<td>SMD 0.10 (-0.25 to 0.45)</td>
<td>SMD -0.24 (-0.73 to 0.24)</td>
</tr>
<tr>
<td>HRSD &gt;7:</td>
<td>HRSD &gt;7:</td>
<td>HRSD &gt;7:</td>
<td>HRSD &gt;7:</td>
</tr>
<tr>
<td>RR 0.55 (0.33 to 0.89)</td>
<td>RR 1.43 (0.85 to 2.39)</td>
<td>RR 1.20 (0.65 to 2.22)</td>
<td>RR 1.05 (0.66 to 1.67)</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1, n=60</td>
<td>K=2, n=124</td>
<td>K=1, n=71</td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical evidence summary

The evidence from one study (Mynors-Wallis1995) indicates problem solving had a significant medium effect in the decrease of clinician-rated (SMD –0.66) and self-rated (SMD –0.69) depression scores when compared to placebo. This effect was also seen for dichotomous scores; clinician-rated (RR 0.65) and self-rated (0.62). A further study (Dowrick2000) indicated a significant decrease in number of people diagnosed with depressive disorder after 6 months of treatment (RR 0.83) when compared to placebo.

There were no significant differences when problem solving was compared to antidepressants or when the combination treatment of problem solving and antidepressants was compared to antidepressants alone but the uncertainty surrounding these results makes it difficult to draw any conclusions.

6.4.4 Couples-focused therapies

Introduction

Therapists have noted that a partner’s critical behaviour may trigger an episode, and/or maintain or exacerbate relapse in the long term (e.g. Hooley & Teasdale, 1989), although other researchers have questioned this (e.g. Hayhurst et al., 1997). There has also been some work looking at differences in the vulnerabilities between men and women within an intimate relationship, with physical aggression by a partner predicting depression in women. Difficulties in developing intimacy, and coping with conflict, also predict depression in both men and women (Christian et al., 1994). Like
other therapies a couple-focused approach has evolved in recent years. For example, Wheeler et al. (2001) have outlined the development of integrative couple behaviour therapy, from traditional cognitive behavioural therapy, with an outline of the key therapeutic principals. Systemic couple therapy aims to give the couple new perspectives on the presenting problem (e.g. depressing behaviours), and explore new ways of relating (Jones & Asen, 1999). Other developments such as those by Jacobson et al (1993) took a much more behavioural approach. In our analysis of couple-focused therapies, where one partner is depressed, we have not focused on a specific approach but define couple-focused therapies more generally.

Couple-focused therapies were defined as time limited, psychological interventions derived from a model of the interactional processes in relationships where:

- Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems.
- The aim is to change the nature of the interactions so that they may develop more supportive and less conflictual relationships.

Clinical evidence for couples-focused therapies

Six RCTs were included in the couples-focused therapies review. Two studies were found in the search for the guideline update (BODENMANN2008 & JACOBSON1993) and four were also reported in the previous guideline. One study was excluded because more than 50% of the participants dropped out from one arm of the study (LEFF2000).

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 44. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

Table 44: Summary study characteristics of couples-focused therapies

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Couples therapy vs. wait list control</th>
<th>Couples therapy vs. CBT</th>
<th>Couples vs IPT</th>
<th>Couples therapy + CBT vs CBT</th>
<th>Couples therapy + CBT vs Couples therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>2 RCTs (81)</td>
<td>4 RCTs (130)</td>
<td>2 RCTs (109)</td>
<td>1 RCT (41)</td>
<td>1 RCT (40)</td>
</tr>
<tr>
<td>N/ % female</td>
<td>(1) 45/100 (2) 36/100</td>
<td>(1) 35/58 (2) 14/52 (3) 60/100 (4) 36/100</td>
<td>(1) 35/58 (2) 13/72</td>
<td>(1) 60/100</td>
<td>(1) 60/100</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 39 (2) 39</td>
<td>(1) 45 (2) 38 (3) 39 (4) 39</td>
<td>(1) 45 (2) 40</td>
<td>(1) 39</td>
<td>(1) 39</td>
</tr>
</tbody>
</table>
Diagnosis
(1) 91% MDD, 9% dysthymia
(2) 89% MDD, 11% dysthymia
(3) 100% MDD
(4) 89% MDD, 11% dysthymia

Comparator
(1) waitlist control
(2) waitlist control
(3) CBT
(4) IPT

Length of treatment
(1) 15 weeks
(2) 16 weeks
(3) 20 weeks
(4) 16 weeks

Follow-up
(1) 12 months
(2) 12 months
(3) not reported
(4) 12 months

Table 45: Summary evidence profile for couples-focused therapy

<table>
<thead>
<tr>
<th></th>
<th>Couples therapy vs. wait list control</th>
<th>Couples therapy vs. CBT</th>
<th>Couples therapy + CBT vs CBT</th>
<th>Couples therapy + CBT vs Couples therapy</th>
<th>Couples therapy vs IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early</td>
<td>RR 1.22 (0.55 to 2.71)</td>
<td>RR 0.67 (0.22 to 2.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>for any reason</td>
<td>Quality</td>
<td>K=3, n=101</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies;</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression self-</td>
<td>SMD -1.35 (-1.95 to -0.75)</td>
<td>SMD -0.10 (-0.58 to 0.38)</td>
<td>SMD -0.06 (-0.68 to 0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>report measures at</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>endpoint Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies;</td>
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<td>K=2, n=67</td>
<td>K=1, n=40</td>
<td></td>
<td></td>
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<tr>
<td>participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinician-report</td>
<td>SMD -0.07 (-0.69 to 0.55)</td>
<td>SMD 0.01 (-0.51 to 0.52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measures at endpoint Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies;</td>
<td>K=1, n=40</td>
<td>K=2, n=58</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical evidence summary

Two studies: Beach1992 & O’Leary1990) indicates a significant large effect in reducing depression self-report scores at post-treatment (SMD -1.35; 95% CI -1.95, -0.75) when compared to wait list control. In a larger dataset where couples therapy is compared to CBT, there was no significant difference in risk for discontinuation (RR 1.22; 95% CI 0.55, 2.71) or depression scores at post-treatment (BDI: SMD -0.10; 95% CI -0.58, 0.38; HRSD: -0.07, 95% CI -0.69, 0.55) or 6-month follow-up (BDI: SMD -0.05, 95% CI -0.67, 0.57) suggesting broadly similar effects to CBT for couples therapy. There is some indication of effect in self-reported depression scores at 1 year follow up (SMD -0.41;
95% CI -0.90 to 0.09) but this effect does not persist to 1.5 years (SMD -0.08, 95% CI -0.70, 0.54). Two studies (BODENMAN2008 & Foley1989) compared couples-focused therapy with interpersonal therapy. There were no clinically significant differences between the groups. In five of the studies included in this review the model used was a behavioural model, two other studies used a model base on IPT.

### 6.4.5 Interpersonal therapy

**Introduction**

Interpersonal psychotherapy (IPT) was developed by Klerman and Weissman (Klerman et al., 1984) initially for depression although it has now been extended to other areas (Weissman et al., 2000). IPT focuses on current relationships, not past ones, and on interpersonal processes rather than intra-psychic ones (such as negative core beliefs or automatic thoughts as in CBT, or unconscious conflicts as in psychodynamic therapy). It is time limited and focused on difficulties arising in the daily experience of maintaining relationships and resolving difficulties whilst suffering an episode of major depression.

The main clinical tasks are to help patients to learn to link their mood with their interpersonal contacts and to recognise that, by appropriately addressing interpersonal situations, they may simultaneously improve both their relationships and their depressive state. Early in the treatment, patient and therapist agree to work on a particular focal area that would include: interpersonal role transitions, interpersonal roles/conflicts, grief and/or interpersonal deficits. IPT is appropriate when a person has a key area of difficulty that is specified by the treatment (e.g. grief, interpersonal conflicts). It can be delivered as an individual focused therapy but has also been developed as a group therapy (Wilfley et al., 2000).

The character of the therapy sessions is, largely, facilitating understanding of recent events in interpersonal terms and exploring alternative ways of handling interpersonal situations. Although there is not an explicit emphasis on ‘homework’, there is an emphasis on effecting changes in interpersonal relationships and tasks towards this end may be undertaken between sessions.

Interpersonal therapy was defined as a discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where the therapist and patient:

- Work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems.
- Seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

**Clinical evidence for interpersonal therapy**

Twenty-one trials were found; 14 were included and 7 were excluded. The most common reasons for exclusion were: that the trials did not report the outcome data, including populations without a diagnosis for depression and using an unclear control
intervention. Of the 14 studies that were included, 7 were found in the new search for the guideline update (including studies in older people and in relapse prevention) and 7 are also reported in the previous guideline. Three studies compared IPT with CBT and are reported in section 1.1.

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 46. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

### Table 46: Summary study characteristics of interpersonal therapies

<table>
<thead>
<tr>
<th>IPT vs Placebo</th>
<th>IPT vs GP care (including ADs)</th>
<th>IPT vs IPT + ADs</th>
<th>IPT + ADs vs ADs</th>
<th>IPT vs ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials</td>
<td>1 RCT</td>
<td>4 RCTs</td>
<td>2 RCTs</td>
<td>3 RCTs</td>
</tr>
<tr>
<td>(Total</td>
<td>(123)</td>
<td>(391)</td>
<td>(78)</td>
<td>(203)</td>
</tr>
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<td>participants</td>
<td></td>
<td></td>
<td></td>
<td>(347)</td>
</tr>
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<td>Study IDs</td>
<td>(1) Elkin1989</td>
<td>(1) Freeman2002</td>
<td>(1) Reynolds1999</td>
<td>(1) de Mello2001</td>
</tr>
<tr>
<td></td>
<td>(2) MARSHALL2008</td>
<td>(2) Weissman1992</td>
<td>(2) Reynolds1999</td>
<td>(2) Reynolds1999</td>
</tr>
<tr>
<td></td>
<td>(3) Schulberg1996</td>
<td>(3) SCHRAMM2007</td>
<td>(3)</td>
<td>Schulberg1996</td>
</tr>
<tr>
<td></td>
<td>(4) SWARTZ2008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 168/70</td>
<td>(1) 96/61</td>
<td>(1) 80/75</td>
<td>(1) 168/70</td>
</tr>
<tr>
<td></td>
<td>(2) 70/69</td>
<td>(2) 25/71</td>
<td>(2) 80/75</td>
<td>(2) 80/75</td>
</tr>
<tr>
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<td>(3) 229/83</td>
<td>(3) 81/65</td>
<td>(3) 81/65</td>
<td>(3) 229/83</td>
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<tr>
<td></td>
<td>(4) 47/100</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean age</td>
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<td>(1) 68</td>
<td>(1) 35</td>
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<td>(2) No info</td>
<td>(2) 70</td>
<td>(2) 70</td>
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<td></td>
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<td>(3) 38</td>
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<tr>
<td></td>
<td>(4) 42</td>
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<td>Diagnosis</td>
<td>(1) 100% RDC MDD</td>
<td>(1) 100% MDD</td>
<td>(1) 100% MDD</td>
<td>(1) 100% RDC MDD</td>
</tr>
<tr>
<td></td>
<td>(2) 100% MDD</td>
<td>(2) 100% moderate/severe MDD</td>
<td>(2) 100% dysthymia</td>
<td>(2) 100% RDC MDD</td>
</tr>
<tr>
<td></td>
<td>(3) 100% MDD</td>
<td></td>
<td>(3) 100% MDD</td>
<td>(2) 100% MDD</td>
</tr>
<tr>
<td></td>
<td>(4) 100% MDD</td>
<td></td>
<td>(4) 100% MDD</td>
<td>(3) 100% MDD</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) Placebo</td>
<td>(1) GP care</td>
<td>(1) Nortriptyline</td>
<td>(1) Moclobemide</td>
</tr>
<tr>
<td></td>
<td>(2) GP care</td>
<td>(2) Alprazolam</td>
<td>(2) Alprazolam</td>
<td>(2) Nortriptyline</td>
</tr>
<tr>
<td></td>
<td>(3) GP care</td>
<td>(2.2mg/day) or</td>
<td>(3) Nortriptyline</td>
<td>(3) Nortriptyline</td>
</tr>
<tr>
<td></td>
<td>(4) GP care</td>
<td>Imipramine (97.5mg/day)</td>
<td>(4) Sertraline</td>
<td>(4) Sertraline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(90mg/day)</td>
<td>(90mg/day)</td>
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<td></td>
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<td>(90mg/day)</td>
<td>(90mg/day)</td>
</tr>
</tbody>
</table>

### Table 47: Summary study characteristics of interpersonal therapies (continued)

<table>
<thead>
<tr>
<th>IPT vs ADs</th>
<th>IPT vs TAU</th>
<th>IPT + ADs vs ADs</th>
<th>IPT + ADs vs IPT + Placebo</th>
<th>IPT + Placebo vs Medication Clinic + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials</td>
<td>1 RCT</td>
<td>1 RCT</td>
<td>1 RCT</td>
<td>1 RCT</td>
</tr>
<tr>
<td>(Total</td>
<td>(184)</td>
<td>(185)</td>
<td>(35)</td>
<td>(43)</td>
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<td>participants)</td>
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</tr>
<tr>
<td>Study IDs</td>
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<td>(1)</td>
<td>(1) de Mello2001</td>
<td>(1) Reynolds1999</td>
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<tr>
<td></td>
<td>Schulberg1996</td>
<td>(1)</td>
<td>(1) de Mello2001</td>
<td>(1) Reynolds1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1)</td>
<td>(1) de Mello2001</td>
<td>(1) Reynolds1999</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 229/83</td>
<td>(1) 229/83</td>
<td>(1) 28/80</td>
<td>(1) 80/75</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 38</td>
<td>(1) 38</td>
<td>(1) 35</td>
<td>(1) 70</td>
</tr>
</tbody>
</table>
Table 48: Summary study characteristics of interpersonal therapies (continued)

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Comparator</th>
<th>Length of treatment</th>
<th>Follow-up</th>
<th>IPT vs IPT + ADs</th>
<th>IPT + ADs vs IPT + Placebo</th>
<th>IPT vs ADs</th>
<th>IPT + ADs vs Medication Clinic + Placebo</th>
<th>IPT vs IPT + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 100% MDD</td>
<td>(1) Nortriptyline (190-270 mg/day)</td>
<td>(1) 4 months</td>
<td>(1) 4 months</td>
<td>1 RCT (94)</td>
<td>2 RCTs (94)</td>
<td>1 RCT (49)</td>
<td>2 RCTs (99)</td>
<td>1 RCT (51)</td>
</tr>
<tr>
<td>(1) 100% MDD</td>
<td>(1) TAU</td>
<td>(1) 4 months</td>
<td>(1) 4 months</td>
<td>1 RCT (54)</td>
<td>2 RCTs (190-270 mg/day)</td>
<td>1 RCT (49)</td>
<td>2 RCTs (99)</td>
<td>1 RCT (54)</td>
</tr>
<tr>
<td>(1) 100% dysthymia</td>
<td>(1) Moclobemide (150-300 mg/day)</td>
<td>(1) 6 months</td>
<td>(1) 5 months</td>
<td>1 RCT (94)</td>
<td>2 RCTs (94)</td>
<td>1 RCT (49)</td>
<td>2 RCTs (99)</td>
<td>1 RCT (54)</td>
</tr>
<tr>
<td>(1) 100% dysthymia</td>
<td></td>
<td></td>
<td></td>
<td>1 RCT (54)</td>
<td>2 RCTs (94)</td>
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<tr>
<td>(1) 100% MDD</td>
<td>(1) Nortriptyline (190-270 mg/day)</td>
<td>(1) 6 months</td>
<td>(1) 5 months</td>
<td>1 RCT (94)</td>
<td>2 RCTs (94)</td>
<td>1 RCT (49)</td>
<td>2 RCTs (99)</td>
<td>1 RCT (54)</td>
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<tr>
<td>(1) 100% MDD</td>
<td>(1) Placebo</td>
<td>(1) 16 weeks</td>
<td>(1) 16 weeks</td>
<td>1 RCT (94)</td>
<td>2 RCTs (94)</td>
<td>1 RCT (49)</td>
<td>2 RCTs (99)</td>
<td>1 RCT (54)</td>
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</tbody>
</table>

Table continued...
### Table 49: Summary study characteristics of interpersonal therapies (continued)

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>No. trials (Total participants)</th>
<th>IPT vs IPT + ADs</th>
<th>IPT + ADs vs ADs</th>
<th>IPT vs ADs</th>
<th>IPT vs Standard care (Netherlands)</th>
<th>IPT as maintenance treatment (2/3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 RCTs (141)</td>
<td>1 RCT (46)</td>
<td>1 RCT (45)</td>
<td>1 RCT (143)</td>
<td>2 RCTs (223)</td>
<td></td>
</tr>
<tr>
<td>(1) Reynolds1999 (2) REYNOLDS2006 (3) Weissman1992</td>
<td>(1) Reynolds1999 (1) Reynolds1999 (1) VAN SCHAUK2006</td>
<td>(1) 80/75 (1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
<td>(1) Reynolds1999 (2) REYNOLDS2006</td>
<td></td>
</tr>
<tr>
<td>N/ % female</td>
<td>(1) 80/75 (1) 129/66 (1) 25/71</td>
<td>(1) 80/75 (1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
<td>(1) 80/75 (1) 99/69</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 68 (1) 68 (1) 68</td>
<td>(1) 68 (1) 68 (1) 68</td>
<td>(1) 68 (1) 68 (1) 68</td>
<td>(1) 68 (1) 68 (1) 68</td>
<td>(1) 68 (1) 68 (1) 68</td>
<td>(1) 68 (1) 68 (1) 68</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) 100% MDD (2) 100% MDD (3) 100% moderate/ severe MDD</td>
<td>(1) 100% MDD (1) 100% MDD (1) 100% depressive disorder</td>
<td>(1) 100% MDD (1) 100% MDD (1) 100% depressive disorder</td>
<td>(1) 100% MDD (1) 100% MDD (1) 100% depressive disorder</td>
<td>(1) 100% MDD (1) 100% MDD (1) 100% depressive disorder</td>
<td>(1) 100% MDD (1) 100% MDD (1) 100% depressive disorder</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) Nortriptyline (2) Paroxetine (10-40mg/day) (3) Alprazolam (2.2mg/day, Imipramine 98mg/day)</td>
<td>(1) Nortriptyline (1) Nortriptyline (1) GP care</td>
<td>(1) Nortriptyline (1) Nortriptyline (1) GP care</td>
<td>(1) Nortriptyline, placebo. (2) Paroxetine (10-40mg/day), placebo, clinical management.</td>
<td>(1) Nortriptyline, placebo. (2) Paroxetine (10-40mg/day), placebo, clinical management.</td>
<td></td>
</tr>
<tr>
<td>Length of treatment</td>
<td>(1) 16 weeks (1) 16 weeks (1) 5 months</td>
<td>(1) 16 weeks (1) 16 weeks (1) 5 months</td>
<td>(1) 16 weeks (1) 16 weeks (1) 5 months</td>
<td>(1) 3 years (1) 2 years</td>
<td>(1) 3 years (1) 2 years</td>
<td>(1) 3 years (1) 2 years</td>
</tr>
<tr>
<td>Follow-up</td>
<td>(1) not reported (1) not reported (1) not reported</td>
<td>(1) not reported (1) not reported (1) not reported</td>
<td>(1) not reported (1) not reported (1) not reported</td>
<td>(1) not reported (1) not reported</td>
<td>(1) not reported (1) not reported</td>
<td>(1) not reported (1) not reported</td>
</tr>
</tbody>
</table>

### Table 50: Summary evidence profile for interpersonal therapy

<table>
<thead>
<tr>
<th></th>
<th>IPT vs Placebo</th>
<th>IPT vs Usual GP care (incl. ADs)</th>
<th>IPT (with/without placebo vs IPT + ADs)</th>
<th>IPT + ADs vs ADs</th>
<th>IPT (with/without placebo vs ADs (with/without clinical management)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving study early for any reason Quality Number of studies; participants Forest plot</td>
<td>RR 0.57 (0.33 to 0.99)</td>
<td>RR 3.31 (1.94 to 5.63)</td>
<td>RR 1.44 (0.72 to 2.86)</td>
<td>RR 0.69 (0.40 to 1.18)</td>
<td>RR 0.94 (0.72 to 1.22)</td>
</tr>
</tbody>
</table>
### Depression self-report measures at endpoint

<table>
<thead>
<tr>
<th>Measure</th>
<th>SMD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD &gt;7</td>
<td>-0.69</td>
<td>(-1.22 to 0.07)</td>
</tr>
<tr>
<td>RR 0.73</td>
<td>0.04</td>
<td>(-0.32 to 0.40)</td>
</tr>
</tbody>
</table>

**Quality**
- Number of studies: 1
- Participants: 123

### Depression clinician-report measures at endpoint

<table>
<thead>
<tr>
<th>Measure</th>
<th>SMD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD &gt;7</td>
<td>-0.43</td>
<td>(-0.79 to -0.07)</td>
</tr>
<tr>
<td>RR 0.73</td>
<td>0.03</td>
<td>(-0.26 to 0.32)</td>
</tr>
</tbody>
</table>

**Quality**
- Number of studies: 1
- Participants: 123

### Relapse

<table>
<thead>
<tr>
<th>Measure</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT + AD vs AD + medication clinic</td>
<td>0.42</td>
<td>(0.02 to 9.34)</td>
</tr>
<tr>
<td>IPT + ADs vs IPT + placebo</td>
<td>0.17</td>
<td>(0.01 to 3.51)</td>
</tr>
</tbody>
</table>

**Quality**
- Number of studies: 1
- Participants: 25
### IPT as maintenance treatment (3 years)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT vs IPT + ADs</td>
<td>0.89 (0.35 to 2.28)</td>
<td>IPT vs Placebo</td>
<td>0.24 (0.06 to 1.01)</td>
<td>IPT vs IPT + ADs vs IPT + Placebo</td>
<td>0.59 (0.11 to 3.22)</td>
<td>IPT vs IPT + ADs vs Placebo</td>
<td>0.60 (0.26 to 1.38)</td>
</tr>
</tbody>
</table>

#### Quality

- Number of studies; participants: K=1, n=51; K=2, n=101; K=1, n=54; K=1, n=49; K=2, n=106; K=2, n=102; K=2, n=103; K=1, n=52

#### Forest plot

- Relapse: RR 1.73 (1.00 to 2.98)
- Quality: K=1, n=51; K=2, n=101; K=1, n=54; K=1, n=49; K=2, n=106

### IPT for the elderly

<table>
<thead>
<tr>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
<th>Study Design</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT vs IPT + ADs</td>
<td>0.87 (0.52 to 1.45)</td>
<td>IPT + ADs vs IPT</td>
<td>0.10 (0.01 to 1.67)</td>
<td>IPT vs IPT + ADs vs IPT + Placebo</td>
<td>0.63 (0.19 to 2.10)</td>
<td>IPT vs IPT vs Standard care (Netherlands)</td>
<td>0.86 (0.62 to 1.18)</td>
</tr>
</tbody>
</table>

#### Quality

- Number of studies; participants: K=3, n=121; K=1, n=41; K=1, n=42

#### Forest plot

- Depression clinician-report measures at endpoint: HRSD >7: RR 2.26 (1.03 to 4.97); HRSD >7: RR 0.71 (0.30 to 1.66); HRSD >7: RR 1.60 (0.94 to 2.75)
- Quality: K=1, n=33; K=1, n=41; K=1, n=42

#### Forest plot

- Depression clinician-report measures at follow-up: MADRS at 2 months: SMD -0.28 (-0.61 to 0.05); MADRS at 6 months: SMD -0.11 (-0.44 to 0.22)
- Quality: K=1, n=143

---

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Clinical evidence summary

There was a higher risk for discontinuation in the placebo group when compared to interpersonal therapy (RR 0.57). Furthermore, there was a significant small to medium effect (SMD –0.43; RR 0.73) of interpersonal therapy in the reduction of clinician-rated depression scores at post-treatment when compared to placebo.

When compared to usual GP care (including medication) there was no significant risk of discontinuation in the interpersonal therapy group. The evidence indicated a significant effect in self-reported depression scores at post-treatment (SMD –0.69). In addition, there was a large effect of interpersonal therapy in reduction of self-report depression scores at 3 (SMD –0.88) and 9 months (SMD –0.73) follow-up and similarly, in clinician-rated depression reports a large effect at 3 (SMD –0.81) and 9 (SMD –0.98) months follow-up.

Based on the evidence of one study (Reynolds1999) combination treatment of IPT plus antidepressants when compared to interpersonal therapy alone had a significant difference in decreasing clinician-rated depression scores (RR 2.26). Furthermore, when combination treatment was compared to antidepressants alone there was a significant medium effect (-0.40) in the reduction of clinician-rated depression measures at post-treatment.

When interpersonal therapy was compared directly to antidepressants the evidence showed no significant differences amongst the two groups.

Interpersonal therapy as a continuation treatment

The evidence of one study (Schulberg1996) showed a small to medium significant effect (SMD –0.44) of interpersonal therapy in the reduction of depression scores after 4 months continuation treatment when compared to treatment as usual.

Based on the evidence of two studies with a continuation time of 3 years (Frank1990; Reynolds1990) the evidence indicates that the combination of interpersonal therapy plus antidepressants has a lower risk of relapse when compared to interpersonal therapy alone (RR 0.42). This significant effect was also seen when combination treatment was compared to antidepressants (RR 0.62) and also when compared to medication clinic (RR 0.22).

Interpersonal therapy for the elderly

The evidence of one study (Reynolds1999) indicated a significant effect (RR 2.26) of the reduction of clinician-rated depression scores in an elderly population, favouring combination treatment of interpersonal therapy plus antidepressants when compared to interpersonal therapy alone.

Also, based on the same one study (Reynolds1999) antidepressants had a significant effect in reduction of clinician-rated depression measures (RR 1.60) when compared to interpersonal therapy.

When interpersonal therapy was studied as a maintenance treatment, combination treatment had a significant effect in lowering the risk of relapse (SMD 0.40) when compared to IPT alone and (SMD 0.22) when compared to medication clinic.
6.4.6 Counselling

Introduction

The British Association for Counselling and Psychotherapy (BACP) defines counselling as ‘a systematic process which gives individuals an opportunity to explore, discover and clarify ways of living more resourcefully, with a greater sense of well-being.

Counselling was developed by Carl Rogers (1957) who believed that people had the means for self-healing, problem resolution and growth if the right conditions could be created. These include the provision of positive regard, genuineness and empathy. Rogers’s original model was developed into structured counselling approaches by Truax and Carkhuff (1967) and, independently, by Egan (e.g. 1990) who developed the three stage model: exploration, personalising and action. Voluntary sector counselling training (e.g. Relate) tends to draw on these models. However, many other therapies now use basic ingredients of client-centred counselling (Roth & Fonagy, 1996) there are differences in how they are used (Kahn, 1985; Rogers, 1986) and counselling has become a generic term used to describe a broad range of interventions delivered by counsellors usually working in primary care. The content of these various approaches may include psychodynamic, systemic or cognitive behavioural elements (Bower et al., 2003).

Clinical evidence for counselling

No new studies that met the inclusion criteria were found for the update search. Three studies (Bedi2000; Simpson2003; Ward2000) were reported in the previous guideline and included in this version update.

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 51. The full evidence profiles and associated forest plots can be found in Appendix 16 and 19, respectively.

Table 51: Summary study characteristics of counselling

<table>
<thead>
<tr>
<th></th>
<th>Counselling vs. ADs</th>
<th>Counselling + GP care vs. GP Care</th>
<th>Counselling vs. GP care</th>
<th>Counselling vs. CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total</td>
<td>1 RCT (103)</td>
<td>1 RCT (145)</td>
<td>1 RCT (134)</td>
<td>1 RCT (130)</td>
</tr>
<tr>
<td>participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 79/77</td>
<td>(1) 116/82</td>
<td>(1) 152/77</td>
<td>(1) 152/77</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 39</td>
<td>(1) 43</td>
<td>(1) 37</td>
<td>(1) 37</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) 100% MDD</td>
<td>(1) depressed criteria (14-40 on BDI)</td>
<td>(1) Depressed or depressed &amp; anxious (=&gt;14 on BDI)</td>
<td>(1) Depressed or depressed &amp; anxious (=&gt;14 on BDI)</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) ADs (no details)</td>
<td>(1) GP care</td>
<td>(1) GP care</td>
<td>(1) CBT</td>
</tr>
<tr>
<td>Length of treatment</td>
<td>(1) 8 weeks</td>
<td>(1) 6-12 sessions</td>
<td>(1) 6-12 sessions</td>
<td>(1) 6-12 sessions</td>
</tr>
<tr>
<td>Follow-up</td>
<td>(1) Not reported</td>
<td>(1) 12 months</td>
<td>(1) 12 months</td>
<td>(1) 12 months</td>
</tr>
</tbody>
</table>
Clinical evidence summary

One study (Bedi2000) compared the effectiveness of counselling versus antidepressants. The evidence did not indicate a significant difference in risk of discontinuation or depression scores after treatment. However, for depression scores at 12 month follow-up, there was a significant difference favouring antidepressants (RR 1.41). Two further studies compared counselling to usual GP care. In one study (Ward2000) there was a significant small to medium effect in self-report depression scores at post treatment (SMD -0.49) but no significant differences between the two treatment groups on discontinuation and self-report depression scores at follow-up. In the other study (Simpson2003) there was no evidence of any important clinical benefit. Ward2000 also compared the effectiveness of counselling against CBT, no significant differences between the two treatments were identified.

6.4.7 Psychodynamic psychotherapy

Introduction

Psychodynamic interventions are psychological interventions, derived from a psychodynamic/psychoanalytic model, and where the therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference). Patients are given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with a technical focus on interpreting and working though conflicts.

As with other schools of therapy there are now many variations and hybrids of the original model with some approaches focusing on the dynamic of drives (e.g. aggression) while others focus on relationships (Greenberg & Mitchell, 1983). Other forms of this type of therapy have been influenced by attachment theory (Holmes, 2001). Clinical trials of psychodynamic psychotherapy have focused on short-term psychological therapy (10 to 20 weeks) usually in comparison with antidepressants or CBT. It is this brief version of psychodynamic therapy, often referred to as Short-term Psychodynamic Therapy that is the focus of this review.

Definition

Psychodynamic interventions were defined as psychological interventions, derived from a psychodynamic/psychoanalytic model, and where:

- Therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference). This leads to patients being given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with a technical focus on interpreting and working though conflicts.

- Therapy is non-directive and recipients are not taught specific skills (e.g. thought monitoring, re-evaluating, or problem-solving).
Clinical evidence for psychodynamic psychotherapy

In total, 17 studies were found in the search for psychodynamic psychotherapy trials. Ten trials were included (6 found in the update search and 4 are also reported in the previous guideline) and 7 were excluded. Reasons for exclusion consisted of: trials not being RCTs, papers not reporting outcome data, trials including participants without a diagnosis of depression and authors replacing drop-outs.

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 51. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

Table 52: Summary study characteristics of psychodynamic psychotherapies

<table>
<thead>
<tr>
<th></th>
<th>PP vs. ADs</th>
<th>PP vs. BT</th>
<th>PP vs. CBT</th>
<th>PP + ADs vs. Supportive therapy + ADs</th>
<th>PP vs. PP + ADs</th>
<th>PP vs. PP + ADs</th>
<th>PP vs. Wait List Control</th>
<th>PP vs. Supportive therapy</th>
<th>ADs vs. PP + ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>3 RCTs (230)</td>
<td>1 RCT (77)</td>
<td>2 RCTs (183)</td>
<td>1 RCT (74)</td>
<td>1 RCTs (191)</td>
<td>1 RCTs (20)</td>
<td>1 RCTs (20)</td>
<td>2 RCTs (220)</td>
<td></td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 76/74</td>
<td>(2) 111/72</td>
<td>(3) 35/68</td>
<td>(1) 60/92</td>
<td>(2) 61/52</td>
<td>(1) 45/61</td>
<td>(1) 128/67</td>
<td>(1) 19/63</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) unextractable</td>
<td>(2) 39</td>
<td>(3) 42</td>
<td>(1) 39</td>
<td>(2) 62</td>
<td>(2) 41</td>
<td>(1) 36</td>
<td>(1) unextractable</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) 100% depressive episode</td>
<td>(2) 100% MDD</td>
<td>(3) mild/moderate episode of MDD</td>
<td>(1) 100% RDC major depressive episode</td>
<td>(1) 100% MDD</td>
<td>(1) 100% dysthymia or minor depression</td>
<td>(1) 100% dysthymia or minor depression</td>
<td>(1) 100% depressive episode</td>
<td>(2) Remission from MDD</td>
</tr>
<tr>
<td>Comparators</td>
<td>(1) Venlafaxine (-225mg/day)</td>
<td>(2) Amitriptyline (150mg/day)</td>
<td>(3) Fluoxetine</td>
<td>(1) CBT (2) CBT</td>
<td>(1) Clomipramine (125mg/day)</td>
<td>(1) GP’s choice of ADs</td>
<td>(1) Wait-list control</td>
<td>(1) Supportive psychotherapy</td>
<td>(1) Range of ADs (2) Citalopram/paroxetine (20-60 mg/day)</td>
</tr>
<tr>
<td>Length of Treatment</td>
<td>(1) 24 weeks</td>
<td>(2) 10 weeks</td>
<td>(3) 16 weeks</td>
<td>(1) 10 weeks</td>
<td>(2) 16 weeks</td>
<td>(1) 10 weeks</td>
<td>(1) up to 6 months</td>
<td>(1) 15-30 weeks</td>
<td>(1) 15-30 weeks</td>
</tr>
<tr>
<td>Follow-up</td>
<td>(1) Not reported</td>
<td>(2) 3 months</td>
<td>(3) 4 months</td>
<td>(1) Not reported</td>
<td>(2) 12 months</td>
<td>(2) not reported</td>
<td>(1) Not reported</td>
<td>(1) Not reported</td>
<td>(1) Not reported</td>
</tr>
</tbody>
</table>

Depression in adults (update): full guideline DRAFT (February 2009)
Clinical evidence summary

Problems with unextractable data and multiple different comparators limited the analyses it was possible to undertake. The evidence based on one study (DEKKER2008) showed a significant medium effect (SMD 0.43) of antidepressants when compared to psychodynamic psychotherapy in the reduction of clinician-rated scores at endpoint. However, a further study (SALMINEN2008) found no significant differences amongst psychodynamic psychotherapy and antidepressants when looking at the mean change from baseline to endpoint (SMD 0.03). One study (McLean1979) indicated a significantly higher risk of discontinuation in those treated with psychodynamic psychotherapy when compared to behaviour therapy (RR 3.02). When compared to wait list control, one study (MAINA2005) showed a significant large effect (SMD -1.09) in clinician-rated depression scores at post-treatment, favouring psychodynamic psychotherapy. This study also indicated a large effect (SMD -0.97) of psychodynamic psychotherapy in clinician-rated depression scores at post-treatment when compared to supportive therapy. In a follow-up study (MAINA2008) showed that adding psychodynamic psychotherapy to antidepressant treatment had a significant medium to large effect at 24-months (SMD 0.52) and at 48 months (SMD 0.59) in reducing clinician-rated depression scores when compared to antidepressants alone.

6.4.8 Rational emotive behavioural therapy

Introduction
Rational Emotive Behaviour Therapy (REBT) is a form of cognitive-behaviour therapy developed by Albert Ellis in the 1950's and 1960's (Ellis, 1962). REBT is a present-focussed, relatively short-term therapy usually delivered one-to-one that uncovers and addresses the relationships between thoughts, feelings and behaviours. There is an emphasis on addressing thinking that underpins emotional and behavioural problems. Patients learn how to examine and challenge their unhelpful thinking.

Compared to other cognitive-behavioural modalities it has been subject to fewer research trials, and only one study met our criteria (David et al., 2008). This study compared REBT with anti-depressant medication and the findings were promising in terms of end of treatment depressive symptoms and positive in terms acceptability and preventing relapse at six month follow up.

**Clinical evidence for rational emotive behavioural therapy**

Only one RCT (DAVID2008) was found and was included in our review. This section reports on the DAVID2008 comparison of treatment REBT versus ADs, comparison with CBT can be found in section 1.1.

Study information and evidence from the important outcomes and overall quality of evidence are presented in Table 54. The full evidence profiles and associated forest plots can be found in Appendix 16 and Appendix 19, respectively.

<p>| Table 54: Summary study characteristics of rational emotive behaviour therapy |</p>
<table>
<thead>
<tr>
<th>No. trials (Total participants)</th>
<th>REBT vs. ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study IDs</td>
<td>(1) DAVID2008</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 113/66</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 37</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) 100% MDD</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) ADs</td>
</tr>
<tr>
<td>Length of Treatment</td>
<td>(1) 14 weeks</td>
</tr>
<tr>
<td>Follow-up</td>
<td>(1) 6 months</td>
</tr>
</tbody>
</table>

**Clinical evidence summary**

The evidence of one study (DAVID2008) showed no clinically significant different effects of the treatment of rational emotive behaviour therapy in depressed patients when compared to antidepressants.

**Health Economic Evidence review and considerations**

5 reports (King et al. 2000, Friedli et al. 2000, Miller et al. 2003, Simpson et al. 2000, Simpson et al. 2003) were identified in the systematic literature review which dealt with cost effectiveness of different psychological/psychosocial interventions in primary care settings. Simpson et al. 2003 was a new addition to this evidence base. These studies compared the counselling to range of interventions listed: usual GP care, CBT and antidepressant therapy. The results show no significant difference in either outcomes or in the costs. It must be noted that many of the RCTs on which the studies were based on included a mixed population of depression and anxiety/depression. As
a result some of the RCTs where excluded from the clinical review. However, due to
the lack of relevant economic evidence these economic studies were not excluded from
this section of the guideline. Three further reports investigated the costs and benefits of
psychological interventions on an outpatient basis. Leff et al. 2000, Scott et al. 2003
were included in the previous guideline. The study by Leff et al. (2000) showed that
couple-focused therapy was superior to antidepressant therapy in terms of clinical
outcomes and that savings in other health service use offset the additional costs of
couple-focused therapy. However, the validity of the results was greatly limited due to
the high dropout rate and limited choice of comparators i.e. SSRIs are increasingly
being prescribed yet the comparators chosen were desipramine, trazodone and
fluvoxamine. (It was excluded from the clinical review in this guideline).

While the study by Scott et al. (2003) reported that CBT in combination with
antidepressant therapy is likely to be cost-effective for relapse prevention in patients
with residual depression. The use of QALYs would have been more relevant to
compare the findings with other cost-effectiveness studies. However this is the only
study addressing relapse prevention.

The study by Simon et al. 2006 refers to the modeling exercise undertaken for the
previous guideline, in which the combination of antidepressant and CBT was
compared to antidepressant therapy alone. For the guideline update, this model was
updated, the details of which follow later in this chapter.

Summary:
The lack of economic evidence found for this update does not provide any support any
change in conclusions regarding counselling, couples therapy or brief psychodynamic
therapy other than reached in the clinical summaries above.

Health state utility studies
Among the studies already assessed for eligibility, seven publications were identified
that reported utility scores relating to specific health states and events associated with
depression (Bennett et al., 2000; King et al., 2000; Peveler et al., 2005; Pyne et al., 2003;
Revicki & Wood, 1998; Sapin et al., 2004; Schaffer et al., 2002).

Three studies used the EQ-5D instrument, currently recommended by NICE as a
measure of patient utility scores for use in cost-effectiveness analyses (King et al., 2000;
Peveler et al., 2005; Sapin et al., 2004). Two studies were based on RCTs measuring
change in patients’ utility scores over 12 months follow-up as a result of specific
interventions such as CBT or antidepressant treatment in the UK primary care setting
(King et al., 2000; Peveler et al., 2005). Both studies showed that patients’ utility scores
improved in the initial period after treatment (baseline to 4 months) whilst these
improvements disappeared at 12 months. The third non-intervention study was based
on a prospective cohort of patients in the French primary care setting who were
assessed at 8 weeks follow-up (Sapin et al., 2004). Utility scores were stratified
according to depression severity, defined by CGI scores, and by clinical response,
defined by MADRS scores, at follow-up. In all three studies, preference values elicited
from the UK population sample were used (Dolan, 1995).

The other four studies used a variety of instruments to measure patient utility (Bennett
et al., 2000; Pyne et al., 2003; Revicki & Wood, 1998; Schaffer et al., 2002). The study by
Bennett et al. (2000) used a disease-specific measure, the McSad instrument, to elicit utility scores for patients with a history of depression. Pyne et al. (2003) used the Quality of Well-Being scale (QWB-SA) in a prospective cohort of US patients treated with antidepressants to measure change in patient utility scores over 4 month follow-up. Utility scores improved during follow-up for treatment responders (defined by HRSD-17) but did not improve for non-responders. Revicki & Wood (1998) used standard gamble (SG) techniques in patients with major depressive disorder (MDD) in order to generate 11 hypothetical depression-related health states according to depression severity and antidepressant treatment. Similarly, the study by Schaffer et al. (2002) used SG techniques to elicit utility scores for 10 individual symptoms of depression plus three depression profiles (mild/moderate/severe) amongst patients with current or past depression.

Summary
Overall, the studies reviewed here reported significant impact of depression on the health-related quality-of-life (HRQoL) of patients with major depressive disorder. A number of studies showed that patients valued the state of severe depression as being close to zero or death (Bennett et al., 2000; Revicki & Wood, 1998). There was some limited evidence to suggest that generic utility measures such as the EQ-5D may be less sensitive than disease-specific measures such as the McSad health state classification system (Bennett et al., 2000). In order to calculate QALYs for the guideline economic models, the utility values obtained by Sapin et al. (2004) were considered to be most suitable. This is because they were obtained from the EQ-5D instrument, as currently recommended by NICE (NICE, 2008) and were stratified according to disease severity and clinical response.

Cost-effectiveness modelling

Background
The aim here was to update the model constructed in the original guideline which evaluated the cost-effectiveness of antidepressant therapy versus a combination of antidepressant therapy and CBT for the routine treatment of moderate/severe depression (NICE, 2004). Key input parameters and assumptions within the model were updated in order to better reflect current medical practice within the UK.

Methods
A pragmatic decision analytic model was constructed using Microsoft Excel XP and a detailed structure of the decision tree is presented in Figure 1. A time horizon of 15 months was chosen to reflect the available comparative clinical evidence. This included 3 months of the initial therapy, followed by 6 months maintenance therapy and 6 months follow-up. The following strategies were considered:

Strategy A: Antidepressant therapy given for 12 weeks with 6 months maintenance therapy and 6 months follow-up (AD).

Strategy B: Combination of 12 weeks of antidepressant therapy and 16 sessions of CBT with 6 months maintenance therapy and 6 months follow-up (COMB).

Originally, three specific strategies for the first-line management of depression were considered. However, similar to the original guideline, the updated clinical evidence review showed no overall superiority for CBT alone on treatment outcomes over antidepressant therapy. The efficacy evidence combined with the significantly higher
treatment cost of CBT compared with the cost of antidepressants resulted in the exclusion of CBT alone from the final analysis.

**Model Assumptions**

**Population**
Two separate models were constructed for a hypothetical cohort of 100 patients with either moderate or severe depression. All patients with moderate depression and a proportion with severe depression were monitored in the primary care setting with the remaining severely depressed patients being monitored in the secondary care setting. CBT for both moderate and severe patients was delivered in the secondary care setting.

**Figure 1: Structure of the Model**

**Antidepressant therapy**
The antidepressant therapy protocol consisted of 12 weeks plus 6 months maintenance period of 40mg of generic citalopram per day for both moderate and severely depressed patients (BNF Sept 2008). Citalopram was used to represent standard pharmacotherapy for patients with moderate or severe depression as it was the most commonly prescribed antidepressant in 2007 in England (Dept. of Health, 2008). As part of patient monitoring, it was assumed that all patients with moderate depression and 50% of patients with severe depression would receive standard GP care whilst the remaining 50% of patients with severe depression would receive specialist mental
health outpatient care (GDG expert opinion). It was also assumed that patient monitoring in both primary and secondary care consists of two fortnightly visits in the first month followed by one visit per month whilst the maintenance therapy period consisted of one GP/specialist visit every two months (GDG expert opinion).

Combination therapy

For both moderate and severely depressed patients, it was assumed that combination therapy would consist of 16 sessions of CBT over 12 weeks, in addition to the antidepressant therapy protocols described above (GDG expert opinion). One CBT session lasts for 55 minutes and is provided by a specialty doctor, clinical psychologist or mental health nurse (Curtis, 2009). During the 6-month maintenance therapy period, it was assumed that both moderate and severely depressed patients would receive an additional two CBT sessions, in addition to the AD maintenance therapy protocols described above (GDG expert opinion).

Clinical outcomes and event probabilities

The outcome measure used for the economic evaluation was the quality-adjusted life years (QALYs) gained from either treatment. No discounting of outcomes was necessary since the time horizon of the model was 15 months. The key clinical parameter estimates – discontinuation rates; remission rates and relapse rates – were collected as part of the updated clinical systematic review undertaken for the guideline. The dichotomous outcome measure of no remission was defined by scores greater than six on the 17-item HRSD or more than eight on the 24-item HRSD.

Event probabilities used in the model were based on intention to treat analysis. For the base case analysis, absolute and relative risk estimates were taken from the guideline meta-analyses. For patients who did not complete their initial therapy, it was assumed that rather than remaining moderately or severely depressed, a small proportion (20%) would spontaneously remit (GDG expert opinion). Furthermore, for these patients in remission, the rate of relapse was estimated as 27% based on a study of patients who were not receiving maintenance therapy (Murphy et al., 1984). These rates were applied to patients in both treatment arms. For the sensitivity analyses, 95% confidence intervals around the relevant relative risks of COMB therapy versus AD therapy were used. In order to estimate QALYs, utility values were obtained from one published study, which reported patient-assigned utility scores according to depression severity and clinical response (Sapin et al., 2004). Uncertainty around these estimates was also explored by sensitivity analysis. Full details of the event probabilities and utility scores are presented in Table 55.

Resource use and unit costs

An NHS perspective was taken for the analysis based on current NICE guidance (NICE, 2008). Therefore, only direct health care costs were considered in the analysis. In order to cost the two therapy pathways, resource utilisation data were collected as part of the literature review or from GDG expert opinion. Unit costs were obtained from a variety of sources including the British National Formulary (2008) and the Personal Social Services Research Unit (2008). Resource utilisation data were then combined with the relevant cost associated with each therapy. All costs were based on 2007/08 prices and were inflated where necessary using Hospital and Community
Health Service indices (Curtis, 2009). As in the case of outcomes, no discounting was applied since the time horizon was 15 months.

For patients who discontinued initial treatment, rather than incur full treatment costs, their costs were revised downwards. For this, it was assumed that patients who discontinued initial therapy would receive 4 weeks of therapy, irrespective of treatment group (Rush et al., 2006; GDG expert opinion). For patients in remission who did not relapse during follow-up, it was assumed that no further additional treatment or mental health care resources were required. However, for patients with unsuccessful treatment outcomes, it was assumed that they would continue to consume additional mental health care resources over the 15-month time horizon. Cost data for subsequent mental health care were taken from a study published by the King’s Fund which estimated annual mental health care costs based on the UK psychiatric morbidity survey (McCrone et al., 2007). These mental health care costs included hospital and outpatient care, social services, residential care, GP visits and medication costs. These annual costs were divided into monthly cost estimates and then projected for the periods during which unsuccessfully treated patients would consume subsequent mental health care estimated in the model. According to the survey, only 65% of people with depression were in contact or receipt of mental health services. Therefore, these subsequent mental health care costs were weighted accordingly. Patients who did not going into remission following therapy incurred full 3-month treatment costs followed by subsequent mental health care thereafter. For patients who relapsed whilst in remission, it was assumed that the average time to relapse was 4 months after which they incurred subsequent mental health care (Rush et al., 2006; GDG expert opinion). All unit cost parameters are presented in Table 55.

Incremental cost-effectiveness of COMB versus AD therapy

The incremental cost-effectiveness of COMB compared with AD therapy for patients with moderate or severe depression was evaluated by assessing the difference in costs and effectiveness of each therapy. The incremental cost-effectiveness ratios (ICERs) were calculated as the difference in the expected health care costs divided by the difference in the overall effectiveness of the two strategies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case value (mean)</th>
<th>Range (95% CI)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of not completing treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>0.30</td>
<td>(0.20 to 0.30)</td>
<td>Guideline meta-analysis</td>
</tr>
<tr>
<td>COMB</td>
<td>0.24</td>
<td>(0.20 to 0.30)</td>
<td>Guideline meta-analysis</td>
</tr>
<tr>
<td>Probability of no remission following treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>0.70</td>
<td>(0.39 to 0.72)</td>
<td>Guideline meta-analysis</td>
</tr>
<tr>
<td>COMB</td>
<td>0.53</td>
<td>(0.39 to 0.72)</td>
<td>Guideline meta-analysis</td>
</tr>
<tr>
<td>Probability of relapse during follow-up:</td>
<td></td>
<td></td>
<td>Blackburn et al.</td>
</tr>
</tbody>
</table>

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Probability of spontaneous remission for patients who drop out of initial treatment:

| BOTH | 0.20 | (0.10 to 0.30) | GDG expert opinion |

Probability of relapse for patients who discontinue initial treatment and in remission:

| BOTH | 0.67 | NA | Murphy et al. (1984) |

Quality-of-life weights

<table>
<thead>
<tr>
<th></th>
<th>Moderate depression</th>
<th>Severe depression</th>
<th>Remission</th>
<th>Remission plus relapse</th>
<th>No Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTH</td>
<td>0.33</td>
<td>(0.29 to 0.37)</td>
<td>0.15</td>
<td>(0.08 to 0.22)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Sapin et al. (2004)

Unit Costs (2007/08 prices)

<table>
<thead>
<tr>
<th></th>
<th>Generic citalopram (40mg pack)</th>
<th>GP consultation</th>
<th>Mental Health outpatient consultation</th>
<th>CBT session</th>
<th>Subsequent depression treatment (per month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTH</td>
<td>£1.87</td>
<td>£36</td>
<td>£130</td>
<td>£58</td>
<td>£180</td>
</tr>
</tbody>
</table>


Sensitivity analyses

Deterministic sensitivity analysis

Given the considerable uncertainty around some of the input parameters used in the base case model and ambiguity surrounding any policy implications of point estimates, one-way sensitivity analysis was required. This involved varying a single parameter between its plausible minimum and maximum values while maintaining all remaining parameters in the model at their base case value. Uncertainty around the various transition probabilities, quality-of-life weights as well as the cost implications of different levels of resource use involved in patient clinical management were all explored.

Probabilistic sensitivity analysis

In order to demonstrate the joint uncertainty between the different parameters probabilistic analysis is required. Using the mean point estimates and their 95% confidence intervals, appropriate distributions were assigned for each parameter estimate. For example, lognormal distributions were applied to relative risk estimates, gamma distributions to cost estimates and beta distributions to utility estimates. For cost estimates that did not have 95% confidence intervals, a standard error based on 30% of the mean estimate was applied in order to reflect any potential uncertainty around these estimates. Effectiveness and cost estimates were then recalculated 10,000 times using Monte Carlo simulation. Whether an intervention is cost-effective or not depends on how decision-makers value the additional health gain achieved by the
therapy. The probability that COMB therapy is cost-effective compared with AD therapy as a function of decision-makers’ maximum willingness-to-pay for an additional successfully treated patient or QALY was illustrated by cost-effectiveness acceptability curves (CEACs) (Briggs, 2000).

Results

Clinical outcomes
The systematic review of the clinical evidence showed that the probability of not completing the initial 3-month therapy was higher for AD than for COMB (RR = 0.80, 95% CI: 0.65 to 1.01) whilst the probability of not achieving remission following therapy was also lower in the COMB group (RR = 0.76, 95% CI 0.55 to 1.03). The two follow-up studies suggested that there is a lower risk of relapse in the COMB therapy arm (RR = 0.68, 95% CI 0.38 to 1.24) over a 12-month follow-up period although this wasn’t statistically significant (p = 0.21). The decision model for patients with moderate depression resulted in an average of 0.68 QALYs per patient in the COMB therapy group and 0.62 QALYs per patient in the AD therapy group. The decision model for patients with severe depression resulted in an average of 0.58 QALYs per patient in the COMB therapy group and 0.50 QALYs in the AD therapy group. Therefore, the average gain in QALYs over 15 months for COMB therapy was 0.06 per patient with moderate depression and 0.08 per patient with severe depression.

Costs and cost-effectiveness
The full cost of a 3-month course of AD therapy plus 6-month maintenance therapy was £270 for patients with moderate depression and £599 for patients with severe depression. The full cost of 3-month COMB therapy, including a full course of CBT, plus 6-month maintenance therapy was £1,314 for patients with moderate depression and £1,643 for patients with severe depression. The expected subsequent health care costs over 15 months for patients who did not complete their initial therapy was £1,638 for both moderate and severe patients. The expected subsequent health care costs over 15 months for patients who did not respond to therapy and go into remission was £1,404 for both patient groups. The expected cost of relapse whilst in remission was £936 for both patient groups.

Incremental cost-effectiveness of COMB versus AD therapy
Overall, COMB therapy was estimated to be significantly more effective and more costly than AD therapy for patients with both moderate and severe depression. On average, the strategy of COMB therapy was £616 more costly per patient with moderate depression and £644 more costly per patient with severe depression. The resulting base case ICERs were £10,078 per QALY gained for moderate depression and £8,035 per QALY gained for severe depression.

Sensitivity Analyses

Deterministic sensitivity analysis
The parameter values used in the sensitivity analyses and the relevant ICERs are presented in Table 56. The results of the deterministic sensitivity analysis indicated that the results were fairly robust when single parameters are varied over their uncertainty ranges. The cost-effectiveness estimates were most sensitive to: (1) the relative risk of no remission following therapy completion and; (2) the relative risk of relapse whilst in remission. Other factors had a much lesser role in the variation of the results.

Table 56: Deterministic sensitivity analysis.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Uncertainty Range</th>
<th>ICER per QALY (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate depression</td>
</tr>
<tr>
<td>Base case analysis</td>
<td></td>
<td>10,078</td>
</tr>
<tr>
<td>Clinical efficacy (COMB vs AD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of discontinuation</td>
<td>0.65 to 1.01</td>
<td>9,782 to 10,505</td>
</tr>
<tr>
<td>Relative risk of non-remission</td>
<td>0.55 to 1.03</td>
<td>4,830 to 84,612</td>
</tr>
<tr>
<td>Relative risk of relapse</td>
<td>0.38 to 1.24</td>
<td>7,234 to 22,333</td>
</tr>
<tr>
<td>Relative risk of non-remission following discontinuation</td>
<td>0.7 to 0.9</td>
<td>9,738 to 10,441</td>
</tr>
<tr>
<td>Quality-of-life weights</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate depression</td>
<td>0.29 to 0.37</td>
<td>9,423 to 10,829</td>
</tr>
<tr>
<td>Severe depression</td>
<td>0.08 to 0.22</td>
<td>NA</td>
</tr>
<tr>
<td>Remission - no relapse</td>
<td>0.83 to 0.87</td>
<td>9,829 to 10,339</td>
</tr>
<tr>
<td>Remission - relapse</td>
<td>0.65 to 0.79</td>
<td>9,057 to 11,357</td>
</tr>
<tr>
<td>No Remission</td>
<td>0.50 to 0.66</td>
<td>9,238 to 11,085</td>
</tr>
<tr>
<td>Resource use and costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe patients - % receiving specialist care</td>
<td>5% to 50%</td>
<td>3,865 to 10,078</td>
</tr>
<tr>
<td>Moderate patients – number of CBT sessions</td>
<td>8 to 16</td>
<td>NA</td>
</tr>
</tbody>
</table>

Probabilistic sensitivity analysis

In order to present the results of the probabilistic sensitivity analysis, cost-effectiveness acceptability curves (CEACs) were constructed (Figure 2). The CEAC indicates the probability of COMB therapy being cost-effective for a range of threshold values. The threshold value represents the maximum a decision maker would be willing to pay for a unit of effect, in this case a QALY.

Current NICE guidance sets a threshold range of £20,000 to £30,000 per QALY (NICE, 2008). Within this threshold range, the probability of COMB therapy being cost-effective for patients with moderate depression was 94-95% and for patients with severe depression was 96-97%.
Discussion

In this economic evaluation, CBT was chosen as the psychotherapy and citalopram as the antidepressant drug being compared. An updated cost-effectiveness model was constructed to investigate the difference in clinical outcomes and direct health care costs between the different strategies. The updated clinical evidence review indicated that CBT alone is likely to be dominated by antidepressant therapy and therefore, it was excluded from the final model. As combination therapy is both more effective and more costly than antidepressant therapy, these strategies were compared in a formal cost-effectiveness analysis.

Two separate analyses were conducted for patients with moderate depression and severe depression respectively. The difference in costs between combination therapy and antidepressant therapy was slightly higher for patients with severe depression, whilst the difference in QALY gains was also slightly higher. The cost results for patients with both moderate and severe depression suggest that although the initial treatment cost of combination therapy is substantially higher, these costs were partially offset by savings due to lower subsequent treatment costs. Overall, the results of the analysis indicate that combination therapy is likely to be a cost-effective first-line treatment for both moderate and severe depression.

Limitations of the analysis
The clinical effectiveness estimates used in the analyses were based on efficacy data obtained from randomised controlled trials, resulting in possible over-estimates of successful outcomes for both treatment options provided within the NHS setting. However, this is unlikely to significantly influence the relative effectiveness of the two treatment options. Furthermore, as a number of the included studies in the clinical review were conducted in the 1980s, issues surround the current applicability of the synthesised clinical evidence.

Another issue concerns the time horizon used for the analysis. A 15-month time horizon was used, with remission rates applied at the end of the initial 3-month treatment and relapse rates applied during the 12 month follow-up period. One study in the clinical evidence review indicated lower relapse rates with combination therapy for up to 6 years after treatment (Fava, 2004). It would have been preferable to evaluate the two strategies over a longer follow-up period but the lack of direct clinical evidence beyond 15 months precluded this.

Depression incurs significant non-healthcare costs such as social service costs, direct costs to patients and their families and lost productivity costs due to morbidity or premature mortality (Thomas & Morris, 2003; McCrone et al., 2007). As this analysis was conducted from the health service perspective, as per NICE guidance, such non-healthcare costs were not considered. It is likely that including such costs would have further increased the probability of combination therapy being cost-effective versus antidepressant therapy.

6.4.9 From evidence to recommendations

This section synthesises the evidence from the clinical summaries from all the interventions reviewed as part of this guideline. This is because some key recommendations about psychological therapies are common to all types of interventions and also because a number of the recommendations draw on evidence from several different reviews On the whole, the evidence indicates that psychosocial interventions have a beneficial effect in the treatment of people with depression do not have an increased risk for discontinuation when compared to antidepressants. However, the evidence suggests that there are differences in the evidence base for the effectiveness amongst the psychological interventions reviewed in section 6b and this form as the basis of this section.

Cognitive and behavioural therapies

With 65 studies, cognitive and behavioural therapies have the largest evidence base. Within this group of studies the largest data set is that which compares CBT with antidepressant medication and which shows broad equivalence of effect across the range of severity (based on APA 2000) and suggest no reason to change the recommendation from the 2004 guideline that CBT is an effective treatment for depression either alone or in combination with antidepressants. The model suggested that combination treatment is cost effective not just for severe depression but also for moderate depression and a result the guideline recommendations were changed. This did not lead to the simple adoption of combination treatment as the first choice but the placing of combination treatment as one of a number of options for the treatment of
moderate depression in which both patient and clinician are encouraged to take into account a number of factors including the demand so adhering to treatment when determining treatment choice. When compared to wait list controls, the effectiveness of cognitive behavioural therapies is significantly greater. The evidence for the role of CBT in relapse prevention, the management of and treatment of residual symptoms and maintenance has improved since the last guideline with a number of new studies providing further support for the effectiveness of CBT in these areas including new data on mindfulness based CBT. In making recommendations about CBT the GDG were conscious of feedback from stakeholders and of their own experience of providing or receiving psychological treatments. This lead the group to specify in greater detail, than previously the way in which all psychological treatment in this guideline (including CBT) should be provided. It also lead the GDG after considering the evidence to remove the previous recommendation about the provision of brief CBT as the GDG did not feel that the evidence justified such a recommendation and there was concern that it has led to an unnecessary restriction on the number of session of psychological intervention being made available.

Group CBT is an effective treatment for mild depression given the duration of the groups was viewed, on cost minimisation grounds as a less showed mixed results in terms of its effectiveness; showing no significant results compared to other forms of psychotherapy when continuous measures were reported but also showed a significant decrease in depression dichotomous scores. There is no evidence to indicate that the use of CBT in relapse prevention is effective. However, CBT-mindfulness treatments showed some beneficial effects in reducing depressive scores. It is important to note that most of these studies entailed 16 to 20 sessions over different lengths of time. The health economic data showed that the combination treatment of CBT plus antidepressants is more cost-effective than either treatment on their own. When CBT is added to antidepressant treatment there is a clear beneficial effect in reducing depressive symptoms in adult and elderly populations. However, when compared to placebo, therapies designed for depression, or to non-directive psychotherapies the results are not significant and remain inconclusive.

**Behaviour activation**

There has been renewed interest in behaviour activation as a treatment for depression and a number of new studies were identified for the review in this guideline. It is a component part of cognitive behavioural interventions for depression and one of the first important trials of a behaviour activation was a deconstruction studies (Jacobson1999). However, despite the emergence of new data the GDG did not feel that this was of sufficient robustness to warrant a separate recommendation although it is expected it will form part of CBT interventions for severe depression and also inform the development of low intensity interventions for depression.

**Problem solving therapy**

Problem solving therapy was recommended as an intervention in the last guideline. No new studies were identified leaving the data small and based only on three studies with much of the evidence for effectiveness being dependant on one study. In light of the improved evidence for a range of low intensity interventions that have emerged since the last guideline the GDG decided not to recommend PST in this guideline.
Couples-focused therapy

In the review for this guideline a number of additional studies were included and one from the last guideline was excluded. The evidence base for couples-focused therapy is relatively modest with just 6 studies but with indication of a beneficial effect in couples with depression when compared to wait list control and broad evidence of similar outcomes for couples-focused therapy when compared to individual CBT and IPT. As a result of the increased evidence identified in this guideline couple therapy is recommended but the GDG did not consider to be equivalent to CBT or IPT but rather suggest that it be focused on patients in established relationships were the relation may play a role in the development, maintenance or resolution of the depressive disorder.

Interpersonal therapy

The evidence for the effectiveness of interpersonal therapy reviewed in this guideline confirms the picture identified in the previous guideline that IPT is potentially as effective a treatment for depression as CBT. The data set is not as large and the range of applications of IPT are not as wide ranging as CBT and there was no economic modelling for IPT Therefore the GDG did not develop recommendations for IPT that were as broad in scope as this for CBT (e.g. the use of combination CBT and antidepressant drugs as the initial treatment for severe depression) but for many patients with moderate depression IPT will be an appropriate alternative to CBT.

Counselling

The evidence base for counselling as a treatment for depression is small (K=3) and an inconsistent picture of the effectiveness of the intervention in depression emerges. The 2004 guideline (NICE, 2004) did recommend counselling in mild to depression but in light of the increased evidence for a range of low intensity interventions and group CBT for mild depression the GDG decided not to support the recommendation for counselling. Nevertheless the GDG felt that counselling might still be consider for people with mild to moderate depression who had failed to benefit from low intensity interventions or group CBT but given the limited evidence felt that it was right that this limited evidence should be drawn to the attention of patient. There was considerable discussion of this recommendation in the GDG which took into account not just the limited evidence for counselling and the increased evidence for other interventions but also contextual changes in the NHS including the significant increase in evidenced based psychological interventions made available through the IPAT programme. Whilst the agreed recommendation did not reflect the view of all GDG members a very substantial number of GDG member supported the recommendation.

Short-term psychodynamic therapy

A small number of new studies were identified for short-term psychodynamic therapy as a treatment for depression. The various comparators used significantly limited the amount of meta-analysis that was possible. Nevertheless from a review of these studies it was not possible to demonstrate a consistent picture of clinically important benefit for short-term psychodynamic therapy. The 2004 guideline (NICE, 2004) recommended
psychodynamic therapy for complex comorbidities but the current data set also offered no clear evidence on the issue of the effectiveness of short-term psychodynamic therapy for complex comorbidities. As a result of the limited evidence for short-term psychodynamic therapy for depression with or without complex comorbidities the GDG did not feel able to endorse the 2004 recommendation and developed a more restrictive recommendation. This recommendation, along with the recommendation on counselling, was influenced by contextual changes in the NHS including the significant increase in evidenced based psychological interventions made available through the IPAT programme. Nevertheless the GDG took the view that short-term psychodynamic therapy might still be consider for people with moderate depression which had failed to benefit from CBT or IPT but given the limited evidence that it was right that this limited evidence should be drawn to the attention of patient. Whilst the agreed recommendation did not reflect the view of all GDG members a very substantial number of GDG member supported the recommendation.

6.5 Recommendations

6.5.1 Effective delivery of interventions for depression

6.5.1.1 All interventions for depression should be delivered by practitioners who are competent to deliver the intervention. Psychological and psychosocial interventions should be based on the relevant treatment manual(s), which practitioners should follow with regard to the structure and duration of the intervention. Staff should:

- use competence frameworks developed from the relevant treatment manual(s)
- receive regular high quality supervision
- use routine outcome measures and ensure that the person with depression is involved in reviewing the efficacy of the treatment
- monitor and evaluate adherence and competence, for example, through the use of video and audio tapes and external audit and scrutiny where appropriate.

6.5.2 Group CBT

6.5.2.1 For people with persistent minor and mild to moderate depression, practitioners should consider group-based CBT for those people who decline an individual low intensity intervention or express a preference for a group-based intervention.

6.5.2.2 Group-based CBT for people with persistent minor and mild to moderate depression should:

- consist of 10 to 12 meetings of 8 to 10 participants
- normally take place over 12 to 16 weeks, including follow up
- be based on a structured model such as ‘Coping with Depression’
- be delivered by two trained and competent practitioners:
6.5.3  Counselling

6.5.3.1 For people with persistent minor and mild to moderate depression who have declined a low intensity intervention or group CBT, counselling may be considered. However, practitioners should take care to explain the uncertainty about the effectiveness of counselling for people with depression.

6.5.3.2 Counselling for people with persistent minor and mild to moderate depression should be:
- based on a non-directive person-centred model
- typically in the range of 6 to 10 sessions over 8 to 12 weeks

6.5.3.3 For people with persistent minor and mild to moderate depression who have not benefited from a low intensity psychosocial intervention, and those with moderate and severe depression, practitioners should consider a high intensity psychological treatment or initiation or review of antidepressant medication. The choice of intervention should be influenced by:
- the person’s treatment preference
- the duration of the episode and the trajectory of symptoms
- the previous illness course and response to treatment.

6.5.4  Treatment options

6.5.4.1 Discuss the relative merits of different interventions with the person with depression and offer:
- antidepressant drugs (normally SSRIs)
- psychological interventions (normally CBT and interpersonal therapy)
- a combination of antidepressants and CBT.

The choice should be based on patient preference, the likelihood of adherence to the treatment, and the likely side effects.

6.5.5  Choice of psychological treatment

6.5.5.1 For people with moderate depression who are offered psychological interventions the choice of treatment should include:
- Individual cognitive behavioural therapy
- IPT if the person expresses a preference for it or if, in the view of the healthcare professional, the person with depression may benefit from it.
6.5.2 Couple-focused therapy may be considered for people with depression who have a regular partner and:

- have not benefited from a low intensity intervention or pharmacological treatment, and
- where in the opinion of the person with depression or the clinician, the current relationship may either contribute to the development or maintenance of depression or the involvement of the partner is considered to be of potential therapeutic benefit

6.5.3 When people with depression present initially with severe depression, combining antidepressants with individual CBT should be considered as this combination is more cost effective than either treatment on its own. Individual CBT should be offered for those who did not take or cannot tolerate antidepressants or who declined antidepressants.

6.5.4 If people do not show adequate improvement, consider aspects of the treatment which could be improved (for example, therapist alliance, conceptualisation of the problem, competence of the treatment delivery), or consider an alternative treatment.

6.5.5 For all psychological interventions the duration of treatment should normally be within the limits indicated in this guideline. As the aim of treatment is to obtain significant improvement or remission:

- the duration of treatment may be shorter if remission has been achieved
- the duration of treatment may be longer if progress is being made, and there is agreement between the practitioner and the person with depression that further sessions would be beneficial, for example if there is comorbid personality disorder or psychosocial factors

6.5.6 For all people with depression receiving individual CBT, the duration of treatment should typically be in the range of 16 to 20 sessions over 6 to 9 months.

- For people with moderate and severe depression consideration should be given to providing 2 sessions per week for the first 2 to 3 weeks of treatment.
- For all people with depression consideration should be given to follow-up sessions, which typically consist of 2 to 4 sessions over 12 months.

6.5.7 For all people with depression receiving IPT the duration of treatment should typically be in the range of 16 to 20 sessions over 6 to 9 months.
• For people with severe depression consideration should be given to providing 2 sessions per week for the first 2 to 3 weeks of treatment.

6.5.8  Couple-focused therapy for depression should normally be based on behavioural principles and an adequate course of therapy should be 15 to 20 sessions over 5 to 6 months.

6.5.6  Short-term psychodynamic psychotherapy

6.5.6.1  For people with moderate depression who have declined or have not benefited from CBT or IPT short-term psychodynamic psychotherapy may be considered. However, practitioners should take care to explain the uncertainty about the efficacy of short-term psychodynamic psychotherapy in the treatment of depression.

6.5.6.2  For all people with depression receiving short-term psychodynamic psychotherapy the duration of treatment should typically be in the range of 16 to 20 sessions over 4 to 6 months.

6.5.7  Treatment choice based on depression sub-types and personal characteristics

6.5.7.1  People with severe depression who have not been in receipt of any effective intervention, should initially be offered a combination of CBT and antidepressant medication.

6.5.8  Combined psychological and drug treatment

6.5.8.1  For a person whose depression has not responded to either pharmacological or psychological interventions, the combination of antidepressant medication with CBT should be considered.

6.5.9  Continuation and relapse prevention

6.5.10  Psychological treatment for relapse prevention

6.5.10.1  People with depression considered to be at significant risk of relapse (including those who have relapsed despite with antidepressant treatment and who are unable or unwilling to continue with antidepressant treatment) or who have residual symptoms, should be offered the following psychological treatments:

• individual or group CBT for those with residual symptoms
• mindfulness-based CBT for people who are currently well but have experienced three or more previous episodes of depression.
6.5.10.2 CBT should be considered for people with depression with recurrent depression who have relapsed despite antidepressant treatment, including those who:
- have had a limited response to other interventions
- express a preference for psychological interventions
- are unable or unwilling to continue with that intervention, and are assessed as being at significant risk of relapse

Psychological treatment delivery

6.5.10.3 Where there remains a risk of relapse, following individual CBT, maintenance CBT or IPT sessions should be considered

6.5.10.4 Mindfulness-based CBT should normally be delivered in groups of 8 to 15 participants and consist of eight 2-hourly weekly meetings and four further follow-up sessions in the 12 months after the end of treatment

6.6 Research recommendations

6.6.1.1 The efficacy of short-term psychodynamic psychotherapy compared with cognitive behaviour therapy (CBT) in the treatment of mild to moderate depression.

In well-defined depression of mild to moderate severity, what is the relative efficacy of short-term psychodynamic psychotherapy compared with cognitive behaviour therapy (CBT)?

This question should be answered using a randomised controlled design which reports short and medium-term outcomes (including cost effectiveness outcomes) of at least 18 months’ duration. There should be particular attention paid to the reproducibility of the treatment model and training and supervision of those providing interventions in order to ensure that the treatments are both robust and generalisable. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design and mediators and moderators of response should be investigated.

Why this is important
Psychological treatments are an important therapeutic option for people with depression. CBT has is the best evidence base for efficacy but it is not effective for everyone. The availability of alternatives drawing from a different theoretical model is therefore important. Psychotherapy based on psychodynamic principles has historically been provided in the NHS but the provision is patchy and there is a lack of a good evidence-base. It is therefore important to establish whether short-term psychodynamic psychotherapy is an effective alternative treatment to CBT and one that should be provided. The results of this study will have important implications for the provision of psychological treatment in the NHS.
6.6.1.2 The cost effectiveness of combined medication and cognitive behaviour therapy (CBT) compared with sequenced treatment for moderate to severe depression

What is the cost-effectiveness of combined medication and cognitive behaviour therapy (CBT) compared with sequenced medication then CBT and vice versa for moderate to severe depression?

This question should be answered using a randomised controlled trial design in which moderately to severely ill people with depression receive either combined treatment from the outset, or single modality treatment with addition of the other modality if there is inadequate response to initial treatment. The outcomes chosen should reflect both observer and patient-rated assessments for acute and medium-term outcomes to at least 6 months, and an assessment of the acceptability and burden of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design together with robust health economic measures.

Why this is important

There is a reasonable evidence base for the superior effectiveness of combined medication and CBT over either treatment alone in moderate to severe depression. However the practicality, acceptability and cost effectiveness of combined treatment over a sequenced approach is less well-established. The answer has important practical implications for service delivery and resource implications for the NHS.

6.6.1.3 The efficacy of cognitive behavioural therapy (CBT) compared with antidepressants for persistent minor depression

6.6.1.4 What is the efficacy of CBT compared with antidepressants for persistent minor depression?

This question should be answered using a randomised controlled design which reports short and medium-term outcomes (including cost effectiveness outcomes) of at least 6 months’ duration. A careful definition of persistence needs to be used which needs to include duration of symptoms and consideration of failure of low-intensity interventions and does not necessarily imply a full diagnosis of dysthymia. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design and mediators and moderators of response should be investigated.

Why this is important

Persistent minor (sub-threshold) depression is increasingly recognised as affecting a considerable number of people and causing significant suffering but the best way to treat it is not known. There are studies of the efficacy of antidepressants for dysthymia (persistent minor depression that has lasted at least 2 years) but a lack of evidence for
CBT. Minor depression of recent onset tends to improve but how long one should wait before offering medication or psychological treatment is not known. This research suggestion is aimed at informing the treatment options available for this group of people with minor depression that persists in spite of low-intensity interventions.
7 Introduction to pharmacological interventions

For the guideline update the following reviews of pharmacological interventions are updated: escitalopram, relapse prevention and next-step treatments (treatments for treatment-resistant depression in the previous guideline), and the following narrative reviews have been updated with new data: effect of sex on antidepressant choice, dosage, discontinuation, cardiotoxicity, and antidepressants and suicide. New reviews are included for TCAs, duloxetine, agomelatine, and therapies for SAD, with new narrative reviews of TMS and VNS, and new sections for chronic depression and residual symptoms. The scope for the update also includes updating the NICE technology appraisal (TA59) on the use of electroconvulsive therapy (for depression) (NICE, 2003). Where reviews have not been updated an explanation has been added to the relevant chapter introduction.

This chapter introduces the pharmacological interventions in the management of depression covered by this guideline (although other physical interventions are also reviewed). It discusses some of the issues that the GDG addressed in assessing the evidence base in order to form recommendations, including that of placebo response. The reviews of pharmacological interventions themselves are presented in the following chapters.

7.1 Introduction

Since the introduction of the monoamine oxidase inhibitors (MAOIs) and the first tricyclic antidepressant (TCA), imipramine, in the late 1950s, many new antidepressants have been introduced and currently approximately 35 different antidepressants in a number of classes are available worldwide. There has been intensive research on the effects of drug therapy on depression and how drugs might alter the natural history of the disorder. Excellent reviews of the topic are to be found in the British Association for Psychopharmacology Evidence-Based Guidelines for Treatment of Depressive Disorder (Anderson et al., 2008) and in the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Unipolar Depressive Disorders Parts 1 and 2 (Bauer et al., 2002a and 2002b).

The severity of depression at which antidepressants show consistent benefits over placebo is poorly defined. In general, the more severe the symptoms, the greater the benefit (Anderson et al, 2008; Kirsch et al, 2008); antidepressants are normally recommended as first-line treatment in patients whose depression is of at least moderate severity. Of this patient group, approximately 20% will respond with no treatment at all, 30% will respond to placebo and 50% will respond to antidepressant drug treatment (Anderson et al, 2008). This gives a number needed to treat (NNT) of 3

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15 Recommendations from TA59 were incorporated into the previous depression guideline according to NICE protocol.
for antidepressant over wait list control and 5 for antidepressant over placebo. Note
though that response in clinical trials is generally defined as a 50% reduction in
depression rating scale scores, a somewhat arbitrary dichotomy, and that change
measured using continuous scales tends to show a relatively smaller mean difference
between active treatment and placebo.

Systematic reviews using meta-analysis suggest that antidepressant drugs when
considered individually or by class, are more effective than placebo in the treatment of
major depression, and are generally equally effective (Gartlehner et al, 2008; Cochrane
Database of Systematic Reviews; original version of this guideline). SSRIs are
considerably safer in overdose than TCAs, generally better tolerated than
antidepressants from other classes, and most are available as generic preparations. An
SSRI was recommended as first-line pharmacological treatment of moderate to severe
depression in the original version of this guideline, and SSRIs are now the most
commonly prescribed group of antidepressants in the UK (see Current Practice of
Antidepressant Prescribing in the UK below).

There are concerns over side effects following short- and long-term treatment, which
limit adherence to treatment with antidepressants. Most side effects of antidepressants
are dose related. SSRIs as a class are associated with headache and gastro-intestinal
symptoms, and a relative higher propensity than other antidepressants to cause sexual
dysfunction, hyponatraemia and GI bleeds. TCAs tend to be associated with a high
burden of anticholinergic side effects, and a higher propensity than other
antidepressants to cause adverse cardiovascular effects including hypotension,
tachycardia and QTc prolongation. Overall, venlafaxine is better tolerated than TCAs,
but not as well tolerated as SSRIs. Some common antidepressant side effects, such as
nausea tend to resolve within the first week of treatment, whereas others such as
anticholinergic effects tend to persist.

Antidepressant treatment has been associated with an increased risk of suicidal
thoughts and acts, particularly in adolescents and young adults, leading to the
recommendation that patients should be warned of this potential adverse effect during
the early weeks of treatment and know how to seek help if required. All
antidepressants have been implicated, as have drugs with a similar pharmacology that
are used for an indication other than depression (eg; atomoxetine). Although the
relative risk of developing suicidal thoughts and acts may be elevated above placebo
rates in some patient groups, the absolute risk remains very small. Overall, the most
effective way to prevent suicidal thoughts and acts is to treat depression.

There is evidence that earlier non-persistent improvement in depressive symptoms
may be due to a placebo response (Quitkin et al., 1987). An eventual response is
unlikely if no improvement is evident after four weeks of treatment (Anderson et al.,
2008). At the present time there are a variety of strategies for improving efficacy
following initial non-response which are supported by existing evidence based
guidelines or systematic reviews. These include dose escalation, switching to another
antidepressant, and augmentating the antidepressant with a second drug such as
lithium, another antidepressant, a second generation antipsychotic or thyroid
hormones. Adjunctive use of psychological therapies, particularly CBT is also
supported by an evidence base. Systematic assessment of the evidence for these
strategies is a major feature of this current review.
An untreated depressive episode typically lasts about six months (Angst & Preisig, 1995; Solomon et al., 1997), and in view of the high recurrence rate if antidepressant medication is stopped immediately after response, it is currently recommended that antidepressant drug treatment is continued for a minimum of six months after remission of major depression (12 months in older adults), and longer if there are factors that increase the risk of relapse.

It is recommended that the same dose of antidepressant is used in this continuation phase. It is also recommended that patients with recurrent major depression should go on to receive maintenance antidepressant drug treatment (NICE, 2003). There is good evidence that patients with residual symptoms are at increasing risk of relapse of major depression and the current practice is to continue treatment for longer in those patients. The recurrence rate is lower when treatment is maintained with the effective acute treatment dose compared with the reduction to half the dose.

All antidepressant drugs can cause discontinuation symptoms with short half-life drugs being most problematic in this respect (see chapter 10).

7.2 Dose and duration of antidepressant treatment: Evidence from clinical practice

7.2.1 Prevalence of antidepressant prescribing
In 1992 the Royal College of Psychiatrists launched the ‘Defeat Depression’ campaign to raise public awareness of depression and improve treatment (Vize & Priest, 1993). During the launch year, 9.9 million prescriptions for antidepressants were dispensed by community pharmacists in England, at a total cost of £18.1 million. However, an epidemiological study conducted in 1995 found that treatment remained sub-optimal (Lepine et al., 1997). Only a third of people with major depression in the UK received a prescription usually, but not always, for an antidepressant drug.

The number of prescriptions for antidepressants dispensed by community pharmacies in England has risen steadily over the last 15 years. In the 3 months to June 2008, over 4.5 million prescriptions were dispensed for SSRIs (almost half of which were for citalopram), over 2.5 million for tricyclic and related antidepressants (over half of which were for amitriptyline), and over 1 million for other antidepressants (the vast majority of which were for venlafaxine or mirtazapine). Although the number of prescriptions written continues to increase, costs are falling due to the availability of an increasing number of antidepressants as generic preparations. Details of the number of antidepressant prescriptions dispensed in primary care, the costs of individual drugs, and prescribing trends can be found on the NHS Business Authority website (www.nhsbsa.nhs.uk).

7.2.2 Dose
Studies of prescribing practice have generally taken 125 mg and above of TCAs (except lofepramine) and licensed doses of SSRIs to be ‘an effective dose’ and compared prescribing in practice with this ideal. It is generally accepted that response to TCAs is partially dose-related but no such effect has been demonstrated for SSRIs. SSRIs are consistently found to be prescribed ‘at an effective dose’ in a much greater proportion
of cases than TCAs. For example, a UK prescribing study that included data from over 750,000 patient records found that, if lofepramine was excluded, the mean doses prescribed for individual TCAs fell between 58 mg and 80 mg. Only 13.1% of TCA prescriptions were for ‘an effective dose’ compared with 99.9% of prescriptions for SSRIs (Donoghue et al., 1996). A further UK study that followed prescribing for 20,195 GP patients found that at least 72% of those prescribed TCAs never received ‘an effective dose’ compared with 8% of those prescribed SSRIs (MacDonald et al., 1996). The prescribing of TCAs in this way is known to be pervasive across different countries and over time (Donoghue, 2000; Donoghue & Hylan, 2001).

In the previous guideline, a systematic review of the efficacy and tolerability of low v high doses of TCAs was undertaken; no difference was found with respect to remission data, while there was insufficient evidence to determine if there was a difference with respect to response or continuous end-point data.

7.2.3 Duration
In a UK study of 16,204 patients who were prescribed TCAs or SSRIs by their GP, 33% of those prescribed an SSRI completed ‘an adequate period of treatment’ compared with 6% of those prescribed a TCA (2.8% if lofepramine was excluded) (Dunn et al., 1999). ‘An adequate period of treatment’ was defined by the authors as: prescriptions covering at least 120 days’ treatment within the first six months after diagnosis. A more recent naturalistic randomised UK study also found that there was a higher rate of switching to another antidepressant with TCAs (including lofepramine) than SSRIs (Peveler et al. 2005).

There is some evidence that the mean figure quoted for SSRIs may mask important differences between drugs: Donoghue (2000) found that in a GP population of 6150 patients who were prescribed SSRIs, 27% of fluoxetine patients were still receiving prescriptions after 120 days compared with 23% of paroxetine patients and 13.5% of sertraline patients. Of course, prescribing patterns cannot be directly linked with outcome in studies of this type.

An RCT conducted in the US randomised 536 adults to receive desipramine, imipramine or fluoxetine (Simon et al., 1996). 60% of the fluoxetine patients completed six months of treatment compared with less than 40% of the TCA patients. Those who discontinued one antidepressant were offered another. There were no differences in overall completers or response rates at endpoint suggesting that initial drug choice did not affect outcome. However, outside of clinical trials, patients may not return to their GP to have their treatment changed and outcome may be less positive. For example: a Swedish study of 949 patients found that 35% only ever received one prescription irrespective of whether it was for a TCA or a SSRI (Isacsson et al., 1999). After six months, 42% of SSRI patients were still receiving prescriptions compared with 27% of TCA patients. There is some evidence from this study that the relapse rate may have been higher in the TCA group: 28% of TCA-treated patients received a subsequent prescription for an antidepressant after a nine-month treatment-free gap compared with 10% of SSRI patients.

7.3 Limitations of the literature: Problems with randomised controlled trials (RCTs) in pharmacology
In RCTs, patients are assigned randomly to different treatment arms in order to control for systematic differences in the allocation of patients that might bias the results. Primary efficacy is usually based on a placebo-controlled RCT in which one of the treatment arms is a ‘placebo’ treatment. A placebo is an inert or innocuous substance and began to be used increasingly in control conditions in clinical trials during the 1950s, although at that time they often contained an active ingredient. The response of patients to the inert substances now used should not be equated with the untreated course of the disorder, as patients receive regular visits to their doctor, supportive help, and a kindly interest in their welfare. In some trials the participants are allowed to contact the therapist at any time to report problems. In short, they receive everything except the pharmacological help from the tablet in the ‘active drug’ arm of the trial. This constitutes a treatment in itself, and almost 30% of patients assigned to placebo respond within six weeks (Walsh et al., 2002). This response has three components as described in the next section. These include spontaneous improvement, which is a function of the duration and severity of the disorder; with shorter and milder depression the chance of improvement is greater. Unfortunately there is a tendency for investigators to recruit patients with less severe depression to RCTs, and these are more likely to recover spontaneously (Khan et al., 2002). High spontaneous improvement rates are a major cause of ‘failed trials’ where active treatment does not separate from placebo.

Conversely, the more severely depressed patients are less likely to be thought suitable for RCTs (despite being more likely to show a true drug effect (Angst 1993; Khan et al., 2002)), since clinicians are reluctant to allow suicidal patients, or patients with severe degrees of depressive phenomena, to run the risk of being randomised to an inactive treatment.

Next, of those enrolled into an RCT, typically 20–35% fail to complete the study – either because they dropout of treatment themselves, or they are withdrawn from the RCT by the anxious clinician (for example, Stassen et al., 1993). Worse still, results are often presented only for ‘completers’, rather than for the full ‘intention-to-treat’ sample.16

Finally, some participants may not be representative of patients seen in clinical practice, as they are recruited by newspaper advertisement and paid for their participation in the study after completing a screening questionnaire (Greist et al., 2002; Thase, 2002).

The inclusion of individuals likely to improve, whatever they are given, as well as those motivated to receive free medication, taken together with the smaller likelihood of severely depressed patients being included, will all reduce the size of the specific drug effect. Confining the study to ‘completers’ introduces unknown biases into an already cloudy picture.

In addition to the factors related to the type of patient recruited into RCTs there are also measurement-related errors and biases. The pressure to recruit patients may lead to ‘rating scale inflation’ which not only leads to patients with milder degrees of depression being studied but also may contribute to the drop in scores after the

16 See introduction to Appendix 17 on the CD and the use of ‘C’ to show which studies present end-point data as completer data (analysis method of completer data).
treatment has started when severity may be more realistically assessed. Although raters may be blind to the treatment arm a patient is allocated to they are not blind to the phase of study, so that patient and rater expectations of improvement may confound assessments. The emergence of drug specific side effects can also un-blind a study. In addition there is the phenomenon of ‘regression to the mean’ which means that subsequent ratings from an extreme value (such as high depression score) will tend to drop simply by virtue of being remeasured. These all add noise to the assessment leading to increased variability and make it difficult to assess the ‘true’ size of any treatment effect.

Most studies of the effects of drugs are sponsored by the drug industry, and these have been shown to be more than four times as likely to demonstrate positive effects of the sponsor’s drug as independent studies (Lexchin et al., 2003). Finally, the tendency of journal editors to publish only studies with positive results (Kirsch & Scoboria 2001; Melander et al., 2003), and the fact that the same patients may appear in several publications (op. cit.), introduces a severe bias in the other direction.

Despite the limitations of RCTs described above, there are few alternatives to using these data because better ways of assessing efficacy have not been developed. Therefore the bulk of our recommendations are based on RCT evidence. However, we have been careful to consider their application to routine practice.

7.4 Studies considered for review – additional inclusion criteria

In addition to the criteria established for the inclusion of trials for the guideline as a whole, the following specific criteria relating to RCTs of pharmacological treatments were established by the Pharmacology Topic Group.

7.4.1 Diagnosis

Trials where some participants had a primary diagnosis of bipolar disorder were included provided at least 85% had a primary diagnosis of major depressive disorder and no more than 15% had a primary diagnosis of bipolar disorder. These figures resulted from discussion, expert opinion and involvement with user groups. The GDG considered that these trials would still have adequate validity for determining efficacy in major depressive disorder.

Trials where some participants had a primary diagnosis of dysthymia were included provided at least 80% of trial participants had a primary diagnosis of major depressive disorder, and no more than 20% had a primary diagnosis of dysthymia. Trials not meeting these criteria are considered in the chapter on minor (subthreshold) depression.

Trials where participants had a diagnosis of atypical depression or seasonal pattern depression (seasonal affective disorder) were included provided all had a primary diagnosis of major depressive disorder.

Studies were included provided data from the HRSD and Montgomery Asberg Depression Rating Scale (MADRS) could be extracted for the following outcomes:
• The number of participants who remitted (achieved below the equivalent 17-item HRSD score of eight)
• The number of participants who responded (achieved at least a 50% reduction in scores)
• Mean endpoint or change scores in the rating scales.

7.4.2 Dose
There is a lack of clear evidence that doses of tricyclics at or below 100 mg are less effective than doses above (Blashki et al., 1971; Thompson & Thompson, 1989; Bollini et al., 1999; Furukawa et al., 2002a) although there might be benefit in more severely ill patients (Ramana et al., 1999). Nevertheless, in order to provide fair comparisons, studies were included provided there was clear evidence that at least 75% of patients received the standard dose or the mean dose used was at least 105% of the standard dose. The standard dose was either that stated by Bollini et al. (1999) or, for drugs not included by Bollini et al., the dose stated by the BNF (March 2003).

7.5 Issues and topics covered by this review
In view of the vast numbers of studies performed investigating pharmacological responses in depression and the limited time available, the Pharmacology Topic Group had to decide which aspects of drug treatment were most important to clinicians and patients. This chapter therefore is not the result of a comprehensive review of all psychopharmacological studies performed in all aspects of the treatment of depression.

7.5.1 Severity
A key issue is whether severity of illness can guide the use of antidepressant medication. Unfortunately there is little data to help with this point. Although most studies report mean baseline HRSD or MADRS, this can be taken only as a guide to baseline severity because of heterogeneous samples with wide standard deviations as well as the fact that results are not presented in a way that allows differential response to be identified.

7.5.2 Setting
Where appropriate studies were categorised by setting: (a) primary care (where this was specifically stated); (b) inpatients – where at least 75% of the patients were initially treated as inpatients; (c) outpatients/secondary care – studies in which this was specified. This is likely to provide some bearing on the issue of setting and type of depression although it is not clear how well setting maps onto severity. A further problem is that because of differences among healthcare systems across the world, the nature of the patients in these different groups varies. Thus considerable uncertainty must be associated with conclusions drawn using these categories.

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17 For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not remitting.
18 For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not responding.
7.5.3 Issues addressed
In broad terms we have tried to address the issue of the comparative efficacy, acceptability and tolerability of the antidepressants most commonly prescribed in the UK, together with specific pharmacological strategies for dealing with treatment-resistant, atypical and psychotic depression. Within each review, where the data allowed, we have looked at the effect on outcomes of severity, setting and age. In addition, we have looked at some of the issues regarding so-called continuation and maintenance therapy, the cardiac safety of antidepressants, dosage, and issues regarding suicidality and completed suicide with antidepressants. Although the number of trial participants leaving treatment early was used as a measure of the tolerability of drugs reviewed, this guideline cannot be seen as a comprehensive review of the issue of the safety, pharmacology, pharmokinetics and pharmaceutical advice regarding these drugs. Readers are referred to conventional texts particularly regarding issues of dosage schedules, acceptability and tolerability for individual patients and regarding drug interactions.

7.5.4 Topics covered
The following topics are covered:

This chapter
- SSRIs versus placebo
- TCAs versus placebo

Chapter 8 Use of individual drugs in the treatment of depression (Section 8.1)
- TCAs (amitriptyline and overview of TCA data)
- Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
- Monoamine oxidase inhibitors (MAOIs): moclobemide, phenelzine
- ‘Third-generation’ drugs: duloxetine, mirtazapine, reboxetine and venlafaxine
- Agomelatine
- St John’s wort

Chapter 9 Factors affecting antidepressant choice
- The pharmacological management of depression in older adults
- The effect of sex on antidepressant choice
- The pharmacological management of psychotic depression
- The pharmacological management of atypical depression
- The pharmacological and physical management of SAD
- The pharmacological management of relapse prevention
- Antidepressant discontinuation symptoms
- The cardio-toxicity of antidepressants
- Depression, suicide and antidepressants
- Dosage issues.
Chapter 10 The pharmacological management of depression which has not responded adequately to treatment

- Increasing the dose
- Switching strategies
- Venlafaxine for treatment-resistant depression
- Augmentation strategies
  - Augmenting an antidepressant with lithium
  - Augmenting an antidepressant with anticonvulsants (lamotrigine, carbamazepine or valproate)
  - Augmenting an antidepressant with another antidepressant
  - Augmenting an antidepressant with pindolol
  - Augmenting an antidepressant with T3
  - Augmenting an antidepressant with a benzodiazepine
  - Augmenting an antidepressant with an antipsychotic
  - Augmenting an antidepressant with buspirone
- ECT
- TMS
- Chronic depression and residual symptoms.

Chapter 10 Relapse prevention

In addition, evidence for the pharmacological treatment of depression symptoms which do not meet threshold for major depressive disorder is considered in chapter X.

7.6 Placebo-controlled RCTs of antidepressants

As mentioned above, the response to placebo in an RCT consist of three main components, spontaneous improvement, measurement errors and biases, and the true ‘placebo response’, which is non-pharmacological benefit due to taking part in the trial. A large part of the placebo response is thought to be due to expectation combined with regular review and monitoring. A recent meta-analysis showed that studies in which patients know they may get a placebo tablet have lower response rates than when they know they will only get active treatments (Sneed et al 2008). This means that the chance of improvement in response to antidepressants in clinical practice may not be the same as those in clinical trials involving placebo. Another systematic review provides suggestive evidence that the chance of responding to treatment with placebo is higher if monitoring is carried out more frequently in the first few weeks of treatment (Posternak & Zimmerman 2007). Taking these factors together it is clear that the exact design of any trial will influence the non-specific benefit that participants will obtain and that the placebo response is not a minor distraction but an integral part of treatment not only in RCTs but also in clinical practice.

In recent years there has been an increasing response to placebo, so that the extent of the placebo response has been shown to correlate with the year of publication in
studies in depression ($r = +0.43$) (Walsh et al., 2002). There is a similar, but less robust, association between extent of the response to active medication and year of publication ($r = +0.26$) (ibid.). This may well indicate an increasing tendency for RCTs to be carried out on people with milder less chronic disorders that have a greater chance of spontaneously improving or having a placebo response.

An important point is that there is evidence that the placebo response is greatest with mild depression, and the drug-placebo difference becomes greater with increasing degrees of severity of depression (Angst, 1993; Khan et al., 2002; Kirsch et al, 2008). This effect cannot be demonstrated in the meta-analyses carried out for the present report since the published studies do not quote data for individual patients, but only for the entire group. Thus, there is considerable overlap between the distributions of HRSD scores between inpatient and outpatient studies, so that the effect is diluted.

The placebo response may also be short-lived, with more patients on placebo relapsing compared with those on antidepressants (Ross et al., 2002). Longer trials are required to be able to fully elucidate the contributions of placebo and the treatment to clinical response. Dago & Quitkin (1995) suggest that greater placebo response is more likely when the presenting episode occurs within the context of a psychosocial stressor.

In three meta-analyses (Kirsch & Sapirstein,1998; Kirsch et al., 2002a; Kirsch et al 2008) it has been argued that up to 80% of the effect of antidepressants may be duplicated by placebo – i.e. that 80% of the effect of antidepressants is placebo response. Although the earlier meta-analysis was criticised because it included only a limited number of published trials, the later work analysed all data submitted to the US Food and Drug Administration (FDA) for the licensing of new antidepressants, including the SSRIs and venlafaxine, although it is not clear how many of the trials involved have subsequently been published.

Many commentators attribute this finding to placebo effects as discussed above. There is also the problem of ‘breaking the blind’ as a result of the side effects of antidepressants (Rabkin et al., 1986, in Kirsch et al., 2002b) leading to possible bias in placebo-controlled clinical trials. One way round this problem is to use an active placebo. A meta-analysis of trials using this technique indicated that the placebo effect of antidepressants may be stronger than that in trials using only inactive placebos. However, there are few trials of active placebo using modern diagnostic criteria and widely accepted ratings (Moncrieff et al., 2001).

The increasing rate of response to placebo and to a lesser extent to antidepressants (Walsh et al., 2002) means that many trials are underpowered as with placebo response rates above 40%, an active drug effect becomes harder to detect (Thase, 2002). Other methodological problems are highlighted by inter-site differences found in many multi-site trials probably resulting from subtly different procedures being adopted by different researchers (Schneider & Small, 2002).

The increase in the drug/placebo difference with severity (Elkin et al., 1989; Angst, 1993; Khan et al., 2002) appears due to the decreasing efficacy of placebo with increasing severity of depression, rather than increasing efficacy of the antidepressant drug per se (Kirsch et al, 2008). The published data did not allow the GDG to address the question of efficacy related to severity systematically since most RCTs merely give mean depression scores (with standard deviations) of large groups of patients, so that
there is very considerable overlap between baseline depression scores of patients in different studies. It was therefore only possible to address important questions relating to the effects of severity, age and gender with relatively weak information about patient characteristics. Nonetheless, our findings are in favour of greater drug/placebo differences with increasing severity (see below). It should also be borne in mind that there are non-mood-related benefits of prescribing antidepressants, for example in helping patients to sleep better and in dealing with anxiety-related symptoms. Improving these factors may help patients to cope with their daily lives thereby contributing to a reduction in depression symptoms.

7.7 Review of SSRIs versus placebo

7.7.1 Introduction

The analysis of SSRIs as a class against placebo was not updated for this guideline although evidence for the most recently marketed SSRI, escitalopram is considered separately in 8.4. The severity categories used in the analyses are those used in the previous guideline. See chapter 2 for a discussion of this issue.

Studies considered for review

One-hundred-and-three studies were found in a search of electronic databases with 481721 being included and 55 being excluded by the GDG.


All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.75 weeks), with 16 trials of eight weeks or longer. Three

19 Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17 on the CD, which also contains a list of excluded studies with reasons for exclusions.

20 Here and elsewhere in the guideline, each study considered for review is referred to by a ‘study ID’ made up of first author and publication date in capital letters (unless a study is in press or only submitted for publication, when first author only is used). References for these studies are in Appendix 18 on the CD.

21 This figure includes a multicentre trial (KASPER1995) as well as two of its constituent trials published independently (DOMINGUEZ1985, LAPIERRE1987) because ‘number of participants leaving the study early for any reason’ was not extractable from KASPER1995. See SSRI versus placebo evidence table in Appendix 17 on the CD.
studies were of inpatients, 31 of outpatients, one in primary care and 13 either mixed or unspecified. In no study were more than 80% of study participants aged 65 years and over. It was possible to determine baseline severity in 19 studies, with four being classified as moderate, six as severe and nine as very severe.

Visual inspection of funnel plots of the meta-analyses of the above studies indicated the possibility of publication bias. It was planned to combine these data with the FDA data reported by Kirsch et al. (2002a). However, it was not possible to determine which of the FDA data had been subsequently published.

Since it is possible that a placebo response is only short-lived, a sub-analysis of studies which lasted eight weeks or longer was undertaken.

### 7.7.2 Evidence statements

**Evidence statements**

**Effect of treatment on efficacy outcomes**

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 1723; n = 3143; RR = 0.73; 95% CI, 0.69 to 0.78).

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 325; n = 729; RR = 0.75; 95% CI, 0.65 to 0.87).

In severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 5; n = 619; RR = 0.63; 95% CI, 0.54 to 0.73).

In very severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 6; n = 866; RR = 0.72; 95% CI, 0.65 to 0.8).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs over placebo on increasing the likelihood of achieving remission as measured by the HRSD (N = 3; n = 468; Random effects RR = 0.8; 95% CI, 0.61 to 1.06).

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22 The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on the CD.


24 Severity categories based on APA (2000) – see previous guideline Appendix 13

25 Studies were excluded from sub-analyses of severity if mean baseline scores were not available.
There is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (\(N = 16; n = 2223; \) Random effects SMD = -0.34; 95% CI, -0.47 to -0.22).

In moderate depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (\(N = 2; n = 386; \) SMD = -0.28; 95% CI, -0.48 to -0.08).

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD (\(N = 4; n = 344; \) SMD = -0.61; 95% CI, -0.83 to -0.4).

In very severe depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms, as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (\(N = 5; n = 726; \) SMD = -0.39; 95% CI, -0.54 to -0.24).

**Acceptability and tolerability of treatment**

There is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early but the size of this difference is unlikely to be of clinical significance (\(N = 3926; n = 7274; \) RR = 0.94; 95% CI, 0.88 to 0.99).

There is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (\(N = 39; n = 7460; \) RR = 2.45; 95% CI, 2.08 to 2.89).

There is some evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of patients reporting side effects (\(N = 11; n = 2290; \) RR = 1.19; 95% CI, 1.13 to 1.25).

**Sub-analysis of trials lasting eight weeks or longer**

In order to assess whether the placebo effect was short-lived, trials lasting eight weeks or longer were analysed separately.

Effect of treatment on efficacy outcomes in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (\(N = 8; n = 1764; \) RR = 0.72; 95% CI, 0.66 to 0.79).

In moderate depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (\(N = 3; n = 729; \) RR = 0.75; 95% CI, 0.65 to 0.87).

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26 One study (COHN1985) was removed from the meta-analysis to remove heterogeneity from the data set.
In severe depression in trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; n = 535; RR = 0.63; 95% CI, 0.53 to 0.74).

In very severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 1; n= 299; RR= 0.72; 95% CI, 0.59 to 0.88).

In trials lasting eight weeks or longer, there is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and placebo on increasing the likelihood of achieving remission as measured by the HRSD (N = 2; n = 456; RR = 0.85; 95% CI, 0.67 to 1.07).

In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 7; n = 1369; Random effects SMD = -0.28; 95% CI, -0.44 to -0.11).

In moderate depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 2; n = 386; SMD = -0.28; 95% CI, -0.48 to -0.08).

In severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD (N = 1; n = 237; SMD = -0.53; 95% CI, -0.79 to -0.27).

In very severe depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 1; n = 283; SMD = -0.43; 95% CI, -0.67 to -0.2).

**Acceptability and tolerability of treatment in trials lasting eight weeks or longer**

In trials lasting eight weeks or longer, there is evidence suggesting that there is no clinically significant difference between SSRIs and placebo on reducing the likelihood of leaving treatment early (N = 13; n = 3069; Random effects RR =0.95; 95% CI, 0.83 to 1.09).

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 13; n = 3069; Random effects RR = 1.93; 95% CI, 1.23 to 3.03).
In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 7; n = 1378; RR = 1.09; 95% CI, 1.03 to 1.16).

7.7.3 Clinical summary

There is strong evidence that SSRIs have greater efficacy than placebo on achieving a 50% reduction in depression scores in moderate and severe major depression. There is some evidence for a similar effect in mild depression. The effect was similar in longer trials. These results should be treated with caution because of publication bias (i.e. that studies with statistically significant findings are more likely to be published than those with non-significant findings).

There is insufficient evidence on the effect on remission because of heterogeneity in the meta-analysis, but the trend is towards a small effect size. There appears to be no difference between SSRIs and placebo on mean endpoint or change scores.

SSRIs produced more side effects than placebo, with more people leaving treatment early because of adverse events. This was also the case in trials lasting eight weeks or longer.

7.8 Review of tricyclic antidepressants versus placebo

7.8.1 Introduction

In the previous guideline, a review of the efficacy and tolerability of TCAs compared with placebo was not undertaken, but are now included. For the updated version of the guideline these analyses were undertaken. This informs the assessment of the relative efficacy and tolerability of different classes of antidepressants, and therefore their utility in everyday clinical practice.

7.8.2 Studies considered for review

A systematic search for RCTs comparing any TCA with UK marketing authorisation with placebo was undertaken (see Table 18).

Table 57: Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008, January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>Any TCA with UK marketing authority where a comparison with placebo was available</td>
</tr>
</tbody>
</table>

In total, xx new trials were found of which 121 met inclusion criteria. Most were for imipramine (n=78) and amitriptyline (n=31). The number of studies is summarised in Table 58, with full study characteristics in Appendix 17. There were no extractable data.
from studies of lofrapramine, and little data for some outcomes from studies of chlomipramine, dosulpin and nortriptyline.

Table 58 Summary of studies for TCAs versus placebo

<table>
<thead>
<tr>
<th>TCA</th>
<th>Number of studies</th>
<th>Study IDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lofepramine</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

(see Table 27).
7.8.3 Outcomes
On all outcome measures of efficacy TCAs are more effective than placebo. Results were similar for each individual drug where there were sufficient data. See Table 59 for the summary evidence profile (and Appendix 15 for the full profile).

Table 59 Summary evidence profile for TCAs versus placebo (efficacy data)

<table>
<thead>
<tr>
<th>Overall (all studies)</th>
<th>Amitriptyline</th>
<th>Clomipramine</th>
<th>Dosulepin</th>
<th>Imipramine</th>
<th>Nortriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean depression scores at endpoint</td>
<td>SMD -0.48 (-0.59 to -0.37)</td>
<td>SMD -0.61 (-0.83 to -0.4)</td>
<td>N/R</td>
<td>SMD -0.49 (-0.7 to -0.29)</td>
<td>SMD -0.41 (-0.54 to -0.27)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=22; n=2445</td>
<td>K=6; n=348</td>
<td>K=1; n=386</td>
<td>K=13; n=1603</td>
<td>K=2; n=108</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 01.01</td>
<td>Pharm TCAs 01.01</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Mean depression change scores at endpoint</td>
<td>SMD -0.35 (-0.53 to -0.18)</td>
<td>SMD -0.5 (-0.67 to -0.34)</td>
<td>N/R</td>
<td>N/R</td>
<td>SMD -0.21 (-0.41 to -0.01)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=7; n=1173</td>
<td>K=3; n=645</td>
<td>K=1; n=386</td>
<td>K=4; n=528</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 01.02</td>
<td>Pharm TCAs 01.02</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Non-response</td>
<td>RR 0.71 (0.66 to 0.75) (43.2% vs 62.8%)</td>
<td>RR 0.71 (0.65 to 0.78) (43.5% vs 67.3%)</td>
<td>RR 0.74 (0.62 to 0.88) (48.5% vs 65.6%)</td>
<td>N/R</td>
<td>RR 0.69 (0.63 to 0.77) (42.1% vs 63.6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=35; n=4735</td>
<td>K=13; n=2145</td>
<td>K=1; n=386</td>
<td>K=21; n=2204</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 01.04</td>
<td>Pharm TCAs 01.04</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.72 (0.64 to 0.82) (61.7% vs 82.1%)</td>
<td>RR 0.66 (0.44 to 1) (51.9% vs 83.1%)</td>
<td>RR 0.58 (0.34 to 1) (45% vs 77.8%)</td>
<td>RR 1.18 (0.18 to 7.48) (11.8% vs 84.5%)</td>
<td>RR 0.77 (0.65 to 0.93) (67.9% vs 84.5%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=1007</td>
<td>K=3; n=152</td>
<td>K=1; n=38</td>
<td>K=3; n=649</td>
<td>K=2; n=113</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 01.03</td>
<td>Pharm TCAs 01.03</td>
<td>Pharm TCAs 01.03</td>
<td>Pharm TCAs 01.03</td>
<td>Pharm TCAs 01.03</td>
</tr>
</tbody>
</table>

N/R = not reported

There was little difference on acceptability for TCAs compared with placebo, although effect sizes were less certain for individual drugs with few data (for example, dosulepin and clomipramine). However, participants taking TCAs were more likely to leave treatment early because of side effects and to report side effects than those taking placebo. This finding was similar across individual drugs, apart from

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chlordiazepoxide which only showed a similar result for number of participants reporting side effects. However, there was only a single study.

**Table 60 Summary evidence profile for TCAs versus placebo (acceptability and tolerability data)**

<table>
<thead>
<tr>
<th></th>
<th>Overall (all studies)</th>
<th>Amitriptyline</th>
<th>Clomipramine</th>
<th>Dosulepinine</th>
<th>Imipramine</th>
<th>Nortriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.99 (0.92 to 1.06)</td>
<td>RR 0.93 (0.79 to 1.1)</td>
<td>RR 0.82 (0.3 to 2.19)</td>
<td>RR 1.09 (0.79 to 1.5)</td>
<td>RR 1.01 (0.93 to 1.09)</td>
<td>RR 0.73 (0.27 to 2.03)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=85; n=9901</td>
<td>K=23; n=2805</td>
<td>K=2; n=58</td>
<td>K=3; n=475</td>
<td>K=54; n=6312</td>
<td>K=3; n=251</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 02.01</td>
<td>Pharm TCAs 02.01</td>
<td>Pharm TCAs 02.01</td>
<td>Pharm TCAs 02.01</td>
<td>Pharm TCAs 02.01</td>
<td>Pharm TCAs 02.01</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 4.02 (3.46 to 4.67) (18.7% vs 4.6%)</td>
<td>RR 4.66 (3.38 to 6.44) (16.7% vs 3.5%)</td>
<td>RR 0.9 (0.14 to 5.74) (10% vs 11.1%)</td>
<td>RR 2.92 (1.47 to 5.8) (14.5% vs 5%)</td>
<td>RR 3.91 (3.27 to 4.67) (20% vs 5.1%)</td>
<td>RR 7.98 (1.51 to 42.09) (18.2% vs 1.5%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=65; n=4173</td>
<td>K=16; n=2350</td>
<td>K=1; n=38</td>
<td>K=2; n=409</td>
<td>K=44; n=5245</td>
<td>K=2; n=113</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 02.02</td>
<td>Pharm TCAs 02.02</td>
<td>Pharm TCAs 02.02</td>
<td>Pharm TCAs 02.02</td>
<td>Pharm TCAs 02.02</td>
<td>Pharm TCAs 02.02</td>
</tr>
<tr>
<td>Number reporting side effects</td>
<td>RR 1.4 (1.25 to 1.56) (74.9% vs 56.6%)</td>
<td>RR 1.44 (1.15 to 1.79) (75.7% vs 51%)</td>
<td>RR 1.6 (0.8 to 3.2) (80% vs 50%)</td>
<td>RR 3.02 (1.27 to 7.18) (56% vs 18.5%)</td>
<td>RR 1.39 (1.21 to 1.59) (74.2% vs 57.9%)</td>
<td>RR 1.18 (1.03 to 1.34) (95.5% vs 81%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=31; n=4547</td>
<td>K=7; n=932</td>
<td>K=1; n=20</td>
<td>K=1; n=52</td>
<td>K=20; n=3414</td>
<td>K=2; n=129</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm TCAs 02.03</td>
<td>Pharm TCAs 02.03</td>
<td>Pharm TCAs 02.03</td>
<td>Pharm TCAs 02.03</td>
<td>Pharm TCAs 02.03</td>
<td>Pharm TCAs 02.03</td>
</tr>
</tbody>
</table>

**7.8.4 Effect of baseline severity on outcomes**

A meta-regression was undertaken using the baseline depression scores as the predictor variable. This showed no consistent relationship between baseline scores and effect sizes calculated from mean endpoint depression score or change score (regression coefficient 0.01 (p=0.46)). Sensitivity analyses for mean endpoint scores and mean change scores separately were performed and a relationship found between...
mean change scores and baseline scores. However, there are only 5 studies in the
analysis from which is not enough to draw conclusions, and it is not reported here.
Figure 4 Meta-regression showing relationship between baseline depression scores and
effect sizes calculated from mean endpoint or mean change scores

![Regression of Baseline depression score on Hedges's g](image)

7.8.5 Clinical summary
TCAs are more effective than placebo in terms of efficacy, and as acceptable. However,
they are more likely to cause side effects. When compared with the review of SSRIs
compared with placebo, the effect sizes from efficacy outcomes tended to be similar for
response outcomes, but larger on mean endpoint data than those seen with SSRIs. This
may be explained by the fact that the included studies were mostly older than those in
the SSRI review, and the differences in effect sizes seen may be explained by a
combination of the timing of the studies and the characteristics of the participants. A
review of SSRIs compared with TCAs is in Chapter 8.

The effect sizes for acceptability and tolerability outcomes were considerably larger
than those seen with SSRIs, with those taking TCAs more likely to report side effects or
leave treatment early because of side effects. On the basis of placebo-controlled trials
therefore, TCAs would seem to be less well tolerated than SSRIs.

7.8.5.1 From evidence to recommendations
There is evidence that antidepressants are more effective than placebo on efficacy
outcomes, but that they are less acceptable (based on attrition rates), and produce more
side effects. There is some evidence that they are less effective in people with less
severe symptoms, and this is clearer with SSRIs. The previous guideline recommended
that antidepressants should not be prescribed for mild depression based on the poor
risk-benefit ratio, but could be considered for persistant symptoms following other
interventions or for those with a history of moderate or severe depression. Given the
evidence in chapter 11 (subthreshold depression) reviewed for the updated guideline,
that antidepressants are not effective in minor depression, but may be effective in dysthymia (persistent minor depression), this recommended is extended to include minor depression.

7.8.6 Clinical practice recommendation

7.8.6.1 Antidepressants are not recommended for the routine treatment of recent-onset minor depression and mild depression because the risk–benefit ratio is poor, but should be considered for people with:

- minor and mild depression which persists after other interventions
- initial presentation of persistent minor depression
- a past history of moderate or severe depression
8 Pharmacological interventions in treatment and management

This chapter reviews the use of individual drugs in the treatment of depression. The GDG did not update the reviews of individual antidepressants undertaken for the previous guideline since most of these were large-scale reviews and a good deal of new evidence would have to have been published to change the overall conclusion that there is little difference in efficacy between drugs. For example, although new RCT data on venlafaxine have become available and several meta-analyses (eg Nemeroff et al, 2008; Weinmann et al, 2008) and systematic reviews (Gartlehner et al, 2008) published, new data do not support clinically important superior efficacy of venlafaxine over other antidepressants. However, some of the recommendations have been revised in light of the safety review conducted by the MHRA, and these were the basis of the revised version of the NICE depression guideline published in 2006.

The relative efficacy and tolerability of SSRIs and SNRIs has been the subject of several meta-analyses (eg Cipriani et al, 2008; Gartlehner et al, 2008). These analyses do not support there being a clinically significant difference in efficacy between drugs, or alter the conclusions in the original guideline with respect to relative tolerability.

The GDG did not update its review of St John’s wort. Although further data have become available to suggest that St John’s wort may be more effective, and better tolerated than standard antidepressants in the acute treatment of mild to moderate depression, there is evidence of publication bias that complicates the interpretation of these data (Linde et al, 2008). In addition, there are few medium term data (Anghelescu et al, 2006; Kasper et al, 2008), or data that support the use of St John’s wort in relapse prevention (Kasper et al, 2008). There is also a lack of efficacy data in people with severe depression and long-term safety data remain scant. The GDG were previously cautious about the use of the St John’s wort partly because there is uncertainty over the active constituent and the majority of preparations are not standardized to contain fixed quantities of individual constituents. Since the original guideline was published Traditional Herbal Registration Certificates have been granted in the UK for standardised preparations of St John’s wort; these certificates are not based on RCT evidence of efficacy and tolerability in the same way that a product licence is for a conventional medicine. The recommendations on St John’s wort are therefore unchanged.

The review of escitalopram has been updated since a large number of new studies have been published.

In the section on factors influencing the choice of antidepressant the reviews of the effects of sex on the effects of antidepressants, antidepressant discontinuation symptoms, cardiotoxicity, and antidepressants and suicide were updated, and a new review of treatments for seasonal pattern major depression (seasonal affective disorder) included since this diagnosis was added to the scope of the updated guideline.
The section on the management of depression in older adults was not updated since there are few new data in older adults which indicate that the existing recommendations should be amended. In addition, since the previous guideline, a separate guideline has been developed specifically for depression in people with chronic physical health problems which covers the issues relevant to many older people with depression (NICE, in preparation).

The section on psychotic depression was not updated and the recommendations left unchanged. The review of atypical depression was also not updated. However, the GDG felt that the previous recommendations should be removed since there was no reason why treatment for people whose depression had atypical features should not follow that for those with major depression. The review of low-dose versus high-dose TCAs was not updated.

8.1 Use of individual drugs in the treatment of depression

8.1.1 Introduction

This section reviews the relative efficacy of individual antidepressants in the treatment of depression. Where there were sufficient data, the effect of patient setting (inpatient, outpatient or primary care) on choice of drug was also examined. It covers the following drugs:

- Tricyclic antidepressants (TCAs)
  - Amitriptyline
  - An overview of TCAs*27

- Selective serotonin reuptake inhibitors (SSRIs)
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline

- Monoamine oxidase inhibitors (MAOIs)
  - Moclobemide
  - Phenelzine

- Third-generation’ drugs
  - Duloxetine
  - Mirtazapine

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27 Many studies in the above reviews used a TCA as a comparator treatment. These data were combined in a review of TCAs to enable the GDG to gain an overview of this class of drugs.
• Reboxetine
• Venlafaxine

• Other preparations
  – St John’s wort.

8.2 Tricyclic antidepressants (TCAs)

8.2.1 Introduction
TCAs have been used to treat depression for over 40 years. Currently nine TCAs are available in the UK. They are thought to exert their therapeutic effect by inhibiting the re-uptake of monoamine neurotransmitters into the presynaptic neurone thus enhancing noradrenergic and serotonergic neurotransmission. Although all TCAs block the reuptake of both amines, they vary in their selectivity with, for example, clomipramine being primarily serotonergic and imipramine noradrenergic.

All TCAs cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, sweating), sedation and postural hypotension. These side effects necessitate starting with a low dose and increasing slowly. In many patients a ‘therapeutic dose’ is never reached either because the patient cannot tolerate it or because the prescriber does not titrate the dose upwards.

All TCAs, except lofepramine, are toxic in overdose with seizures and arrhythmias being a particular concern (see Sections 8.2.9 and 8.2.10). This toxicity, and the perceived poor tolerability of these drugs in general, has led to a decline in their use in the UK over the last decade.

Amitriptyline
Although amitriptyline was not the first TCA and is not the best tolerated or the most widely prescribed, it is the standard drug against which new antidepressants are compared with respect to both efficacy and tolerability. Amitriptyline may be marginally more effective than other antidepressants, a potential benefit that is offset by its poorer tolerability (Barbui & Hotopf, 2001). Efficacy benefits may be more marked in hospitalised patients (Anderson et al., 2000).

8.2.1.1 Studies considered for review
The GDG used an existing review (Barbui & Hotopf, 2001) as the basis for this section, for which the authors made their data available to the NCCMH team. The original review included 184 studies of which 144 did not meet the inclusion criteria set by the GDG. Eight additional studies were identified from searches undertaken for other sections of this guideline. Thus 48 trials are included in this section providing 28 Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17 on the CD, which also contains a list of excluded studies with reasons for exclusions.

29 Here and elsewhere in the guideline, each study considered for review is referred to by a study ID (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).
Data were available to compare amitriptyline with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine, dothiepin/dosulepin, doxepin, imipramine, lofepramine, minaprine, nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine.

The original systematic review on which this section is based included measures, responders and mean endpoint scores. It did not include data on remission and this has not been extracted for the present review.

### 8.2.1.2 Evidence statements

#### Effect of treatment on efficacy

There appears to be no clinically important difference in efficacy between amitriptyline and other antidepressants, either when compared together or by class:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression scores as measured by the HRSD ($N = 16; n = 1541; RR = 1.06; 95\% CI, 0.96$ to $1.18$).

There is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD and MADRS, but the size of this difference is

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30 It is not always possible to extract data for all outcomes from each study, therefore the figures given are for the outcome with the largest number of participants.
31 Not available in the UK.
32 The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on the CD.
33 The authors of the review on which this review is based entered data into Review Manager so that amitriptyline is on the right-hand side of the forest plot and comparator treatments on the left.
34 Where it made a difference to results the following studies were removed from efficacy analyses because >50% left treatment early: COHN1990, FAWCETT1989, GUY1983, PRESKORN1991, SHAW1986, STUPPAECK1994, WILCOX1994.
unlikely to be of clinical significance (N = 32; n = 2760; SMD = 0.09; 95% CI, 0.01 to 0.16).

There is evidence suggesting that there is no clinically significant difference between:

- other TCAs and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 5; n = 285; SMD = 0.04; 95% CI, -0.19 to 0.27)
- SSRIs and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 9; n = 837; RR = 1.09; 95% CI, 0.95 to 1.25)
- SSRIs and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 19; n = 1648; SMD = 0.06; 95% CI, -0.03 to 0.16).

There is insufficient evidence to determine whether there is a clinically significant difference between other TCAs and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 2; n = 68; RR = 0.96; 95% CI, 0.60 to 1.53).

Effect of setting on treatment efficacy

There appears to be no clinically important difference between amitriptyline and other antidepressants in different treatment settings:

In inpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 6; n = 600; RR = 1.08; 95% CI, 0.9 to 1.29).

In inpatients there is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N = 11; n = 752; SMD = 0.16; 95% CI, 0.02 to 0.30).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N = 9; n = 1,002; SMD = 0.13; 95% CI, 0.00 to 0.25).

In outpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 7; n = 666; RR = 1.03; 95% CI, 0.89 to 1.2).

In patients in primary care there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing
depression symptoms by the end of treatment as measured by the HRSD (N = 2; n = 132; SMD = -0.09; 95% CI, -0.44 to 0.27).

Acceptability and tolerability of treatment

When compared with all antidepressants, amitriptyline appears to be equally tolerable in terms of leaving treatment early for any reason. However, patients taking other antidepressants report fewer side effects:

There is evidence suggesting that there is no clinically significant difference between amitriptyline and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 43; n = 4884; RR = 0.92; 95% CI, 0.84 to 1.003).

There is strong evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of leaving the study early due to side effects (N = 34; n = 4034; RR = 0.71; 95% CI, 0.61 to 0.83).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of patients reporting side effects (N = 5; n = 773; RR = 0.78; 95% CI, 0.65 to 0.93).

Acceptability and tolerability of treatment by setting

For inpatients, there appears to be little difference between the tolerability of amitriptyline and other antidepressants:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving the study early for any reason (N = 15; n = 1320; RR = 0.96; 95% CI, 0.82 to 1.13).

There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving treatment early due to side effects (N = 8; n = 855; RR = 0.78; 95% CI, 0.55 to 1.1).

There is evidence suggesting that there is no clinically significant difference between paroxetine and amitriptyline on reducing the likelihood of inpatients reporting side effects (N = 2; n = 131; RR = 0.88; 95% CI, 0.68 to 1.12).

Amitriptyline was less well tolerated in outpatients.

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of outpatients leaving treatment early for any reason (N = 19; n = 2647; Random effects RR = 0.87; 95% CI, 0.72 to 1.06).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of outpatients leaving treatment early due to side effects (N = 18; n = 2396; RR = 0.75; 95% CI, 0.62 to 0.9).
There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of outpatients reporting side effects (N = 2; n = 552; RR = 0.8; 95% CI, 0.61 to 1.04).

Although much of the evidence was too weak to make a valid comparison of tolerability in primary care, more patients reported side effects in amitriptyline than paroxetine, which was the only comparator drug available:

In patients in primary care there is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of leaving treatment early either for any reason or due to side effects.

There is some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline on reducing the likelihood of primary care patients reporting side effects (N = 1; n = 90; RR = 0.55; 95% CI, 0.35 to 0.86).

8.2.1.3 Clinical summary

Amitriptyline is as effective as other antidepressants, although patients taking the drug report more adverse events and tend to leave treatment early due to side effects.

8.2.1.4 Tricyclic antidepressants – an overview of selected data

This section combines data from other reviews where a TCA was used as a comparator treatment. It is, therefore, not a systematic review since a systematic search for all trials of TCAs was not conducted. It specifically does not include comparisons of TCAs with other TCAs.

8.2.1.5 Studies considered for review

In all, 94 studies from other reviews included a TCA as a comparator drug. Seventy studies were sourced from the review of SSRIs (Section 8.1.3), seven from the review of mirtazapine (Section 8.1.5.1), eight from phenelzine (Section 8.1.4.3), three from reboxetine (Section 8.1.5.2) and six from venlafaxine (Section 8.1.5.3). Data were available from the following TCAs: clomipramine, doxepin, desipramine, imipramine, dothiepin/dosulepin, nortriptyline, amineptine and lofepramine. Efficacy data were available from up to 6848 patients, and tolerability data from up to 8967 patients.

All included studies were published between 1981 and 2002. Twenty-four studies were of inpatients, 48 of outpatients and three undertaken in primary care. In the remaining 19, it was either not clear from where participants were sourced or they were from mixed sources. In 11 more than 80% of study participants were aged 65 years and over, and, in two, participants had depression with additional atypical features (MCGRATH2000, QUITKIN1990).

8.2.1.6 Evidence statements
Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference between other antidepressants and TCAs on:

- increasing the likelihood of achieving a 50% reduction in symptoms as measured by the HRSD or the MADRS ($N = 1535; n = 2364; RR = 0.91; 95\% CI, 0.83 to 1.01$)
- increasing the likelihood of achieving remission as measured by the HRSD ($N = 336; n = 534; RR = 0.98; 95\% CI, 0.84 to 1.15$)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS ($N = 70; n = 6,848; SMD = 0.02; 95\% CI, -0.03 to 0.07$).

Effect of setting on treatment efficacy

Inpatients

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms in inpatients as measured by the HRSD ($N = 437; n = 765; RR = 0.98; 95\% CI, 0.82 to 1.18$).

There is evidence suggesting that there is a statistically significant difference favouring TCAs over alternative antidepressants on reducing depression symptoms, as measured by the HRSD or the MADRS, in inpatients by the end of treatment, but the size of this difference is unlikely to be of clinical significance ($N = 20; n = 1681; SMD = 0.12; 95\% CI, 0.03 to 0.22$).

Outpatients

There is some evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD ($N = 5; n = 733; RR = 0.74; 95\% CI, 0.64 to 0.87$).

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS ($N = 33; n = 3275; SMD = -0.03; 95\% CI, -0.1 to 0.04$).

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35 BRUIJN1996 and QUITKIN1990 were removed from the meta-analysis to remove heterogeneity from the imipramine data set
36 QUITKIN1990 was removed from the meta-analysis to remove heterogeneity from the imipramine data set
37 BRUIJN1996 was removed from the meta-analysis to remove heterogeneity from the imipramine data set.
There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and nortriptyline on increasing the likelihood of achieving remission in outpatients by the end of treatment as measured by the HRSD (N = 138; n = 60; RR = 1.28; 95% CI, 0.78 to 2.09).

Primary care

There is insufficient evidence to determine whether there is a clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in patients in primary care by the end of treatment as measured by the HRSD or MADRS (N = 2; n = 213; SMD = –0.14; 95% CI, –0.42 to 0.13).

Acceptability and tolerability of treatment

There is evidence suggesting that there are statistically significant differences favouring alternative antidepressants over TCAs on the following outcomes, but the size of these differences is unlikely to be of clinical significance:

- on reducing the likelihood of leaving treatment early for any reason (N = 83; n = 8967; RR = 0.88; 95% CI, 0.83 to 0.94)
- on reducing the likelihood of patients reporting adverse effects (N = 25; n = 3007; Random effects RR = 0.91; 95% CI, 0.86 to 0.96).

There is strong evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on reducing the likelihood of leaving treatment early due to side effects (N = 80; n = 8888; RR = 0.71; 95% CI, 0.65 to 0.78).

When TCAs were examined individually, only dothiepin/dosulepin appears to be more acceptable than alternative antidepressants:

There is some evidence suggesting that there is a clinically significant difference favouring dothiepin/dosulepin over alternative antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 5; n = 336; RR = 1.42; 95% CI, 1.02 to 1.98) and on reducing the likelihood of leaving treatment early due to side effects (N = 5; n = 336; RR = 2.02; 95% CI, 1.09 to 3.76).

8.2.1.7 Clinical summary

TCAs have equal efficacy compared with alternative antidepressants but are less well tolerated particularly in outpatients.

8.3 Selective serotonin reuptake inhibitors (SSRIs)

8.3.1.1 Introduction

38 QUITKIN1990 was removed from the meta-analysis to remove heterogeneity from the imipramine data set.
The selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin into the presynaptic neurone thus increasing neurotransmission. Although they ‘selectively’ inhibit serotonin reuptake, they are not serotonin specific. Some of the drugs in this class also inhibit the reuptake of noradrenaline and/or dopamine to a lesser extent.

As a class, they are associated with less anticholinergic side effects and are less likely to cause postural hypotension or sedation. Dosage titration is not routinely required so subtherapeutic doses are less likely to be prescribed. They are also less cardiotoxic and much safer in overdose than the TCAs or MAOIs. These advantages have led to their widespread use as better-tolerated first-line antidepressants.

The most problematic side effects of this class of drugs are nausea, diarrhoea and headache. Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes (Mitchell, 1997) precipitating many significant drug interactions. Sertraline is less problematic although enzyme inhibition is dose-related and citalopram is relatively safe in this regard.

There are other important differences among the SSRIs (Anderson & Edwards, 2001), as outlined below.

**Citalopram**

Citalopram is the most serotonin selective of the SSRIs included in this section. In animals, one of its minor metabolites is cardiotoxic (Van der Burght, 1994) and it is pro-convulsant at high dose (Boeck et al., 1982). The issue of its safety in overdose is discussed below (see Section 8.2.9.3). It is available as a generic preparation.

**Escitalopram**

Citalopram is a racemic mixture of s-citalopram and r-citalopram. With respect to SSRI potency, escitalopram (s-citalopram) is 100 times more potent than r-citalopram. The observation that escitalopram 10 mg is as effective as citalopram 20 mg confirms that escitalopram is responsible for most or perhaps all of the antidepressant efficacy of citalopram (Waugh & Goa, 2003). It has been suggested that r-citalopram contributes only to side effects and by using the active isomer only, efficacy will be maintained and side effects reduced.

**Fluoxetine**

Fluoxetine is the most widely prescribed SSRI. It is associated with a lower incidence of nausea than fluvoxamine but a higher incidence of rash. It has a long half-life, which may cause problems with washout periods when switching to other antidepressant drugs but has the advantage of causing less discontinuation symptoms. It is available as a generic preparation.

**Fluvoxamine**

Fluvoxamine was the first of the currently available SSRIs to be marketed in the UK. It is associated with a higher incidence of nausea than the other SSRIs and so is not widely prescribed.

**Paroxetine**
Paroxetine is associated with a higher incidence of sweating, sedation and sexual dysfunction than other SSRIs and more problems on withdrawal (Anderson & Edwards, 2001; see also Section 8.2.8 on antidepressant discontinuation symptoms). It is available as a generic preparation.

**Sertraline**

Sertraline is a well-tolerated SSRI. It is more likely to be associated with upwards dosage titration during treatment than the other SSRIs (Gregor et al., 1994).

### 8.3.1.2 Studies considered for review

The GDG used an existing review (Geddes et al., 2002) as the basis of this section, for which the authors made their data available to the NCCMH team. Since this review did not cover escitalopram which achieved its UK licence in late 2001, a separate review of this drug was undertaken. The two reviews are presented separately.

**Review of SSRIs apart from escitalopram**

The Geddes et al. (2002) review included 126 studies of which 72 did not meet the inclusion criteria set by the GDG. In addition one trial (Peselow et al., 1989) included in the original review was considered to be part of a multicentre trial (FEIGHNER92) rather than a separate trial. Another (FEIGHNER1989), excluded in the original review, was included in this review because it contained tolerability data (which the original review did not include). A further two trials excluded by the original review were also considered part of the FEIGHNER92 multicentre trial (Dunbar et al., 1991; Feighner & Boyer, 1989).

Since the original review compared SSRIs with TCAs only, 59 additional studies were identified from other reviews undertaken for this guideline, including two identified from hand searching reference lists. Thirty-three of these were included and 26 excluded. Thus 107 trials are included in this review providing data from up to 11,442 participants. A total of 97 trials were excluded.

All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.5 weeks). Twenty-four studies were of inpatients, 51 of outpatients and six undertaken in primary care. In the remaining 26, it was either not clear from where participants were sourced, or they were from mixed sources. In 11, more than 80% of study participants were aged 65 years and over (although only eight of these reported extractable efficacy outcomes). In two studies participants had depression with additional atypical features.

In addition to the standard diagnostic criteria, most studies required a minimum baseline HRSD score of between 10 and 22 on the 17-item version (61 studies) or between 18 and 22 on the 21-item version (28 studies). The ten studies reporting MADRS scores required minimum baseline scores of between 18 and 30.

Data were available to compare SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with amineptine, amitriptyline, clomipramine, desipramine, dothiepin/dosulepin, doxepin, imipramine, lofepramine, nortriptyline, maprotiline,
mianserin, trazodone, phenelzine, moclobemide, mirtazapine, venlafaxine and reboxetine.

The original systematic review on which this review is based and for which the data were made available to the GDG included only one outcome measure, mean endpoint scores, and did not include tolerability data. Tolerability data, but not additional efficacy outcomes, have been extracted by the NCCMH team.

Review of escitalopram

A new review was undertaken with two studies being identified from a search of electronic databases, one of which met inclusion criteria. Two further studies were identified from other searches undertaken for this guideline, both of which met inclusion criteria. Two unpublished studies, both of which met inclusion criteria, were supplied by Lundbeck. Thus a total of six studies are included in this review (ALEXOPOULOS2003, BIELSKI2003, BURKE2002, MONTGOMERY2001, MONTGOMERY2002, WADE2002) providing data from up to 2,045 participants. One study (RAPPAPORT2004) was excluded because it reported on the maintenance phase of a trial.

All included studies were published between 2001 and 2003 and were eight weeks long. In two studies participants were classified outpatients, in three primary care and in one the setting was unclear. Participants were aged between 18 years and 85 years, although in no study were all participants over 65 years. Participants received between 10 mg and 20 mg of escitalopram, with two studies specifically comparing 10 mg with 20 mg.

All studies reported mean baseline MADRS scores between 28.7 to 30.7. Three studies reported baseline HRSD scores. These ranged from 25.8 to 28.6.

Data were available to compare escitalopram with citalopram, sertraline, venlafaxine and placebo.

8.3.1.3 Evidence statements for SSRIs apart from escitalopram

There is no clinically significant difference between SSRIs and other antidepressants, whether combined as a group or divided by drug class:

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 8239; n = 8,668; SMD = 0.08; 95% CI, 0.03 to 0.12).

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS between:

39 Studies where >50% of participants left treatment early were retained in the analysis since removing them made no difference to the results
SSRIs and TCAs (N = 49; n = 4,073; SMD = 0.05; 95% CI, –0.01 to 0.12)
SSRIs and MAOIs (N = 7; n = 469; SMD = 0.03; 95% CI, –0.15 to 0.22).

There is evidence suggesting that there is a statistically significant difference favouring third-generation antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 17; n = 3665; SMD = 0.13; 95% CI, 0.06 to 0.19).

Effect of setting on treatment efficacy

In inpatients there is no difference between the efficacy of SSRIs and other antidepressants, apart from third-generation antidepressants:

- SSRIs and other antidepressants (N = 20; n = 1258; SMD = 0.09; 95% CI, –0.02 to 0.2)
- SSRIs and TCAs (N = 15; n = 970; SMD = 0.12; 95% CI, –0.01 to 0.24).

There is some evidence suggesting that there is a clinically significant difference favouring third-generation antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in inpatients (N = 1; n = 67; SMD = 0.58; 95% CI, 0.09 to 1.07).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and MAOIs on reducing depression symptoms as measured by the HRSD or MADRS in inpatients.

In outpatients there is no difference between the efficacy of SSRIs and other antidepressants:

- There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients but the size of this difference is unlikely to be of clinical significance (N = 38; n = 4666; SMD = 0.06; 95% CI, 0 to 0.12).
- There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS in outpatients between SSRIs and TCAs (N = 24; n = 2304; SMD = 0.02; 95% CI, –0.07 to 0.1).
- There is evidence suggesting that there is a statistically significant difference favouring ‘third-generation’ antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients, but the size of this difference is unlikely to be of clinical significance (N = 9; n = 2096; SMD = 0.13; 95% CI, 0.05 to 0.22).

Mirtazapine, venlafaxine and reboxetine
There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and MAOIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients.

There is a similar picture in primary care:

There is evidence suggesting that there is no clinically significant difference between SSRIs and other antidepressants on reducing depression symptoms as measured by the HRSD or MADRS in primary care (N = 4; n = 922; SMD = 0.08; 95% CI, –0.05 to 0.21).

**Acceptability and tolerability of treatment**

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N = 97; n = 11442; RR = 0.91; 95% CI, 0.87 to 0.96).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N = 89; n = 10898; RR = 0.78; 95% CI, 0.71 to 0.85).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients reporting adverse effects but the size of this difference is unlikely to be of clinical significance (N = 42; n = 5658; RR = 0.94; 95% CI, 0.91 to 0.97).

A sub-analysis against TCAs showed similar results:

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N = 62; n = 6446; RR = 0.88; 95% CI, 0.82 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early due to side effects (N = 59; n = 6145; RR = 0.69; 95% CI, 0.62 to 0.77).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on the likelihood of patients reporting adverse events but the size of this difference is unlikely to be of clinical significance (N = 17; n = 1846; RR = 0.86; 95% CI, 0.81 to 0.9).

**8.4 Review of escitalopram**

Escitalopram was reviewed for the original guideline but a relatively large number of studies (compared with the number previously available) have been published since and so the review was updated. For the present review both published and
unpublished double-blind randomised controlled trials were sought which compared escitalopram either with placebo or with another antidepressant. The marketing authorisation holder, Lundbeck, was also contacted for data. The electronic databases searched for published trials are given in Table 18. Details of the search strings used are in appendix 7.

Table 61: Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>Escitalopram, placebo, other antidepressants</td>
</tr>
</tbody>
</table>

A total of 6 trials were included in the original review and these were supplemented by another 18 trials. Some of the studies used in the original review which had been unpublished have been published since with different first authors, thus changing the study identifier. Four studies in the current review are unpublished and supplied by the drug’s manufacturer.

Data were available to compare escitalopram with placebo, and with a range of other antidepressants. Sub-analyses were undertaken to assess the effect of severity of depression at baseline and escitalopram dose, and to ascertain effectiveness against individual drugs, in particular, against citalopram, other SSRIs and other non-SSRI antidepressants.

Summary study characteristics of the included studies are in Table 62 with full details in Appendix 17 which also includes details of excluded studies.

Table 62 Summary study characteristics of studies of escitalopram

<table>
<thead>
<tr>
<th>No. trials (Total participants)</th>
<th>Versus placebo</th>
<th>Versus citalopram</th>
<th>Versus other SSRIs</th>
<th>Versus other antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study IDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study IDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) BOSE2008</td>
<td>(1) BURKE2002*</td>
<td>(1) BALDWIN2006</td>
<td>(1) BIELSKI2004</td>
<td></td>
</tr>
<tr>
<td>(2) BURKE2002</td>
<td>(2) COLONNA2005</td>
<td>(2) CLAYTON2006</td>
<td>(2) CLAYTON2006 study 1**</td>
<td></td>
</tr>
<tr>
<td>(3) CLAYTON2006 study 1**</td>
<td>(3) LEPOLA2003**</td>
<td>(3) KASPER2005**</td>
<td>(3) CLAYTON2006 study 2**</td>
<td></td>
</tr>
<tr>
<td>(4) CLAYTON2006 study 2**</td>
<td>(4) MOORE2005</td>
<td>(4) MOORE2005</td>
<td>(4) MAO2008</td>
<td></td>
</tr>
<tr>
<td>(5) KASPER2005**</td>
<td>(5) SCT-MD-02**</td>
<td>(5) SCT-MD-09</td>
<td>(5) MONTGOMERY2002</td>
<td></td>
</tr>
<tr>
<td>(6) LEPOLA2003**</td>
<td>(6) YEVTSHENKO2007**</td>
<td>(6) SCT-MD-16</td>
<td>(6) NIERENBERG2007**</td>
<td></td>
</tr>
<tr>
<td>(7) NIERENBERG2007**</td>
<td>(7) SCT-MD-27**</td>
<td>(7) SCT-MD-27**</td>
<td>(7) WADE2007</td>
<td></td>
</tr>
<tr>
<td>(8) SCT-MD-02**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9) SCT-MD-26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10) SCT-MD-27**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(11) WADE2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/ female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) 267/58</td>
<td>(1) 369/64</td>
<td>(1) 325/73</td>
<td>(1) 198/58</td>
<td></td>
</tr>
<tr>
<td>(2) 366/64</td>
<td>(2) 357/74</td>
<td>(2) 459/68</td>
<td>(2) 284/61</td>
<td></td>
</tr>
<tr>
<td>(3) 283/61</td>
<td>(3) 310/72</td>
<td>(3) 338/76</td>
<td>(3) 297/54</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 68</td>
<td>(2) 40</td>
<td>(3) 36</td>
<td>(4) 37</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Escitalopram dose (mean if given)</td>
<td>(1) 20mg</td>
<td>(2) 10mg and 20mg</td>
<td>(3) 13mg</td>
<td>(4) 13mg</td>
</tr>
<tr>
<td>Comparator (mean dose if given)</td>
<td>Placebo</td>
<td>(1) Citalopram 40mg</td>
<td>(2) 20mg</td>
<td>(3) 20/40mg</td>
</tr>
<tr>
<td>Setting</td>
<td>(1) Outpatients</td>
<td>(2) Outpatients</td>
<td>(3) Unclear</td>
<td>(4) Unclear</td>
</tr>
<tr>
<td>Length of treatment (weeks)</td>
<td>(1) 12 days</td>
<td>(2) 8</td>
<td>(3) 8</td>
<td>(4) 8</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 40</td>
<td>(2) 46</td>
<td>(3) 43</td>
<td>(4) 45</td>
</tr>
<tr>
<td>Escitalopram dose (mean if given)</td>
<td>(1) 10mg and 20mg</td>
<td>(2) 10mg</td>
<td>(3) 10mg</td>
<td>(4) 20mg</td>
</tr>
<tr>
<td>Comparator (mean dose if given)</td>
<td>Placebo</td>
<td>(1) Citalopram 40mg</td>
<td>(2) 20mg</td>
<td>(3) 20/40mg</td>
</tr>
<tr>
<td>Setting</td>
<td>(1) Outpatients</td>
<td>(2) Outpatients</td>
<td>(3) Unclear</td>
<td>(4) Unclear</td>
</tr>
<tr>
<td>Length of treatment (weeks)</td>
<td>(1) 8</td>
<td>(2) 6 months</td>
<td>(3) 8</td>
<td>(4) 8</td>
</tr>
</tbody>
</table>
8.4.1 Escitalopram versus placebo

Eleven studies were found which compared escitalopram with placebo. Those which used a fixed dose of 10mg or 20mg were included in sub-analyses by dose.

See Table 63 for the summary evidence profile and Appendix 15 for the full profile.

Table 63 Summary evidence profile for escitalopram versus placebo

<table>
<thead>
<tr>
<th>Non-response</th>
<th>Non-remission</th>
<th>Mean depression scores at endpoint/mean change</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Number reporting side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 0.81 (0.75 to 0.88) (49.8% vs 60.2%)</td>
<td>RR 0.88 (0.82 to 0.94) (61.1% vs 68.6%)</td>
<td>SMD -0.24 (-0.35 to -0.13) / SMD -0.26 (-0.34 to -0.19)</td>
<td>RR 1.11 (0.95 to 1.29) (22% vs 19.3%)</td>
<td>RR 1.8 (1.18 to 2.73) (6.3% vs 3.2%)</td>
<td>RR 1.09 (1.04 to 1.15) (71.7% vs 64.7%)</td>
</tr>
</tbody>
</table>

Quality of evidence: Moderate

Number of studies/participants: K=11; n=3495

Forest plot: Pharm Esc 01.01

| 10mg effect size | RR 0.84 (0.72 to 0.98) (53.7% vs 61.8%) | RR 0.92 (0.81 to 1.06) (62.1% vs 65.4%) | SMD -0.23 (-0.46 to -0.01) / SMD -0.28 (-0.41 to -0.15) | RR 0.99 (0.75 to 1.3) (19.9% vs 18.9%) | RR 2.02 (0.9 to 4.54) (5.9% vs 2.9%) | RR 1.04 (0.94 to 1.15) (61.1% vs 58.7%) |

Quality of evidence: Moderate

Number of studies/participants: K=4; n=1386

Forest plot: Pharm Esc 01.01

| 20mg effect size | RR 0.68 (0.55 to 0.84) (49.6% vs 73%) | SMD -0.46 (-0.71 to -0.2) / SMD -0.48 (-0.74 to -0.22) | RR 1.17 (0.77 to 1.77) (28.8% vs 24.6%) | RR 4.23 (1.24 to 14.47) (10.4% vs 2.5%) | RR 1.21 (1.06 to 1.39) (85.6% vs 70.5%) |

Quality of evidence: High/moderate

Number of studies/participants: K=4; n=1386

Forest plot: Pharm Esc 01.01
Escitalopram was effective compared with placebo although effect sizes were small and the quality of evidence graded moderate largely because of heterogeneity. Sub-analyses by dose indicated that both 10mg and 20mg doses were effective, although effect sizes were larger with the larger dose. However, more people left treatment early both for any reason and because of side effects, and more people reported side effects amongst those taking 20mg compared with those taking 10mg.

8.4.2 Escitalopram versus all other antidepressants

21 studies were found which compared escitalopram with other antidepressants. In the following analyses escitalopram is compared with all other antidepressants together, and in the analyses below separate analyses are presented for escitalopram compared with SSRIs, citalopram and other antidepressants separately.

See Table 64 for the summary evidence profile and Appendix 15 for the full profile.

<table>
<thead>
<tr>
<th>Non-response</th>
<th>Non-remission</th>
<th>Mean depression scores at endpoint/mean change</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Number reporting side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 0.9 (0.85 to 0.96) (37.7% vs 41.4%)</td>
<td>RR 0.93 (0.88 to 0.98) (46.3% vs 49.7%)</td>
<td>SMD -0.1 (-0.17 to -0.02) / SMD -0.07 (-0.12 to -0.02)</td>
<td>RR 0.85 (0.74 to 0.98) (18.9% vs 21.6%)</td>
<td>RR 0.64 (0.53 to 0.78) (5.6% vs 8.6%)</td>
<td>RR 0.94 (0.91 to 0.98) (63.9% vs 64.4%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=19; n=55832</td>
<td>K=17; n=520</td>
<td>K=11; n=300</td>
<td>K=21; n=619</td>
<td>K=20; n=580</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm Esc 02.01</td>
<td>Pharm Esc 02.02</td>
<td>Pharm Esc 02.03/04</td>
<td>Pharm Esc 02.05</td>
<td>Pharm Esc 02.06</td>
</tr>
</tbody>
</table>

Compared with all antidepressants for which there are data, escitalopram was marginally more effective although effect sizes were very small. Fewer participants taking escitalopram left treatment early for any reason or because of side effects compared with those taking other antidepressants, although the number reporting side effects were roughly equal.
### 8.4.3 Escitalopram versus SSRIs

Eight studies were found which compared escitalopram with SSRIs. Escitalopram is also compared with citalopram separately.

See Table 65 for the summary evidence profile and Appendix 15 for the full profile.

**Table 65 Summary evidence profile for escitalopram versus SSRIs**

<table>
<thead>
<tr>
<th></th>
<th>Non-respons</th>
<th>Non-remissio</th>
<th>Mean depression scores at endpoint/mean change</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Number reporting side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All SSRIs Effect size</strong></td>
<td>RR 0.89 (0.82 to 0.97) (36.1% vs 39.6%)</td>
<td>RR 0.9 (0.83 to 0.98) (41.6% vs 46.2%)</td>
<td>SMD -0.11 (-0.19 to -0.03)/ SMD -0.1 (-0.18 to -0.02)</td>
<td>RR 0.86 (0.71 to 1.03) (16.8% vs 18.6%)</td>
<td>RR 0.75 (0.58 to 0.96) (5.8% vs 7.6%)</td>
<td>RR 0.94 (0.9 to 0.98) (64.8% vs 67.7%)</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>High</td>
<td>High/High</td>
<td>High/High</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Number of studies/participant s</strong></td>
<td>K=12;n=3650</td>
<td>K=10;n=3024</td>
<td>K=9;n=2434/k=13;n=3337</td>
<td>K=14;n=4019</td>
<td>K=13;n=3639</td>
<td>K=13;n=3652</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm Esc 03.01</td>
<td>Pharm Esc 03.02</td>
<td>Pharm Esc 03.03/04</td>
<td>Pharm Esc 03.05</td>
<td>Pharm Esc 03.06</td>
<td>Pharm Esc 03.07</td>
</tr>
<tr>
<td><strong>Citalopram Effect size</strong></td>
<td>RR 0.85 (0.76 to 0.95) (40.2% vs 45.6%)</td>
<td>RR 0.82 (0.72 to 0.94) (41% vs 50.1%)</td>
<td>SMD -0.12 (-0.24 to 0)/ SMD -0.17 (-0.28 to -0.05)</td>
<td>RR 0.82 (0.6 to 1.11) (15.2% vs 15.4%)</td>
<td>RR 0.8 (0.49 to 1.29) (5.6% vs 6.7%)</td>
<td>RR 0.95 (0.86 to 1.04) (64.7% vs 64.2%)</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>High</td>
<td>High/High</td>
<td>High/High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Number of studies/participant s</strong></td>
<td>K=5;n=1594</td>
<td>K=3;n=968</td>
<td>K=4;n=1143/k=6;n=1639</td>
<td>K=6;n=1924</td>
<td>K=5;n=1569</td>
<td>K=5;n=1583</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm Esc 03.01</td>
<td>Pharm Esc 03.02</td>
<td>Pharm Esc 03.03/04</td>
<td>Pharm Esc 03.05</td>
<td>Pharm Esc 03.06</td>
<td>Pharm Esc 03.07</td>
</tr>
<tr>
<td><strong>Fluoxetine Effect size</strong></td>
<td>RR 0.92 (0.78 to 1.08) (39.8% vs 35.9%)</td>
<td>RR 0.92 (0.8 to 1.06) (44.9% vs 48.7%)</td>
<td>SMD -0.2 (-0.34 to -0.06)/ SMD -0.06 (-0.24 to 0.13)</td>
<td>RR 0.91 (0.58 to 1.42) (19.98% vs 21.9%)</td>
<td>RR 0.77 (0.47 to 1.26) (6.6% vs 8.6%)</td>
<td>RR 0.92 (0.82 to 1.03) (56.3% vs 61.7%)</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>High</td>
<td>High/High</td>
<td>High/High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Number of studies/participant s</strong></td>
<td>K=3;n=783</td>
<td>K=3;n=783</td>
<td>K=3;n=759/k=3;n=449</td>
<td>K=4;n=813</td>
<td>K=4;n=805</td>
<td>K=4;n=804</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm Esc 03.01</td>
<td>Pharm Esc 03.02</td>
<td>Pharm Esc 03.03/04</td>
<td>Pharm Esc 03.05</td>
<td>Pharm Esc 03.06</td>
<td>Pharm Esc 03.07</td>
</tr>
<tr>
<td><strong>Sertraline Effect size</strong></td>
<td>RR 1.01 (0.8 to 1.28) (35.8%)</td>
<td>RR 1.02 (0.86 to 1.22) (50.6%)</td>
<td>SMD -0.02 (-0.29 to 0.25)/ SMD 0.01 (-0.17)</td>
<td>RR 1.19 (0.81 to 1.74) (19.3% vs 4.2%)</td>
<td>RR 1.11 (0.38 to 3.22) (4.2% vs 89%)</td>
<td>RR 0.93 (0.87 to 1) (83.2% vs 89%)</td>
</tr>
</tbody>
</table>
Compared with all SSRIs together, escitalopram is marginally more effective although the effect sizes are small. Compared with individual SSRIs, there were no differences on efficacy outcomes other than compared with citalopram, where escitalopram was also marginally more effective. Escitalopram was also more acceptable and tolerable than SSRIs, apart from sertraline, although differences were small.

### 8.4.4 Escitalopram versus non-SSRI antidepressants

Seven studies were found which compared escitalopram with non-SSRI antidepressants.

See Table 66 for the summary evidence profile and Appendix 15 for the full profile.

### Table 66 Summary evidence profile for escitalopram versus non-SSRIs

<table>
<thead>
<tr>
<th>Non-response</th>
<th>Non-remission</th>
<th>Mean depression scores at endpoint/mean change</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Number reporting side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine Effect size</td>
<td>RR 0.81 (0.57 to 1.15) (43.4% vs 48.8%)</td>
<td>RR 0.97 (0.83 to 1.13) (55.6% vs 56%)</td>
<td>SMD -0.19/-0.42 to 0.04/-0.11 to 0.17</td>
<td>RR 0.7 (0.49 to 1) (21.3% vs 29.9%)</td>
<td>RR 0.78 (0.16 to 3.7) (78.8% vs 77.2%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate/high</td>
<td>Moderate</td>
<td>High</td>
</tr>
</tbody>
</table>

---

**Compared with all SSRIs together, escitalopram is marginally more effective although the effect sizes are small. Compared with individual SSRIs, there were no differences on efficacy outcomes other than compared with citalopram, where escitalopram was also marginally more effective. Escitalopram was also more acceptable and tolerable than SSRIs, apart from sertraline, although differences were small.**
There were no differences between escitalopram and duloxetine, venlafaxine or bupropion on efficacy measures, although all effect sizes favoured escitalopram. Escitalopram was mostly more acceptable and tolerable, although differences were very small.

8.4.5 Clinical summary for escitalopram

Escitalopram is superior to placebo in the treatment of depression. There is some evidence than 20mg may be more effective than 10mg but at the expense of increased side effects. Escitalopram is more effective than citalopram although the effect size is very small. It is at least as effective as other SSRIs and marginally better tolerated except against sertraline. Escitalopram is as effective as duloxetine, venlafaxine and bupropion.

There does not seem to be any advantage for escitalopram over other antidepressants. The differences in efficacy measures compared with placebo are small. Both 10mg and 20mg appeared effective, although larger effect sizes were calculated for 20mg.
Escitalopram was marginally more effective than other antidepressants, with statistically significant differences versus SSRIs (although effect sizes are very small and clinically not significant), but not against other antidepressants ( duloxetine, venlafaxine and bupropion). Effect sizes compared with citalopram were largest, although these were still relatively small. This was particularly the case for escitalopram at 20mg. It was also marginally more acceptable and tolerable, apart from compared with sertraline. However, differences were very small.

Overall the quality of the evidence tended to be downgraded because heterogeneity between trials. Since escitalopram is still in patent it is acquisition costs are relatively high compared to antidepressants available in generic form.

8.4.6 Clinical summary
SSRIs are relatively well-tolerated drugs with equal efficacy compared with alternative antidepressants. They are particularly suitable for women who may respond preferentially to SSRIs and for those with suicidal intent, due to their safety in overdose (see section 8.2.10).

8.5 Monoamine oxidase inhibitors (MAOIs)

8.5.1 Introduction
Monoamine oxidase inhibitors (MAOIs) exert their therapeutic effect by binding irreversibly to monoamine oxidase, the enzyme responsible for the degeneration of monoamine neurotransmitters such as noradrenaline and serotonin. This results in increased monoamine neurotransmission. The first antidepressant drug synthesised was an irreversible MAOI and drugs in this class have been available in the UK for nearly 50 years.

All MAOIs have the potential to induce hypertensive crisis if foods containing tyramine (which is also metabolised by MAO) are eaten (Merriman, 1999) or drugs that increase monoamine neurotransmission are co-prescribed (Livingstone & Livingstone, 1996). These foods and drugs must be avoided for at least 14 days after discontinuing MAOIs. Reversible inhibitors of MAO (RIMAs) are also available. Moclobemide is the only RIMA licensed in the UK.

Dietary restrictions, potentially serious drug interactions and the availability of safer antidepressants have led to the irreversible MAOIs being infrequently prescribed in the UK, even in hospitalised patients. However, MAOIs are still widely cited as being the most effective antidepressants for the treatment of atypical depression (see Section 8.2.5).

For this class of drugs the GDG chose to review phenelzine and moclobemide.

8.5.2 Moclobemide

Introduction
Moclobemide is a reversible selective inhibitor of monoamine oxidase A (a RIMA) as opposed to the traditional MAOIs that inhibit both MAO A and MAO B irreversibly. It
has the advantages over the traditional MAOIs that strict dietary restrictions are not required, drug interactions leading to hypertensive crisis are less problematic and shorter washout periods are required when switching to other antidepressants. Moclobemide is generally well-tolerated as it is associated with a low potential for producing anticholinergic side effects, weight gain and symptomatic postural hypotension. It is not widely prescribed in the UK.

Studies considered for review

Forty-four studies were found in a search of electronic databases with twelve meeting the inclusion criteria set by the GDG and 32 being excluded. Twenty-seven additional studies were identified from other searches undertaken for this guideline, 14 of which met inclusion criteria with 13 being excluded. Thus a total of 26 studies are included in this review (BAKISH1992, BARRELET1991, BEAUMONT1993, BECKERS1990, BOUGEROL1992, CASACCHIA1984, DUARTE1996, GATTAZ1995, GEERTS1994, GUELFI1992, HEBENSTREIT90, HELL1994, JOUVENT1998, KOCZKAS1989, KRAHGSORENSEN95, LAPIERRE1997, LARSEN1989, LECRUBIER1995, NAIR1995, NEWBURN1990, OSE1992, REYNAERT1995, SILVERSTONE94, TANGHE1997, VERSIANI1989, WILLIAMS1993) providing efficacy data from up to 1742 participants and tolerability data from up to 2149 participants. A total of 45 studies were excluded.


All included studies were published between 1984 and 1998 and were between four and seven weeks long (mean length = 5.34 weeks). In seven studies participants were classified inpatients, in a further seven, outpatients, in two, primary care and in 10 they were either a mixture of inpatients and outpatients or the setting was unclear. In one study (NAIR1995) the patients were exclusively older adults (aged 60 to 90). None of the included studies described participants as having depression with atypical features. Participants received between 150 mg and 600 mg of moclobemide with most receiving at least 300 mg.

Data were available to compare moclobemide with amitriptyline, clomipramine, dothiepin/dosulepin, imipramine, nortriptyline, fluoxetine, fluvoxamine and placebo.

Evidence statement for moclobemide compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 3; n = 490; Random effects SMD = -0.6; 95% CI, -1.13 to -0.07).
There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on increasing the likelihood of achieving at least a 50% reduction in depression symptoms as measured by the HRSD (N = 3; n = 606; Random effects RR = 0.7; 95% CI, 0.5 to 0.99).

There is insufficient evidence to determine whether there is a clinically significant difference between moclobemide and placebo on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 2; n = 111; RR = 0.88; 95% CI, 0.73 to 1.05).

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and placebo on:

• reducing the likelihood of leaving treatment early for any reason (N = 7; n = 819; Random effects RR = 0.95; 95% CI, 0.74 to 1.22)
• reducing the likelihood of leaving treatment early due to side effects (N = 6; n = 785; RR = 1.11; 95% CI, 0.6 to 2.04)
• reducing the likelihood of patients reporting side effects (N = 5; n = 615; Random effects RR = 1.12; 95% CI, 0.94 to 1.32).

Evidence statements for moclobemide compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on:

• reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1341; n = 1222; SMD = 0; 95% CI, -0.12 to 0.11)
• increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 5; n = 402; RR = 1; 95% CI, 0.86 to 1.18)
• increasing the likelihood of achieving at least a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 13; n = 2070; RR = 1.02; 95% CI, 0.93 to 1.13).

Similar results were found in sub-analyses by antidepressant class and setting.

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 20; n = 2458; RR = 0.97; 95% CI, 0.85 to 1.11).

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41 Two studies (DUARTE1996 and TANGHE1997) were removed from this analysis to remove heterogeneity from the data set; this did not affect the results.
Similar results were found in sub-analyses by antidepressant class and setting.

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over other antidepressants on reducing the likelihood of leaving treatment due to side effects (N = 18; n = 2292; RR = 0.57; 95% CI, 0.44 to 0.75).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over other antidepressants on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 12; n = 1472; RR = 0.85; 95% CI, 0.79 to 0.92).

Similar results were found in sub-analyses by setting but not by antidepressant class:

There is evidence suggesting that there is no clinically significant difference between moclobemide and SSRIs on reducing the likelihood of patients reporting side effects (N = 6; n = 519; RR = 0.9; 95% CI, 0.79 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 6; n = 660; RR = 0.96; 95% CI, 0.59 to 1.57).

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over TCAs on reducing the likelihood of leaving treatment due to side effects (N = 12; n = 1632; RR = 0.46; 95% CI, 0.34 to 0.64).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over TCAs on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical importance (N = 6; n = 953; RR = 0.83; 95% CI, 0.76 to 0.91).

**Clinical summary**

There is some evidence that moclobemide is more effective than placebo, but insufficient evidence of its tolerability and acceptability. There is evidence that it is equally as effective as other antidepressants (TCAs and SSRIs). Whilst moclobemide is equally as acceptable and tolerable to patients as SSRIs, there is strong evidence that patients receiving moclobemide are less likely to leave treatment early due to side effects than patients receiving TCAs.

**8.5.3 Phenelzine**

**Introduction**

Phenelzine is the best tolerated MAOI. Established side effects include hypotension, drowsiness, dizziness, dry mouth and constipation. It has been associated with hepatotoxicity.

**Studies considered for review**

Twenty-seven studies were found in a search of electronic databases with nine being included and 18 being excluded by the GDG.
Eight studies compared phenelzine with TCAs (DAVIDSON81, DAVIDSON87, GEORGOTAS86, QUITKIN199042, RAFT1981, ROBINSON1983, SWANN1997, VALLEJO87) and one with SSRIs (PANDE1996). These provided efficacy data from up to 634 trial participants and tolerability data from up to 481 participants.

All included studies were published between 1981 and 1997 and were between three and seven weeks long (mean = 5.56 weeks). Participants were described as outpatients in eight studies and as inpatients in the other study (GEORGOTAS86). This study was also the only one in which all participants were 55 years of age or older (mean age 65 years). Studies reported mean doses of between 30 mg and 90 mg of phenelzine. All participants in PANDE1996 and 67% of those in QUITKIN1990 were diagnosed with depression with additional atypical features.

Data were available to compare phenelzine with amitriptyline, desipramine43, imipramine, nortriptyline and fluoxetine.

Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 2; n = 325; RR = 0.66; 95% CI, 0.52 to 0.83).

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 7; n = 634; Random effects SMD = –0.02; 95% CI, –0.33 to 0.28).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and other antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 3; n = 385; Random effects RR = 0.97; 95% CI, 0.55 to 1.70).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and SSRIs on any efficacy measure, or between phenelzine and TCAs on reducing the likelihood of achieving remission by the end of treatment.

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 1; n = 285; RR = 0.66; 95% CI, 0.52 to 0.83).

42 The data from QUITKIN1990 was supplied as raw individual patient data by the authors to the NCCMH review team
43 Not licensed for use in the UK
There is evidence suggesting that there is no clinically significant difference between phenelzine and TCAs on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 6; n = 594; Random effects SMD = –0.07; 95% CI, –0.40 to 0.27).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and other antidepressants on reducing the likelihood of leaving treatment early for any reason and on reducing the likelihood of leaving treatment early due to side effects.

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on reducing the likelihood of patients reporting adverse effects (N = 1; n = 60; RR = 0.97; 95% CI, 0.87 to 1.09).

A sub-analysis by antidepressant class gave similar results.

Clinical summary

There is some evidence suggesting a superior efficacy for response for phenelzine compared with other antidepressants. These findings are probably explained by the high proportion of patients with depression with atypical features in the studies reporting response (71% of patients had depression with atypical features) and remission (56% of patients had depression with atypical features). A separate review of the pharmacological treatment of atypical depression is provided in Section 8.2.5.

There is no difference in mean endpoint scores between the two groups of treatments in patients with major depressive disorder regardless of additional atypical features. This is also evident in comparisons with TCAs alone. Evidence from studies comparing phenelzine with SSRIs was too weak to draw any conclusions.

There is insufficient evidence to draw any conclusions on the comparative tolerability of phenelzine against alternative antidepressants.

8.6 Third-generation antidepressants

This diverse group of antidepressants was marketed after the SSRIs. The aim was to broaden the mechanism of action beyond serotonin in order to improve efficacy without incurring the side effects or toxicity in overdose associated with the TCAs.

8.6.1 Duloxetine

Introduction

Duloxetine is similar to venlafaxine in that it inhibits the re-uptake of both serotonin and noradrenaline, and is a weak inhibitor of dopamine reuptake. Although duloxetine is said to have no affinity for other receptors, it is associated with dry

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44 Although these are classified ‘other antidepressants’ by the BNF, to avoid confusion with the guideline’s use of ‘other antidepressants’ to mean all other antidepressants, the GDG uses the term ‘third-generation antidepressants’ to describe this group of drugs
mouth and constipation (which are anticholinergic side effects), as well as nausea and headache. Duloxetine can also increase blood pressure. It is one of the few antidepressants that has been tested in double-blind, placebo-controlled trials in elderly patients. Duloxetine is available under two brand names from the same manufacturer. One is licensed primarily for depression, and the other for stress urinary incontinence.

Duloxetine has been licensed since the publication of the original guideline.

**Review of clinical evidence**

Duloxetine was licensed for the treatment of depression since the publication of previous guideline. For the present review both published and unpublished double-blind randomised controlled trials were sought which compared duloxetine either with placebo or with another antidepressant. The marketing authorisation holder, Eli Lilly, was also contacted for data. The electronic databases searched for published trials are given in **Table 67**. Details of the search strings used are in appendix 8.

**Table 67: Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological treatments**

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008; January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>Duloxetine, placebo, other antidepressants</td>
</tr>
</tbody>
</table>

In total, 27 acute-phase trials were sourced from searches of electronic databases and from the website of the drug’s manufacturer, Eli Lilly, which included links to the clinical trials website [www.clinicaltrialresults.org](http://www.clinicaltrialresults.org) from where full trial reports were downloaded. Only published data were supplied directly by Eli Lilly. In all, 18 trials (4 unpublished) were included with 9 being excluded (7 unpublished). (One trial is also included in the relevant section on treatment-resistant depression since it re-randomised patients who did not respond to acute phase treatment.) Only data from patients given at least the licensed dose (60 mg) were included in the analyses, apart from in trials which used a variable dose and in trials where comparisons with the licensed dose were possible.

Data were available to compare duloxetine with placebo, with duloxetine at different doses, and with other antidepressants (SSRIs or venlafaxine). In addition, 3 trials continued treatment for those with at least a partial response (> 30% improvement in baseline depression scores). Summary study characteristics of the included studies are in Table 62 with full details in Appendix 17 which also includes details of excluded studies.

**Table 68 Summary study characteristics of studies of duloxetine**

<table>
<thead>
<tr>
<th></th>
<th>Versus placebo</th>
<th>Versus different doses</th>
<th>Versus other antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>12 RCTs (5069)</td>
<td>5 RCTs (1242)</td>
<td>12 RCTs (3367)</td>
</tr>
</tbody>
</table>
### Study IDs

- BRANNAN2005
- BRECHT2007
- DETKE2002
- DETKE2002A
- DETKE2004
- ELI LILLY HMAQ
- ELI LILLY HMAT-A
- DETKE2004*
- ELI LILLY HMAQ**
- DETKE2002
- GOLDSTEIN2004*
- PERAHIA2006B
- WHITMYER2007**
- NIERENBERG2007
- PERAHIA2006B*
- WADE2007

### N/%

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Female N/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>282/65</td>
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<tr>
<td>2</td>
<td>327/74</td>
</tr>
<tr>
<td>3</td>
<td>267/69</td>
</tr>
<tr>
<td>4</td>
<td>245/67</td>
</tr>
<tr>
<td>5</td>
<td>281/73</td>
</tr>
<tr>
<td>6</td>
<td>157/67</td>
</tr>
<tr>
<td>7</td>
<td>174/62</td>
</tr>
<tr>
<td>8</td>
<td>140/64</td>
</tr>
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<td>9</td>
<td>180/62</td>
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<tr>
<td>10</td>
<td>410/65</td>
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<tr>
<td>11</td>
<td>295/70</td>
</tr>
<tr>
<td>12</td>
<td>311/60</td>
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</tbody>
</table>

### Mean Age

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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<tr>
<td>5</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
</tr>
</tbody>
</table>

### Duloxetine Dose

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Duloxetine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60 mg</td>
</tr>
<tr>
<td>2</td>
<td>60 mg</td>
</tr>
<tr>
<td>3</td>
<td>60 mg</td>
</tr>
<tr>
<td>4</td>
<td>60 mg</td>
</tr>
<tr>
<td>5</td>
<td>60 mg, 120 mg</td>
</tr>
<tr>
<td>6</td>
<td>60 mg, 120 mg</td>
</tr>
<tr>
<td>7</td>
<td>60 mg, 120 mg</td>
</tr>
<tr>
<td>8</td>
<td>60 mg, 120 mg</td>
</tr>
<tr>
<td>9</td>
<td>60 mg, 120 mg</td>
</tr>
<tr>
<td>10</td>
<td>60 mg</td>
</tr>
<tr>
<td>11</td>
<td>80 mg, 120 mg</td>
</tr>
<tr>
<td>12</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

### Comparator

- Placebo
- Duloxetine (doses as above)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Duloxetine (doses as above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>paroxetine 20 mg</td>
</tr>
<tr>
<td>2</td>
<td>fluoxetine 20 mg</td>
</tr>
<tr>
<td>3</td>
<td>venlafaxine 150 mg</td>
</tr>
<tr>
<td>4</td>
<td>venlafaxine 150 mg, 75 mg</td>
</tr>
<tr>
<td>5</td>
<td>paroxetine 20 mg</td>
</tr>
<tr>
<td>6</td>
<td>fluoxetine 20 mg</td>
</tr>
<tr>
<td>7</td>
<td>paroxetine 20 mg</td>
</tr>
<tr>
<td>8</td>
<td>escitalopram 10 mg</td>
</tr>
<tr>
<td>9</td>
<td>paroxetine 20 mg</td>
</tr>
<tr>
<td>10</td>
<td>escitalopram 10 mg</td>
</tr>
<tr>
<td>11</td>
<td>paroxetine 20 mg</td>
</tr>
</tbody>
</table>
Duloxetine versus placebo

Although the effect sizes for all 3 efficacy outcomes for duloxetine (dose at least as large as the licensed dose, 60mg) versus placebo were statistically significant and favoured duloxetine, with only that for non-response approaching clinical significance. There were similar effect sizes for duloxetine at different doses when these data were looked at separately, although that for duloxetine at 120 mg versus placebo was larger than those for lower does (WMD = -2.57 (-3.77 to -1.37) thought this is still a small difference. The data for duloxetine at different doses can be seen in the full profile and forest plots (Appendix 19).

Two trials specifically examined depression-related pain using the self-report BPI scale. There was an average reduction of three-quarters of a point (on an 11-point Likert scale) for the ‘average pain in last 24 hours’ item.

There was little difference between the number of people receiving duloxetine who left treatment early for any reason and those receiving placebo on this measure. However, of those leaving treatment early, twice as many taking duloxetine as those taking placebo left specifically because of side effects whilst twice as many taking placebo left because of lack of efficacy. The numbers reporting side effects were high in both groups, with more amongst those taking duloxetine. Those taking duloxetine also experienced a small average weight loss compared with those on placebo, although these data were of low quality largely because of heterogeneity. The quality of the evidence was moderate or low, largely because of the selective population included in the studies.

See Table 69 for the summary evidence profile and Appendix 16 for the full profile.
Table 69 Summary evidence profile for duloxetine versus placebo (acute phase)

<table>
<thead>
<tr>
<th>Clinician-rated effect size</th>
<th>Mean depression change scores at endpoint</th>
<th>Non-response</th>
<th>Non-remission</th>
<th>Depression-related pain (average pain in last 24 hours)</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Leaving treatment early due to lack of efficacy</th>
<th>N reporting side effects</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMD - 1.9 (-2.44 to -1.35)</td>
<td>RR 0.78 (0.74 to 0.83) (51.6% vs 67.3%)</td>
<td>RR 0.83 (0.79 to 0.87) (62% vs 75.2%)</td>
<td>WMD - 0.74 (-1.13 to -0.34)</td>
<td>RR 1.02 (0.91 to 1.15) (26.9% vs 28.4%)</td>
<td>RR 2.22 (1.66 to 2.95) (10% vs 5%)</td>
<td>RR 2.22 (1.66 to 2.95) (4% vs 8%)</td>
<td>RR 1.38 (1.12 to 1.24) (66% vs 51%)</td>
<td>RR 0.69 (1 to 0.38)</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>K=10; n=2249</td>
<td>K=12; n=3078</td>
<td>K=11; n=2789</td>
<td>K=2; n=583</td>
<td>K=11; n=2695</td>
<td>K=11; n=2191</td>
<td>K=6; n=2173</td>
<td>K=10; n=2647</td>
<td>K=8; n=1663</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Dul 01.02*</td>
<td>Dul 01.04*</td>
<td>Dul 01.06*</td>
<td>Dul 01.09</td>
<td>Dul 02.02</td>
<td>Dul 02.04</td>
<td>Dul 02.07</td>
<td>Dul 02.09</td>
<td>Dul 02.11</td>
</tr>
</tbody>
</table>

* The full data for these outcomes for different doses are shown in Dul 01.01, Dul 01.03 and Dul 01.05 respectively.

Three studies continued patients who achieved at least partial response to acute-phase treatment (defined as >= 30% decrease in baseline HAMD scores) (DETKE2004; ELI LILLY HMAQ; PERAHIA2006B), although there were no extractable data in ELI LILLY HMAQ. There was no difference in depression symptoms or on acceptability and tolerability measures between duloxetine at either 80 mg or 120 mg and placebo.

Table 70 Summary evidence profile for duloxetine vs placebo (continuation phase for partial responders)

<table>
<thead>
<tr>
<th>Mean depression change scores at endpoint</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Leaving treatment early due to lack of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>WMD -1 (-2.5 to 0.5)</td>
<td>RR 0.94 (0.81 to 1.08) (82% vs 87%)</td>
<td>RR 0.96 (0.34 to 2.73) (5% vs 5%)</td>
</tr>
<tr>
<td>Clinician-rated effect size</td>
<td>Quality of evidence</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>K=1; n=140</td>
<td>Number of studies/participants</td>
<td>Dul 07.01</td>
<td>Dul 07.02</td>
</tr>
<tr>
<td>Forest plot</td>
<td>120 mg</td>
<td>WMD -0.2 (-1.78 to 1.38)</td>
<td>RR 0.88 (0.75 to 1.02) (77% vs 87%)</td>
</tr>
<tr>
<td>Clinician-rated effect size</td>
<td>Quality of evidence</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>K=1; n=142</td>
<td>Number of studies/participants</td>
<td>Dul 07.02</td>
<td>Dul 07.03</td>
</tr>
<tr>
<td>Forest plot</td>
<td>120 mg</td>
<td>WMD -0.2 (-1.78 to 1.38)</td>
<td>RR 0.88 (0.75 to 1.02) (77% vs 87%)</td>
</tr>
</tbody>
</table>
### Duloxetine comparing different doses

Data were available to compare duloxetine at 40 mg (less than the licensed dose) with 80 mg, 30 mg with 60 mg, and 80 mg with 120 mg. There were no statistically or clinically significant differences between the doses on either efficacy or acceptability and tolerability outcomes, although there were few trials. See Error! Reference source not found. for the summary evidence profile and Appendix 16 for the full profile.

#### Table 71 Summary evidence profile for duloxetine comparing different doses (acute phase)

<table>
<thead>
<tr>
<th>Details</th>
<th>Mean depression change scores at endpoint</th>
<th>Non-response</th>
<th>Non-remission</th>
<th>Leaving treatment early</th>
<th>Leavin treatment early due to side effects</th>
<th>Leaving treatment early due to lack of efficacy</th>
<th>N reporting side effects</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg vs 80 mg</td>
<td>WMD 0.58 (-0.87 to 2.03)</td>
<td>RR 1.1 (0.84 to 1.45)</td>
<td>RR 1.15 (0.92 to 1.44)</td>
<td>RR 0.73 (0.57 to 0.95)</td>
<td>RR 0.77 (0.45 to 1.31)</td>
<td>No data</td>
<td>RR 0.99 (0.97 to 1.07)</td>
<td>WMD -0.19 (-0.69 to 0.31)</td>
</tr>
<tr>
<td>30 mg vs 60 mg</td>
<td>WMD 0.83 (-0.43 to 2.09)</td>
<td>RR 0.96 (0.84 to 1.08)</td>
<td>RR 0.97 (0.84 to 1.11)</td>
<td>RR 0.82 (0.62 to 1.07)</td>
<td>RR 0.47 (0.24 to 0.91)</td>
<td>RR 0.98 (0.25 to 3.87)</td>
<td>RR 0.99 (0.9 to 1.1)</td>
<td>WMD -0.35 (-1 to 0.3)</td>
</tr>
<tr>
<td>80 mg vs 120 mg</td>
<td>WMD 0.7 (-0.28 to 1.68)</td>
<td>RR 1.13 (0.85 to 1.5)</td>
<td>RR 1.02 (0.85 to 1.22)</td>
<td>RR 1.15 (0.65 to 2.03)</td>
<td>RR 1.2 (0.44 to 5.44)</td>
<td>RR 1.56 (0.45 to 49% vs)</td>
<td>RR 1.12 (0.9 to 1.4)</td>
<td>WMD -0.08 (-0.69 to 0.31)</td>
</tr>
</tbody>
</table>
One study comparing duloxetine at different doses included a continuation phase for those who achieved at least partial response to acute-phase treatment (defined as >= 30% decrease in baseline HAMD scores) (PERAHIA2006B). This showed no difference between the doses. The quality of the evidence was low or very low. See Table 72.

Table 72 Summary evidence profile for duloxetine comparing different doses (continuation phase for partial responders)

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Mean depression change scores at endpoint*</th>
<th>Leaving treatment early</th>
<th>Leaving treatment early due to side effects</th>
<th>Leaving treatment early due to lack of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>80 mg vs 120 mg</td>
<td>Clinician-rated effect size</td>
<td>RR 0.76 (0.13 to 4.42) (3% vs 4%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=150</td>
<td>RR 0.07 (0.91 to 1.26) (82% vs 77%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Dul 08.01</td>
<td>RR 0.07 (0.91 to 1.26) (82% vs 77%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
</tr>
<tr>
<td></td>
<td>Dul 08.02</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
<td>RR 0.29 (0.03 to 2.49) (1% vs 5%)</td>
</tr>
</tbody>
</table>

*D change from end of acute phase

Duloxetine versus other antidepressants

Data were available to compare duloxetine with paroxetine, fluoxetine, escitalopram and venlafaxine. There was no difference between duloxetine and other antidepressants, other than venlafaxine which was more effective on mean change scores at endpoint (although the effect size was small and not quite statistically significant). Duloxetine was less acceptable to patients as measured by the number leaving treatment early, and more people taking duloxetine left specifically because of adverse reactions. However, there was no difference between duloxetine and other antidepressants on numbers leaving treatment early because of lack of efficacy, or on...
the number of people reporting side effects or on weight change. The quality of the evidence was moderate, low or very low, largely because of the selective population included in the studies.

See Error! Reference source not found. for the summary evidence profile and Appendix 16 for the full profile.

Table 73 Summary evidence profile for duloxetine versus other antidepressants (acute phase)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Paroxetine</th>
<th>Fluoxetine</th>
<th>Escitalopram</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean depression change scores at endpoint</td>
<td>WMD 0.19 (-0.44 to 0.81)</td>
<td>WMD -0.2 (-1.14 to 0.74)</td>
<td>WMD -1.1 (-3.03 to 0.83)</td>
<td>WMD 0.66 (-0.61 to 1.93)</td>
<td>WMD 1.06 (-0.02 to 2.14)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=12; n=3145</td>
<td>K=5; n=1292</td>
<td>K=2; n=217</td>
<td>K=3; n=1096</td>
<td>K=2; n=648</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Dul 05.01</td>
<td>Dul 05.01</td>
<td>Dul 05.01</td>
<td>Dul 05.01</td>
<td>Dul 05.01</td>
</tr>
<tr>
<td>Non-response</td>
<td>RR 1.05 (0.95 to 1.17) (49% vs 46%)</td>
<td>RR 1.01 (0.81 to 1.26) (44% vs 43%)</td>
<td>RR 0.99 (0.72 to 1.36) (53% vs 53%)</td>
<td>RR 1.04 (0.94 to 1.16) (59% vs 57%)</td>
<td>RR 1.23 (0.92 to 1.64) (40% vs 32%)</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>K=12; n=2008</td>
<td>K=5; n=1200</td>
<td>K=2; n=222</td>
<td>K=3; n=619</td>
<td>K=2; n=667</td>
<td></td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 1.02 (0.94 to 1.11) (58% vs 56%)</td>
<td>RR 0.99 (0.9 to 1.10) (56% vs 56%)</td>
<td>RR 1.21 (0.56 to 2.61) (61% vs 52%)</td>
<td>RR 1.06 (0.89 to 1.26) (61% vs 60%)</td>
<td>RR 1.06 (0.88 to 1.27) (54% vs 51%)</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>Very low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>K=12; n=3208</td>
<td>K=5; n=1200</td>
<td>K=2; n=222</td>
<td>K=3; n=1069</td>
<td>K=2; n=667</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 1.21 (1.01 to 1.45) (32% vs 24%)</td>
<td>RR 1.21 (1.01 to 1.45) (29% vs 24%)</td>
<td>RR 0.87 (0.59 to 1.27) (32% vs 37%)</td>
<td>RR 1.64 (0.97 to 2.78) (32% vs 21%)</td>
<td>RR 1.37 (1.09 to 1.72) (35% vs 26%)</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>Very low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>K=11; n=2894</td>
<td>K=5; n=1200</td>
<td>K=2; n=222</td>
<td>K=3; n=825</td>
<td>K=2; n=667</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 1.54 (1.2 to 1.99) (10% vs 7%)</td>
<td>RR 1.32 (0.9 to 1.93) (9% vs 7%)</td>
<td>RR 3.3 (0.42 to 25.74) (10% vs 3%)</td>
<td>RR 2.62 (0.67 to 10.3) (9% vs 4%)</td>
<td>RR 1.58 (1.04 to 2.42) (15% vs 9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Low</td>
<td>Very low</td>
<td>Very low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>K=10; n=2795</td>
<td>K=5; n=1200</td>
<td>K=1; n=103</td>
<td>K=2; n=825</td>
<td>K=2; n=667</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early due to lack of efficacy</td>
<td>RR 1.58 (1.04 to 2.42) (3% vs 3%)</td>
<td>RR 2.29 (0.6 to 8.78) (2% vs 1%)</td>
<td>No Data</td>
<td>RR 0.88 (0.51 to 1.53) (5% vs 6%)</td>
<td>RR 1.24 (0.52 to 2.95) (3% vs 3%)</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>K=7; n=2341</td>
<td>K=3; n=846</td>
<td>K=2; n=825</td>
<td>K=2; n=667</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dul 06.03</td>
<td>Dul 06.03</td>
<td>Dul 06.03</td>
<td>Dul 06.03</td>
<td>Dul 06.03</td>
</tr>
</tbody>
</table>
Two studies comparing duloxetine with other antidepressants included a continuation phase for those who achieved at least partial response to acute-phase treatment (defined as >= 30% decrease in baseline HAMD scores) (DETKE2004; PERAHIA2006B). Both studies compared duloxetine with paroxetine. Only one outcome was reported by both studies. This showed no difference between the doses. The quality of the evidence was low. See Table 74.

Table 74 Summary evidence profile for duloxetine versus other antidepressants (continuation phase for partial responders)

<table>
<thead>
<tr>
<th>N reporting side effects</th>
<th>RR 1.02 (0.98 to 1.07) (79% vs 76%)</th>
<th>RR 1.07 (0.99 to 1.15) (71% vs 65%)</th>
<th>RR 0.97 (0.85 to 1.12) (89% vs 91%)</th>
<th>RR 1.02 (0.96 to 1.09) (88% vs 87%)</th>
<th>RR 0.99 (0.88 to 1.11) (86% vs 87%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>K=9; n=2517</td>
<td>K=5; n=1200</td>
<td>K=1; n=103</td>
<td>K=1; n=547</td>
<td>K=2; n=667</td>
<td></td>
</tr>
<tr>
<td>Dul 06.04</td>
<td>Dul 06.04</td>
<td>Dul 06.04</td>
<td>Dul 06.04</td>
<td>Dul 06.04</td>
<td></td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>WMD 0 (-0.03 to 0.03)</td>
<td>WMD 0 (-0.03 to 0.03)</td>
<td>WMD -0.01 (-0.74 to 0.72)</td>
<td>WMD 0.06 (-1.08 to 1.2)</td>
<td>WMD 0.39 (-0.09 to 0.86)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>K=7; n=2058</td>
<td>K=3; n=834</td>
<td>K=1; n=68</td>
<td>K=1; n=547</td>
<td>K=2; n=579</td>
<td></td>
</tr>
<tr>
<td>Dul 06.05</td>
<td>Dul 06.05</td>
<td>Dul 06.05</td>
<td>Dul 06.05</td>
<td>Dul 06.05</td>
<td></td>
</tr>
</tbody>
</table>

* change from end of acute phase
One study comparing duloxetine with other antidepressants included a continuation phase for all those entering the study regardless of response during the acute phase of the study (WADE2007). This compared duloxetine with escitalopram. There was no difference in outcomes other than in patients leaving treatment early specifically because of side effects which favoured escitalopram. See Table 75.

**Table 75 Summary evidence profile for duloxetine versus other antidepressants (continuation phase for all)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean depression change scores at endpoint</strong></td>
<td>WMD 1.34 (-0.25 to 2.93)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=187</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.01</td>
</tr>
<tr>
<td><strong>Non-response</strong></td>
<td>RR 1.16 (0.82 to 1.65) (33% vs 28%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=194</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.02</td>
</tr>
<tr>
<td><strong>Non-remission</strong></td>
<td>RR 1.32 (0.86 to 2.02) (26% vs 20%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=194</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.03</td>
</tr>
<tr>
<td><strong>Leaving treatment early</strong></td>
<td>RR 1.13 (0.74 to 1.72) (25% vs 22%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=194</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.04</td>
</tr>
<tr>
<td><strong>Leaving treatment early due to side effects</strong></td>
<td>RR 1.89 (1.01 to 3.54) (17% vs 9%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=194</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.05</td>
</tr>
<tr>
<td><strong>Leaving treatment early due to lack of efficacy</strong></td>
<td>RR 0.27 (0.06 to 1.28) (1% vs 5%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=194</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Dul 11.06</td>
</tr>
</tbody>
</table>

* change from end of acute phase

Clinical summary for duloxetine
There does not seem to be any advantage for duloxetine over other antidepressants. The difference in endpoint depression scores compared with placebo is small, and there does not seem to be a significant reduction in pain associated with depression in those trials which reported this measure (WMD = -0.74 (-1.13 to -0.34) i.e., ¼ of a point.
difference between the groups). There was no advantage in continuing treatment for partial responders. There appears to be no advantage for doses of duloxetine above the licensed dose of 60 mg, although there are few trials comparing higher doses, and no trials comparing 60 mg with higher doses.

Overall the quality of the evidence was downgraded because of the highly selective patient populations in the trials, with evidence for some outcome-comparison combinations being downgraded further largely because of low numbers of trials. Since duloxetine is still in patent it is acquisition costs are relatively high compared to antidepressants available in generic form. See section 8.8.2 below.

### 8.6.2 Mirtazapine

#### Introduction

Mirtazapine is a noradrenaline and specific serotonin antidepressant (NaSSA) which blocks presynaptic alpha 2 receptors on both NA and 5HT neurones and also blocks postsynaptic 5HT2 (less sexual dysfunction but possible worsening of the symptoms of obsessive compulsive disorder) and 5HT3 (less nausea) receptors. It can cause weight gain and sedation.

#### Studies considered for review

Twenty-five studies were found in a search of electronic databases and details of a study in press were provided by Organon Laboratories Ltd (WADE2003). Fifteen were included (although the efficacy data from one of these, WADE2003, were excluded because more than 50% of participants left treatment early) and 11 excluded by the GDG.


All included studies were published between 1990 and 2003 and were between five and 24 weeks long (mode = six weeks). In five studies participants were described as inpatients, in six as outpatients, one was from primary care and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (SCHATZBERG2002) all participants were 65 years of age or older. Studies reported mean doses of between 22 mg and 76.2 mg of mirtazapine.

Data were available to compare mirtazapine with amitriptyline, clomipramine, doxepin, imipramine, trazodone, citalopram, fluoxetine, paroxetine and venlafaxine.

#### Evidence statements

Effect of treatment on efficacy outcomes
There is no difference between the efficacy of mirtazapine and other antidepressants for which comparisons were available:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N = 1445; n = 2440; RR = 0.92; 95% CI, 0.84 to 1.01)
- reducing depression symptoms by the end of treatment as measured by the HRSD or the MADRS (N = 14; n = 2314; SMD = -0.03; 95% CI, -0.11 to 0.05).

There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over other antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N = 4; n = 819; RR = 0.91; 95% CI, 0.83 to 0.99).

Similar results were found in sub-analyses by antidepressant class, other than for SSRIs:

- There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over SSRIs on reducing depression symptoms by the end of treatment, but the size of this difference is unlikely to be of clinical significance (N = 4; n = 888; SMD = -0.13; 95% CI, -0.27 to 0.00).

Effect of setting on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on:

- reducing depression symptoms by the end of treatment in inpatients as measured by the HRSD or MADRS (N = 5; n = 854; Random effects SMD = 0.05; 95% CI, -0.15 to 0.24)
- increasing the likelihood of achieving remission in outpatients by the end of treatment (N = 2; n = 387; RR = 0.93; 95% CI, 0.81 to 1.05)
- reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or the MADRS (N = 6; n = 915; SMD = -0.1; 95% CI, -0.23 to 0.03).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring mirtazapine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N = 6; n = 957; RR = 0.86; 95% CI, 0.73 to 1).

In inpatients there is insufficient evidence to determine whether there is a clinically significant difference between mirtazapine and other antidepressants on increasing the

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45 One study (WADE2003) was removed because >50% of participants left the study early
likelihood of achieving a 50% reduction in depression symptoms or on achieving remission.

No data were available to determine efficacy in patients in primary care.

Acceptability and tolerability of treatment

Mirtazapine appears to be as acceptable to patients as other antidepressants, except that fewer patients leave treatment early due to side effects:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 15; n = 2637; RR = 0.88; 95% CI, 0.78 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring mirtazapine over other antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N = 15; n = 2637; RR = 0.69; 95% CI, 0.55 to 0.87).

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on reducing the likelihood of patients reporting side effects (N = 6; n = 1253; RR = 0.99; 95% CI, 0.93 to 1.05).

Findings were similar in sub-analyses by setting and class of antidepressant.

Clinical summary

There is no difference between mirtazapine and other antidepressants on any efficacy measure, although in terms of achieving remission mirtazapine appears to have a statistical though not clinical advantage. In addition, mirtazapine has a statistical advantage over SSRIs in terms of reducing depression symptoms, but the difference is not clinically important.

However, there is strong evidence that patients taking mirtazapine are less likely to leave treatment early because of side effects, although this is not the case for patients reporting side effects or leaving treatment early for any reason.

Therefore, although mirtazapine is as effective as other antidepressants, it may have an advantage in terms of reducing side effects likely to lead to patients leaving treatment early.

8.6.3 Reboxetine

Introduction

Reboxetine is a relatively selective noradrenergic reuptake inhibitor. Side effects include insomnia, sweating, dizziness, dry mouth and constipation (Holm & Spencer, 1999). It may also lower serum potassium (ABPI, 2003). It is not licensed for use in older adults.

Studies considered for review
Eight studies were found in a search of electronic databases, with six (ANDREOLI2002, BAN1998, BERZEWSKI1997, KATONA1999, MASSAN1999, VERSIANI2000B) being included and two excluded.

Three studies compare reboxetine with placebo (ANDREOLI2002, BAN1998, VERSIANI2000B), three with TCAs (BAN1998, BERZEWSKI1997, KATONA1999) and two with SSRIs (ANDREOLI2002, MASSAN1999). These provided efficacy and tolerability data from up to 1068 trial participants.

All included studies were published between 1997 and 2002 and were between four and eight weeks long (mean = 6.66 weeks). In two studies participants were described as inpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (KATONA1999) all participants were aged 65 years and over. Apart from this study where participants received a dose of 6 mg, doses were between 8 mg and 10 mg of reboxetine.

Data were available to compare reboxetine with desipramine, imipramine, fluoxetine and placebo.

Evidence statements for reboxetine compared with placebo

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; n = 479; RR = 0.61; 95% CI, 0.51 to 0.73).

There is some evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on increasing the likelihood of achieving remission by the end of treatment (N = 1; n = 254; RR = 0.71; 95% CI, 0.59 to 0.87).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and placebo on any measure of acceptability or tolerability.

Evidence statements for reboxetine compared with other antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 5; n = 1068; RR = 0.87; 95% CI, 0.76 to 1.01)
- increasing the likelihood of achieving remission by the end of treatment (N = 4; n = 895; RR = 0.96; 95% CI, 0.84 to 1.09)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 3; n = 618; SMD = –0.09; 95% CI, –0.24 to 0.07).
Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on increasing the likelihood of patients reporting side effects (N = 4; n = 895; RR = 0.98; 95% CI, 0.9 to 1.06).

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and other antidepressants on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

Clinical summary

Reboxetine is superior to placebo and as effective as other antidepressants in the treatment of depression. There is insufficient evidence to comment on reboxetine’s tolerability compared with placebo or alternative antidepressants.

8.6.4 Venlafaxine

Introduction

Venlafaxine was the first of the new generation dual-action antidepressants. It inhibits the reuptake of both serotonin and noradrenaline in the same way as the TCAs. At the standard dose of 75 mg it is an SSRI with dual action emerging at doses of 150 mg and above. At higher doses it also inhibits dopamine reuptake.

Venlafaxine has a broad range of side effects similar to those of the TCAs and SSRIs. It can increase blood pressure at higher doses, is associated with a high incidence of discontinuation symptoms (see Section 8.2.8) and is more toxic than the SSRIs in overdose (see Section 8.2.9).

Studies considered for review

The GDG used an existing review (Smith et al., 2002) as the basis of this review. The original review included 31 studies of which nine did not meet the inclusion criteria set by the GDG. Fifteen additional studies were identified from new searches, and four from another review (Einarson et al., 1999). None of these studies met the inclusion criteria set by the GDG. Two studies were sourced from other reviews in this chapter, both of which met inclusion criteria, and details of ten additional unpublished studies were provided by Wyeth Laboratories, five of which met inclusion criteria. Thus a total of 33 studies are excluded from this review with 29 trials being included (014NEMEROFF, 015SCHATZBERG, 102TSAL, 332RICKELS, 349WYETH, 428CASABONA, 626KORNAAT, 671LENOX-SMITH, ALVES1999, BENKERT96, BIELSKII2003, CLERC1994, COSTA1998, CUN’HAM94, DIERICK96, GUELF2001, HACKETT96, LECRUBIE97, MAHAPATRA97, MCPARTLIN98, MONTGOMERY2002, POIRIER99, RUDOLPH99, SAMUELIAN98, SCHWEIZER94, SIL’STONE99, SMERALDI98, TYLEE1997, TZANAKAKI00). Together these provide tolerability data from up to 5063 participants and efficacy data from up to 4198 participants.

All included studies were published between 1994 and 2003 and were between four and 13 weeks long (mean = 8.03 weeks). Three studies were of inpatients, 16 of
outpatients and four were undertaken in primary care. In the remaining six, it was either not clear from where participants were sourced or they were from mixed sources. In three (MAHAPATRA97, 015SCHATZBERG, SMERLADI98) participants were aged 64 years and over. Mean HRSD scores at baseline ranged from 22.4 to 30.6 (various HRSD versions).

Data were available to compare venlafaxine with clomipramine, dothiepin/dosulepin, imipramine, trazodone, citalopram, escitalopram, fluoxetine, paroxetine and mirtazapine.

Studies reported mean doses equivalent to at least 100 mg of amitriptyline. Eight studies (102TSAI, 428CASABONA, 671LENOX-SMITH, BIELSKI2003, HACKETT96, MONTGOMERY2002, RUDOLPH1999, SIL’STONE99) used ‘extended release’ (XR) venlafaxine and the remainder ‘immediate release’ (IR) venlafaxine. Doses ranged from 75 mg to 375 mg. A sub-analysis was performed by dose of venlafaxine, with studies achieving a maximum dose of no more than 150 mg classified low dose (102TSAI, 349WYETH, 428CASABONA, ALVES1999, COSTA1998, DIERICK96, HACKETT96, LECRUUIBE97, MAHAPATRA97, MCPARTLIN98, MONTGOMERY2002, SAMUELIAN98, SMERALDI98, TYLEE1997) and those achieving a minimum dose of no less than 150 mg classified high dose (BENKERT96, BIELSKI2003, CLERC1994, GUELFI2001, POIRIER99, 332RICKELS, TZANAKAKI00). In addition, studies with a dose of 75 mg were analysed separately (102TSAI, 428CASABONA, MCPARTLIN98, TYLEE1997). Some participants in one study, GUELFI2001, received the comparator treatment (mirtazapine) at a dose higher than BNF limits. Where this gave heterogeneity, sub-analyses were performed removing this study. Results are presented only where clinically significant differences were found.

Evidence statements

Effect of treatment on efficacy

Venlafaxine is no more effective in treating depression than other antidepressants:

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 23; n = 4198; Random effects RR = 0.92; 95% CI, 0.83 to 1.02)
- increasing the likelihood of achieving remission as measured by the HRSD (N = 20; n = 3849; RR = 0.96; 95% CI, 0.91 to 1.01).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over other antidepressants on reducing depression symptoms, but the size of this difference is unlikely to be of clinical significance (N = 20; n = 3637; SMD = -0.09; 95% CI, -0.15 to -0.02).

Similar results were found in sub-analyses by class of antidepressant:

There is evidence to suggest that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving:
• a 50% reduction in depression symptoms (N = 16; n = 3268; RR = 0.92; 95% CI, 0.84 to 1.005)
• remission (N = 19; n = 3692; RR = 0.95; 95% CI, 0.9 to 1.002).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over SSRIs on reducing depression symptoms by the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 13; n = 2741; SMD = –0.10; 95% CI, –0.17 to –0.02).

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and TCAs on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 6; n = 773; Random effects RR = 0.91; 95% CI, 0.71 to 1.17).

There is evidence suggesting that there is no clinically significant difference between venlafaxine and TCAs on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 6; n = 744; SMD = –0.12; 95% CI, –0.27 to 0.02).

Effect of setting on treatment efficacy

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine and mirtazapine.

Inpatients

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N = 3; n = 383; Random effects SMD = –0.04; 95% CI, –0.46 to 0.38).

There is insufficient evidence to determine whether there is a clinically significant difference between venlafaxine and other antidepressants on either increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 3; n = 392; Random effects RR = 1.04; 95% CI, 0.71 to 1.53) or on increasing the likelihood of achieving remission (N = 2; n = 225; Random effects RR = 0.85; 95% CI, 0.45 to 1.62).

However, compared with SSRIs, venlafaxine is more effective in inpatients:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over SSRIs on:

• reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N = 1; n = 67; SMD = –0.58; 95% CI, –1.07 to –0.09)
• increasing the likelihood of achieving remission in inpatients as measured by the HRSD (N = 1; n = 68; RR = 0.60; 95% CI, 0.39 to 0.92).

Outpatients

Data from studies of venlafaxine in outpatients were available to make comparisons with imipramine, clomipramine, fluoxetine and paroxetine.
There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms in outpatients as measured by the HRSD (N = 11; n = 2023; RR = 0.83; 95% CI, 0.74 to 0.93).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over other antidepressants on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 9; n = 1804; SMD = –0.17; 95% CI, –0.26 to –0.08).

Results were similar against TCAs alone. However, when venlafaxine was compared with SSRIs there is evidence suggesting that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving remission in outpatients (N = 12; n = 2199; RR = 0.95; 95% CI, 0.89 to 1.02).

In outpatients, there is evidence suggesting that there are statistically significant differences favouring venlafaxine over SSRIs on the following outcomes, but the size of these differences is unlikely to be of clinical significance on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment (N = 9; n = 1775; RR = 0.85; 95% CI, 0.75 to 0.96)
- reducing depression symptoms in outpatients by the end of treatment (N = 7; n = 1572; SMD = –0.15; 95% CI, –0.25 to –0.05).

Primary care

Data were available to compare venlafaxine against imipramine, paroxetine and fluoxetine in primary care.

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 3; n = 824; SMD = –0.07; 95% CI, –0.21 to 0.06).

There is evidence suggesting that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving remission (N = 3; n = 995; RR = 0.98; 95% CI, 0.88 to 1.11).

Effect of dose on treatment efficacy

Venlafaxine at 75 mg

Data were available to compare venlafaxine at 75 mg with fluoxetine and paroxetine.

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (75 mg) and SSRIs on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 4; n = 882; Random effects RR = 0.87; 95% CI, 0.6 to 1.26).
There is evidence to suggest that there is no clinically significant difference between venlafaxine (75 mg) and SSRIs on:

- increasing the likelihood of patients achieving remission as measured by the HRSD or MADRS (N = 4; n = 882; RR = 0.98; 95% CI, 0.88 to 1.09)
- reducing depression symptoms as measured by the HRSD at the end of treatment (N = 3; n = 792; SMD = -0.08; 95% CI, -0.21 to 0.06).

Low-dose venlafaxine (mean ≤ 150 mg)

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (≤ 150 mg) and other antidepressants on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 12; n = 2418; Random effects RR = 0.86; 95% CI, 0.72 to 1.02).

There is evidence suggesting that there is no clinically significant difference between venlafaxine (≤ 150 mg) and other antidepressants on increasing the likelihood of achieving remission (N = 9; n = 2125; RR = 0.98; 95% CI, 0.9 to 1.06).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine (≤ 150 mg) over other antidepressants on reducing depression symptoms as measured by the HRSD or MADRS at the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 11; n = 2256; SMD = -0.11; 95% CI, -0.19 to -0.03).

Results were similar in sub-analyses by antidepressant class.

High-dose venlafaxine (mean ≥ 150 mg)

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (≥ 150 mg) and other antidepressants on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 6; n = 822; Random effects RR = 1; 95% CI, 0.78 to 1.28).

There is evidence suggesting that there is no clinically significant difference between venlafaxine (≥ 150 mg) and other antidepressants:

- on reducing depression symptoms (N = 6; n = 807; Random effects SMD = 0.03; 95% CI, -0.18 to 0.23)
- on increasing the likelihood of achieving remission (N = 6; n = 706; Random effects RR = 0.94; 95% CI, 0.79 to 1.12).

Results were similar in sub-analyses by antidepressant class.

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- Reducing the likelihood of leaving treatment early for any reason (N = 23; n = 4196; RR = 0.98; 95% CI, 0.88 to 1.08)
• Reducing the likelihood of patients reporting adverse events (N = 21; n = 3757; RR = 1.01; 95% CI, 0.97 to 1.05).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over venlafaxine on reducing the likelihood of patients leaving treatment early due to side effects (N = 27; n = 5063; RR = 1.21; 95% CI, 1.04 to 1.41).

In sub-analyses by antidepressant class, results were similar for venlafaxine compared with SSRIs, except for fluoxetine:

There is evidence suggesting that there is a statistically significant difference favouring fluoxetine over venlafaxine on reducing the likelihood of patients reporting side effects, but the size of this difference is unlikely to be of clinical significance (N = 10; n = 1871; RR = 1.06; 95% CI, 1 to 1.11).

Acceptability and tolerability of treatment by setting

Inpatients

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine and mirtazapine. Heterogeneity was a problem in the meta-analysis assessing the tolerability of venlafaxine against all antidepressants in inpatients. This was because in the study comparing venlafaxine with mirtazapine, fewer participants taking mirtazapine left the study early compared with those taking venlafaxine, whereas this was not the case in other studies. Therefore, the result against TCAs and SSRIs only were considered:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over TCAs and SSRIs on reducing the likelihood of inpatients leaving treatment early (N = 2; n = 235; RR = 0.61; 95% CI, 0.41 to 0.92).

Outpatients

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

• reducing the likelihood of outpatients leaving treatment early for any reason (N = 11; n = 2021; RR = 0.95; 95% CI, 0.82 to 1.1)
• reducing the likelihood of outpatients reporting side effects (N = 10; n = 1736; RR = 1.03; 95% CI, 0.98 to 1.09).

When compared with SSRIs:

There is some evidence suggesting that there is a clinically significant difference favouring SSRIs over venlafaxine on reducing the likelihood of outpatients leaving treatment early due to side effects (N = 11; n = 2085; RR = 1.48; 95% CI, 1.16 to 1.90).

Primary care
There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 4; n = 1148; RR = 0.94; 95% CI, 0.77 to 1.15)
- reducing the likelihood of patients reporting adverse events (N = 3; n = 787; RR = 1.08; 95% CI, 0.9995 to 1.16).

Acceptability and tolerability of treatment by dose
Venlafaxine at 75 mg

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (75 mg) and SSRIs on:

- reducing the likelihood of patients leaving treatment early (N = 3; n = 768; RR = 0.93; 95% CI, 0.75 to 1.16)
- reducing the likelihood of patients leaving treatment early due to side effects (N = 3; n = 768; Random effects RR = 1.07; 95% CI, 0.68 to 1.7)
- reducing the likelihood of patients reporting side effects (N = 3; n = 521; RR = 1.12; 95% CI, 0.996 to 1.25).

Low-dose venlafaxine (≤ 150 mg)

There is evidence suggesting that there is no clinically significant difference between low-dose venlafaxine and other antidepressants on reducing the likelihood of leaving treatment early (N = 12; n = 2471; RR = 1.04; 95% CI, 0.91 to 1.19).

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over low-dose venlafaxine on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 12; n = 2224; RR = 1.06; 95% CI, 1.001 to 1.12).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over venlafaxine (<150 mg) on reducing the likelihood of patients leaving treatment early due to side effects (N = 12; n = 2471; RR = 1.25; 95% CI, 1.002 to 1.55).

In sub-analyses by class of antidepressant, results were similar except that:

There is strong evidence that there is a clinically significant difference favouring fluoxetine over low-dose venlafaxine on reducing the likelihood of leaving treatment early due to side effects (N = 5; n = 1190; RR = 1.61; 95% CI, 1.15 to 2.24).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose venlafaxine and TCAs on reducing the likelihood of leaving treatment early due to side effects.

High-dose venlafaxine (≥ 150 mg)

There is insufficient evidence to determine whether there is a clinically significant difference between high-dose venlafaxine and other antidepressants on reducing the
likelihood of leaving treatment early (N = 6; n = 822; Random effects RR = 1; 95% CI, 0.7 to 1.41) or on reducing the likelihood of leaving treatment early due to side effects (N = 7; n = 873; Random effects RR = 1.48; 95% CI, 0.71 to 3.05).

There is evidence suggesting that there is no clinically significant difference between high-dose venlafaxine and other antidepressants on reducing the likelihood of patients reporting side effects (N = 6; n = 674; RR = 0.95; 95% CI, 0.85 to 1.05).

Clinical summary

There are no clinically significant differences between venlafaxine (at any dose) and other antidepressants on any efficacy outcome. This was also the case for most acceptability and tolerability outcomes. However, there is some evidence that patients taking venlafaxine are more likely to leave treatment early due to side effects, particularly when low-dose (≤ 150 mg) venlafaxine is compared with fluoxetine.

Results were similar in sub-analyses by setting, other than for inpatients, with those taking venlafaxine being less likely to stop treatment early compared with TCAs and SSRIs. In addition, one small study of inpatients found that venlafaxine was superior to SSRIs on efficacy. In outpatients, there was some evidence for increased efficacy compared with other antidepressants, but only on response.

8.7 **St John’s wort**

Introduction

St John’s wort, an extract of the plant Hypericum perforatum, has been used for centuries for medicinal purposes including the treatment of depression. It is not licensed as a medicine in the UK but can be bought ‘over the counter’ from health food shops, herbalists and community pharmacies. Many different branded preparations are available. St John’s wort is licensed in Germany for the treatment of depression.

St John’s wort is known to contain at least 10 constituents or groups of components that may contribute to its pharmacological effects (Linde & Mulrow, 2003), but its exact mode of action is unknown. These include naphthodianthrons, flavonoids, xanthons and biflavonoids (Wagner & Bladt, 1994). In common with all herbal preparations, the quantity and proportions of each constituent varies among batches (Wang et al., in press). Most commercial products are standardised with respect to hypericin content but it is not known if this is the only active component. Individual brands or batches of the same brand may, therefore, not be therapeutically equivalent. Many clinically significant drug interactions have been reported (Committee on Safety of Medicines, 2000). St John’s wort may also cause photosensitivity.

Studies considered for review

Forty studies were found in a search of electronic databases, with 19 being included and 21 being excluded by the GDG.
Ten studies were available for a comparison with placebo (DAVIDSON02, HANSGEN1996, KALB2001, LAACKMANN98, LECRUBIER02, PHILIPP99, SCHRADER98, SHELTON2001, VOLZ2000, WITTE1995); four studies for a comparison with TCAs (PHILIPP99, WOEILK2000, BERGMANN1993, WHEATLEY1997); one with TCA-related antidepressants (HARRER94); and six studies for a comparison with SSRIs (BEHNKE2002, BRENNER00, DAVIDSON02, HARRER99, SCHRADER00, VANGURP02). Data from up to 1520 participants were available from studies comparing St John’s wort with placebo, and data from up to 1629 participants were available from comparison with antidepressants.

All included studies were published between 1993 and 2002 and were between four and 12 weeks long (mean number of weeks = 6.47). In 16 studies participants were described as outpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (HARRER99) all participants were aged 60 years and over. All participants had either moderate or severe depression.

It is very difficult to assess the exact content of the preparation of St John’s wort used in included studies so no study was excluded on grounds of inadequate dose. Included studies described the following range of preparations:

- 2 x 150 mg (300 mg) @ 0.450 to 0.495 mg total hypericin per tablet
- 900 mg LI 160
- 4 x 200 mg (800 mg) LoHyp-57: drug extract ratio 5–7:1
- 3 x 300 mg (900 mg) WS5572: drug extract ratio 2.5–5:1, 5% hyperforin
- 3 x 300 mg (900 mg) WS5573: 0.5% hyperforin
- 3 x 300 mg (900 mg) WS5570: 0.12–0.28% hypericin
- 3 x 300 mg (900 mg) LI 160 = 720–960 mcg hypericin
- 2 to 6 x 300 mg (900 mg to 1800 mg) @ 0.3% hypericum
- 3 x 300 mg (900 mg) LI 160 = 720–960 mcg hypericin
- 2 x 250 mg (500 mg) ZE117: 0.2% hypericin
- 200–240 mg Psychotonin forte
- 3 x 30 drops Psychotonin (500 mg)
- 3 x 30 drops Hyperforat: 0.6 mg hypericin.

In addition six studies with low doses of standard antidepressants were also included.

Evidence statements for St John’s wort compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring St John’s wort over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD in:

46 DAVIDSON02 and PHILIPP99 are 3-arm trials
• the data set as a whole (N = 647; n = 995; RR = 0.79; 95% CI, 0.71 to 0.88)
• moderate depression (N = 1; n = 162; RR = 0.64; 95% CI, 0.51 to 0.79)
• severe depression (N = 548; n = 898; RR = 0.81; 95% CI, 0.72 to 0.9).

There is insufficient evidence to determine if there is a clinically significant difference between St John’s wort and placebo on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 3; n = 804; Random effects RR= 0.80; 95% CI, 0.53 to 1.22).

There is evidence suggesting that there is a statistically significant difference favouring St John’s wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance in:

• the data set as a whole (N = 649; n = 1031; SMD = -0.35; 95% CI, -0.47 to -0.22)
• severe depression (N = 550; n = 891; SMD = -0.34; 95% CI, -0.47 to -0.2).

However, in moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John’s wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 2; n = 299; Random effects SMD = -0.71; 95% CI, -1.28 to -0.13).

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between St John’s wort and placebo on reducing the likelihood of patients leaving treatment early for any reason (N = 8; n = 1472; RR = 0.96; 95% CI, 0.74 to 1.25).

There is insufficient evidence to determine if there is a clinically significant difference between St John’s wort and placebo on reducing the likelihood of patients leaving treatment early due to adverse effects (N = 5; n = 1127; RR = 0.88; 95% CI, 0.32 to 2.41).

There is evidence suggesting that there is no clinically significant difference between St John’s wort and placebo on reducing the likelihood of patients reporting adverse effects (N = 7; n = 1106; RR = 0.89; 95% CI, 0.72 to 1.1).

Evidence statements for St John’s wort compared with antidepressants

Effect of treatment on efficacy outcomes

47 Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.
48 Two studies (DAVIDSON02, HANGSEN1996) were removed from the meta-analysis to remove heterogeneity from the data set.
49 Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.
50 Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.
There is evidence suggesting that there is no clinically significant difference between St John’s wort and antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 10; n = 1612; Random effects RR = 1.03; 95% CI, 0.87 to 1.22)
- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 224; RR = 1.01; 95% CI, 0.87 to 1.17)
- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 9; n = 1168; SMD = –0.02; 95% CI, –0.13 to 0.1).

A sub-analysis by severity found no difference in these results except for response rates in those with moderate depression:

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John’s wort over antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; n = 481; RR = 0.77; 95% CI, 0.62 to 0.95).

Sub-analyses by antidepressant class and by antidepressant dose (therapeutic versus low dose) found similar results.

A sub-analysis combining severity and antidepressant dose also found similar results apart from for response rates in severe depression:

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring low dose antidepressants over St John’s wort on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 4; n = 521; RR = 1.2; 95% CI, 1 to 1.44).

Acceptability and tolerability of treatment

With regard to reducing the likelihood of patients leaving treatment early for any reason, there is insufficient evidence to determine a difference between St John’s wort and either all antidepressants or low dose antidepressants. However, there is some evidence suggesting that there is a clinically significant difference favouring St John’s wort over antidepressants given at therapeutic doses (N = 5; n = 1011; RR = 0.69; 95% CI, 0.47 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring St John’s wort over antidepressants on:

- reducing the likelihood of patients leaving treatment early due to side effects (N = 10; n = 1629; RR = 0.39; 95% CI, 0.26 to 0.6)
- reducing the likelihood of patients reporting adverse effects (N = 8; n = 1358; RR = 0.65; 95% CI, 0.57 to 0.75).

Clinical Summary

St John’s wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing depression symptoms in moderate depression.
There appears to be no difference between St John’s wort and other antidepressants, other than in moderate depression where it is better at achieving response and in severe depression where it is less effective than low dose antidepressants in achieving response.

However, St John’s wort appears as acceptable as placebo, and more acceptable than antidepressants, particularly TCAs, with fewer people leaving treatment early due to side effects and reporting adverse events.

8.7.1 Clinical practice recommendation

8.7.1.1 Although there is evidence that St John’s wort may be of benefit in mild or moderate depression, practitioners should:

- not prescribe or advise its use by people with depression because of uncertainty about appropriate doses, persistence of effect, variation in the nature of preparations and potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anticonvulsants)
- advise people with depression of the different potencies of the preparations available and of the potential serious interactions of St John’s wort with other drugs.  

8.8 Health Economics Evidence

8.8.1 Systematic Literature review and economic considerations

The systematic search of the economic literature undertaken for the guideline update identified 13 eligible studies on antidepressants for people with depression. Details on the method used for the systematic review of economic literature in the guideline update are described in Chapter 3; references to included studies and evidence tables for all economic studies included in the systematic literature review are provided in Appendix 16.

The systematic search identified 11 studies. Of these, 4 studies (Borghi & Guest, 2000; Doyle et al. 2001; Freeman et al. 2000; Tome & Isaac. 1998) were included in the previous guideline. 2 unpublished evaluations submitted by pharmaceutical companies were also included. Pharmacological companies producing the drugs under review were identified and contacted to provide/recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the evidence base for the guideline.

51 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
8.8.2  Citalopram, Duloxetine

5 industry-funded studies assessed the cost effectiveness of Escitalopram and Duloxetine against various antidepressant comparators (FERNANDEZ2005, WADE2005, WADE2005, BENEDICTE, WADE2008)

Wade2005 investigated the cost-effectiveness of escitalopram at a dose of 20 mg per day compared with citalopram at 40mg per day in those with severe depression (MADRS =>30) in primary and secondary care in the UK. This cost-effective analysis was reported to be an adaptation of models described in other studies, Borghi2000 being one of them.

A decision tree with a 6-month time horizon was used with a univariate sensitivity analysis and Monte Carlo simulation to evaluate the effect of uncertainty. It incorporated effectiveness data derived from a study review and expert opinion. Response rates etc. at 8 weeks were extrapolated to 6 months from a 506-sample meta-analysis. Costs were calculated from the societal perspective as well as that of the NHS and reported in 2003-pound sterling. Conventional resource use directly related to treatment as well as treatment-emergent adverse events and attempted suicide was also included. Lost productivity costs due to absenteeism from work were calculated using the human capital approach, based on mean market wages for 2003. Cost estimates for the majority of the resources used were derived from national published studies. The primary outcome measure was patient treated successfully, defined as a patient in remission (MADRS<=12 at week 24) while the secondary outcome measure was first line success i.e. remission without switch of drug treatment.

From the NHS perspective, the expected total cost per patient was £422[£404-£441] for escitalopram and £454[£436-471] for citalopram. The expected total cost per successfully treated patient was £786 (£702-£876) for escitalopram and £932 (£843-£1028) for citalopram. Escitalopram also proved to fare better in terms of the effectiveness outcomes e.g. Overall success 53.7 % (50.3-57.5) compared to 48.7% (45.8-51.7) for citalopram.

The analysis suggested that escitalopram was a cost saving alternative to citalopram for the treatment of those with severe depression in the UK despite the price of escitalopram being higher than other generic drugs. Cost savings were shown from both perspectives. Multivariate sensitivity analysis further demonstrated that Escitalopram was dominant at all ranges of probabilities tested in more than 99% of cases.

This study is deemed to be of good quality however, depression is a chronic disease and a 6 month time horizon may well be too short to capture all costs and benefits. There are many commonly used drugs for depression; other comparators from other drug classes could have been relevant as well for analysis and their inclusion could be possibly more informative. The primary and secondary outcome measures chosen were context specific and could only be compared with other severe depression studies, and not other economic evaluations. Use of QALYs may have enhanced abilities to make comparisons across studies.

Another study by Wade et al. 2005 (Wade, 2005) examined the cost effectiveness of three drug therapies for the treatment of MDD in primary care i.e. escitalopram (10 - 20 mg daily) compared with venlafaxine-XR (75 - 150 mg daily) and then generic
citalopram (20 - 40 mg daily) over a 6 month time horizon from the perspective of the NHS and society. 2 separate analyses were run due to an absence of relevant head to head studies.

A published Austrian cost-effectiveness model was adapted for the UK. The model encompassed remission, treatment failure, and referral to secondary care, dosage titration and switching of antidepressants as required. A decision tree representation was provided.

Clinical effectiveness data was sourced from a meta-analysis of 4 studies (n=1472), the GPRD (General Practice Research Database) was searched for treatment pattern data and expert opinion was also sought.

From the NHS perspective it was reported that Escitalopram dominated citalopram and venlafaxine. Patients treated with escitalopram had lower average expected treatment costs and showed higher expected savings per successfully treated patient. The results however when compared with venlafaxine-xr were less distinct. Outcomes were similar for both drugs, however a small cost saving was shown for escitalopram after 6 months of treatment.

Sensitivity analysis showed robust findings for the analysis between escitalopram and citalopram. However, the comparison with venlafaxine was sensitive to parameters used in the model.

The summary measure of benefit was depression specific and not easily compared with benefit summaries of other potential NHS interventions. Quality of life is an important dimension in the MDD spectrum and the impact of these interventions on QOL may have proven to be informative. An indirect comparison analysis could have been conducted had there been relevant head-to-head trials published. The authors did point out that an indirect comparison would not have changed the conclusions of the analysis.

This analysis, by Fernandez et al. 2005 aimed to assess the cost effectiveness of ecitalopram (10-20mg/day) compared with Venlafaxine XR (75-150 mg/day) in UK primary care patients with MDD. The effectiveness data was derived from a double blind, multi-national randomised clinical trial with 8-week follow up (n=293). Costing was undertaken prospectively on the same patient sample. The perspectives of the NHS and society were adopted.

The direct costs for the average patient were reported to be 40% higher for venlafaxine-xr than for escitalopram. The effective analysis was based on the basis of treatment completers only. The primary health outcome was the expressed in terms of the Quality of life depression scale (QLDS). Mean QLDS scores decreased in both groups, there were no statistically significant difference observed in either group.

The incremental cost-effectiveness analysis was reported in the form of incremental cost effectiveness ratio (ICER) confidence surface. Cost effectiveness acceptability curves were not produced due to there being no significant differences in efficacy. The ICER confidence surface was reported to be show higher health care costs for venlafaxine-xr than escitalopram and no difference in the EQ5D quality of life score.
The author’s concluded that based on the analysis escitalopram is as effective as venlafaxine-xr on the treatment of MDD and may be associated with lower costs from both perspectives.

Sensitivity analysis was not conducted, thereby leaving the question of robustness of the results unanswered. Limited details of the effectiveness study were reported making it difficult to assess the study quality or validity. An 8 week follow up is quite short for a depression related study and as a result long term costs and benefits may not be captured. However, all relevant cost details were reported and the use of a validated benefit measure like the EQ-5D, should allow comparisons of the study results across different interventions.

Benedicte et al. submitted an economic evaluation of duloxetine in MDD in Scotland, in which the clinical and economic effects of Duloxetine were compared to those of SSRIs, venlafaxine XR and mirtazapine over 1 year in 2 separate analyses. Patient groups, treatment settings, efficacy data, drug dosages and resource utilization differed in both. Patients with MDD who failed on first line SSRIs made up the study population. Those with moderate to severe MDD (HAMD-17 =>19) were evaluated in a primary care setting, while those with =>25 on HAMD-17 in secondary care. The perspective adopted was that of the NHS.

The clinical effectiveness parameters were from published and unpublished RCT data, other clinical study data and expert interviews. Resource use estimates were sourced from the Scottish Psychiatrists panel, literature and UK practicing GPs. Direct medical costs accounted for all outpatient and inpatient visits and drug costs. The main outcome of the model was QALYs.

Duloxetine was found to be less costly and marginally more effective than venlafaxine in the overall MDD population and separately in a more severe patient population. Duloxetine dominated SSRIs and Mirtazapine in primary care and was cost saving against mirtazapine in more severe patients.

The study limitations considered: efficacy data had been collected from different sources; this carries the risk of bias given the incomparability of trial populations. SSRIs data was taken from other duloxetine trials and mirtazapine from fairly old meta-analysis.

A year’s time horizon may not have captured the relevant cost and benefits of a MDD episode. Venlafaxine and duloxetine have been shown to have fairly similar efficacy as a result the results of this comparison were sensitive to changes in model parameters. Further causinf the cost inputs to have a more significant effect on results.

A later study by Wade et al. 2008 evaluated the cost-effectiveness of Escitalopram and Duloxetine in the treatment of patients with MDD in the outpatient setting. This analysis was carried out alongside a double-blind, multinational randomised study. The study time horizon was 24 weeks and the resource use estimates over this time was sourced from the health economic assessment questionnaires taken alongside the trial. The societal perspective was adopted and results were reported in 2006 UK pound sterling.
The effectiveness outcome of the analysis included the Sheehan Disability Scale (SDS) score, response and remission.

The results showed that over the study period escitalopram was associated with significant cost savings compared to duloxetine (£1127 versus £2001 total/patient cost). Escitalopram also resulted in significantly lower sick leave duration than duloxetine (31 versus 62 days). Escitalopram dominated duloxetine in the primary analysis i.e. when assessed with the SDS scale.

Indirect costs due to sick leave accounted for two-thirds of the total costs. This result highlights the importance of this cost in decision making from a societal perspective. However, this result is slightly less useful for those making decisions on behalf of health services. The form in which outcomes were reported was disease specific and as a result limits the ability to use them to make comparisons with other studies not reporting results in such scales. The time horizon may not capture all the costs and benefits of the drugs in a MDD setting.

8.8.3 Lofepramine

Peveler et al. 2005 aimed to determine the relative cost-effectiveness of three classes of antidepressants: TCAs, SSRIs, and the modified TCA lofepramine, as first choice treatments for depression in primary care. An open, pragmatic, controlled trial with three randomised arms and one preference arm with 265 patients with a new episode of depressive illness according to GP diagnosis and followed up for 12 months provided effectiveness and resource use data.

Costs were reported form the NHS perspective; there were no significant differences between arms in mean cost per depression-free week. The primary effectiveness outcome was the number of depression-free weeks, QALYs were also reported. The results highlighted that there were no significant differences between arms in mean cost per depression-free week. TCAs were least likely to be cost-effective. The authors highlighted that choosing lofepramine was likely to lead to a greater proportion of patients switching treatment in the first few weeks. SSRIs were likely to be the most cost-effective strategy, although the CEACs showed the probability of this was less than 0.6.

One of the main weaknesses of the study highlighted by the authors was its failure to recruit to the sample size estimated by the power calculation; thus, the power to detect differences between the classes of antidepressant was limited. They also highlighted that the duration of follow-up (1 year) was chosen to yield data of maximum relevance to decision making, however due to the chronic nature of MDD it may have missed important differences emerging over the longer course of illness. The authors stated that the measure of ‘depression-free weeks’ was chosen as a measure of effect because it is now fairly commonly used in other clinical areas. It is however still quite limited in generalisability with other studies. Furthermore, they pointed out that a formal evidence-based assessment of the validity of depression-free weeks has yet to be shown.

Kendrick et al. 2006 also assessed the cost-effectiveness of TCAs, SSRIs, and lofepramine in the treatment of depression in adult patients in the UK. The study was...
carried out an alongside a prospective, randomised, open-label, clinical trial in primary care from the perspective of the health service. This trial provided effectiveness and costing data. The costing was carried out prospectively on the same sample (n=327) of patients. The length of follow-up was 12 months.

The primary clinical measure was the number of weeks free from depression (HADS-D <8). No statistically significant differences between the groups were observed in this measure or any other outcome measure. QALYs were also reported. The differences in the total costs did not reach statistical significance either. In the incremental analysis the cost effectiveness acceptability curve showed statistically non-significant differences in benefits and costs. Overall, the analysis showed a lack of statistically significant differences in costs and benefits among the three treatments considered for patients with depression in primary care. However, there was an indication that SSRIs may be the most cost-effective strategy.

This analysis was based on a trial that was well described, and reflected usual practice. It also drew from a population that was representative of the wider UK population as it drew form several centres across the UK. The study was limited by a failure to recruit the desired number of patients. The robustness of the comparison was also limited by the loss to follow-up. Depression free days were used as a benefit measure; this is a depression specific measure and may prove difficult to compare it with the benefits of interventions for other conditions. However, QALYs were also reported and this allows for comparisons with the benefits of other interventions.

8.8.4 Mirtazapine, Venlafaxine

2 studies compared mirtazapine to older agents such TCAs and SSRIs. The study by Borghi & Guest, 2000 was described in the previous guideline. Romeo et al. compared the cost-effectiveness of 30-to 45-mg/d mirtazapine to 20-to 30-mg/day paroxetine for those with MDD treated in primary care. The model data was sourced from an RCT done by Wade et al in 2003. The effectiveness data and costing, which was conducted prospectively, was sourced from a sub-group of patients participating in the trial. The study was conducted in general practices in Scotland and had a 24-week follow-up.

Costs were reported from the NHS perspective. There were no significant differences in costs. Effectiveness outcomes were reported in the form of number of HAMD responders (i.e. patients with a 50% decrease in the 17- HAMD score) and the change in QLDS score (from baseline), at the 24-week end point to capture change in quality of life. Both antidepressants were efficacious for 24 weeks of treatment in depressed primary care patients. Compared with paroxetine, mirtazapine was associated with greater improvements in quality of life.

The author’s concluded that compared with paroxetine, mirtazapine might be a cost-effective treatment choice for depression in a primary care setting. However, when considering improvements in quality of life following the administration of these two agents, it can be inferred that mirtazapine should be considered the treatment of choice. The potential limitations are that the analysis may be subject to potential selection bias. The sub-group used consisted of treatment completers only. No further statistical analyses, to account for potential biases and confounding factors, were undertaken. Disease-specific outcome measures were used, so the results from this economic analysis are not comparable with those of analyses on other diseases.
The earlier study by Borghi and Guest, 2000 concluded that mirtazapine is a cost-effective antidepressant compared to amitriptyline and fluoxetine in the management of moderate and severe depression in the UK while this later study showed no significant differences in cost or effect.

Freeman et al. 2000 and Doyle et al. 2000 were 2 studies based on identical models discussed in the previous guideline. These studies compared Venlafaxine with SSRIs and TCAs and concluded that venlafaxine was more cost effective. Lennox-Smith et al. 2004 presented an analysis with the same comparators set in primary care. It adopted the perspective of the NHS and used clinical effectiveness data from a review of published literature. Outcomes were reported in terms of Symptom free days. The conclusion mirrored those of the earlier studies. The ability to assess the validity of this study is limited by the lack of details related to methodology; cost calculations, literature review and comparator descriptions. The outcome measure also limits comparisons.

In the previous guideline, pharmacoeconomic evidence suggested that SSRIs were more cost-effective than TCAs for the first-line treatment of major depression. Venlafaxine was shown to be more cost effective than SSRIs however, the clinical evidence review at the time highlighted that the clinical estimates used in the economic studies of the drugs compared were inconsistent with the results of the NCCMH clinical evidence review. Therefore an opportunity cost approach was adopted and primary care costs of the different antidepressants were considered alongside the clinical evidence.

1 study, reviewed in the previous guideline, looked at the cost-effectiveness of an augmentation strategy. Pindolol was compared to an SSRI plus placebo, the results of this study with moderate internal validity favoured augmentation.

8.8.5 Summary

The pharmacoeconomic evidence presented shows no clear evidence of one antidepressant drug being superior in terms of costs and benefits to any of the others evaluated in the first line treatment of major depressive disorder in the UK. There is a weak trend which reflects that SSRIs may be more cost effective than TCAs. However, the nature of the economic data is piecemeal; no study compares all the relevant antidepressants drugs in a single evaluation. Such an evaluation may prove valuable to inform guideline recommendations.

However, the guideline meta-analysis of clinical evidence points to similar levels of effectiveness across the antidepressants reviewed i.e. showing no obvious superiority in terms of effectiveness. Most of the drugs reviewed are off patent and available in generic form. In the case of newer drugs the lack of any greater effect than older drugs makes the added cost potentially not worthwhile (See Table 76). Therefore, when making a treatment decision regarding the use of an antidepressant many factors should be taken into consideration e.g. patient choice, clinical history, side effect profile, cost of drug and patient choice.

No new pharmacoeconomic evidence on relapse prevention, maintenance therapy or switching and sequencing patterns were identified in the UK setting.
### Table 76: Drug acquisition costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADQ Unit</th>
<th>Unit cost (BNF 56, September 2008)</th>
<th>Weekly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>10mg</td>
<td>Cipralex®(Lundbeck) 10 mg (scored), 28-tab pack = £14.91</td>
<td>£3.73</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>100mg</td>
<td>Efexor® XL(Wyeth) 75 mg 28-cap pack = £23.41; Cymbalta®(Lilly) 60 mg 28-cap pack = £27.72</td>
<td>£7.80</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60 mg</td>
<td>Cymbalta®(Lilly) 60 mg 28-cap pack = £27.72</td>
<td>£6.93</td>
</tr>
<tr>
<td>Agametamine</td>
<td>Not available</td>
<td>Not available</td>
<td>£ -</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20 mg</td>
<td>20 mg, 28-tab pack = £1.24</td>
<td>£0.31</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg</td>
<td>50 mg, net price 28-tab pack = £1.31</td>
<td>£0.33</td>
</tr>
</tbody>
</table>

**8.8.5.1 From evidence to recommendations**

Apart from the review of escitalopram, the reviews of individual drugs undertaken for the previous guideline were not updated, and therefore, the recommendations concerning the choice of antidepressants have been updated only to ensure compatibility with the current NICE house style. A review of the new antidepressant drug duloxetine was added, but the drug was found to be no more effective than other antidepressant drugs, and therefore could not be specifically recommended. Similarly, the updated review of escitalopram did not show any clinically significant advantage for this drug over other antidepressants, and no specific recommendation is made. The overall conclusion that antidepressants have largely equal efficacy, and that choice should largely depend on side effect profile, patient preference and previous experience of treatments, propensity to cause discontinuation symptoms and safety in overdose, is not altered. An increasing number of newer antidepressants are available as generics, and these drugs are generally preferred on grounds of cost. Clinicians should consider the potential for drug interactions when prescribing an antidepressant for people taking concomitant medication. More information on this topic is provided in a new NICE guideline on treating depression in people with chronic physical health problems (in preparation).

It is also important to allow an adequate trial of an antidepressant before taking the decision to alter the dose or try another treatment.

### 8.9 Clinical practice recommendations

**8.9.1.1 Discuss antidepressant treatment options with the person with depression, including the following:**

- their perception of the efficacy and tolerability of individual drugs if they have previously received antidepressants
- the choice of antidepressants including discussion of the anticipated side-effect profile and potential interactions with concomitant medication or physical illness

**8.9.1.2 When an antidepressant is to be prescribed, it should normally be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are equally effective as other antidepressants, are better tolerated, have a favourable**
8.9.3 When prescribing an SSRI, practitioners should consider using a product in a generic form. It should be noted that:

- fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs. Practitioners should consult Appendix 1 of the BNF for information on drug interactions.
- paroxetine is associated with a higher incidence of discontinuation symptoms.

8.9.4 When prescribing drugs other than SSRIs, practitioners should take into account:

- the increased likelihood of the person with depression stopping treatment because of side effects, and with venlafaxine and TCAs, the consequent need to increase the dose gradually.
- the specific cautions, contraindications, and monitoring requirements for some drugs. For example, the possibility of exacerbation of hypertension with venlafaxine and duloxetine; the risk of hypokalaemia with reboxetine; the need for haematological monitoring with mianserin. Consult the BNF for detailed information.
- that non-reversible MAOIs, such as phenelzine, should normally be prescribed only by specialist mental health professionals.
- that dosulepin should not be initiated.

Starting and initial phase of treatment

8.9.5 People started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after 2 weeks. Thereafter they should be seen on an appropriate and regular basis, for example, at intervals of 2 to 4 weeks in the first 3 months and at longer intervals thereafter, if response is good.

8.9.6 If a person with depression experiences side effects following prescription of an antidepressant early in treatment, the prescriber should, in discussion with the person:

- monitor symptoms closely where side effects are mild and acceptable to the person.

52 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
• stop or change to a different antidepressant if the person with depression prefers
• consider short-term concomitant treatment with a benzodiazepine (not normally for more than 2 weeks) where anxiety, agitation and/or insomnia are problematic.

8.9.1.7 When improvement is not occurring on the first antidepressant the prescriber should check that the drug has been taken regularly and in the prescribed dose.

8.9.1.8 If, after 4 weeks of treatment with a therapeutic dose of an antidepressant, response is minimal:
• consider increasing the dose in line with the schedule suggested by the Summary of Product Characteristics if there are no significant side effects,
• consider switching to another antidepressant as described in section 1.8 (Sequencing Treatment) if there are side effects or the person expresses a preference for changing treatment.

8.9.1.9 If the person’s depression shows some improvement, continue treatment for another 2 to 4 weeks and, then, if response is not adequate; if there are side effects or the person expresses a preference for changing treatment, consider switching to another antidepressant as described in section 1.8 (Sequencing Treatment).
9 Factors influencing choice of antidepressants

9.1 Introduction
Whilst the previous section reviewed the relative efficacy of different antidepressants, this section looks at factors that may affect the choice of antidepressant, including:

- The pharmacological management of depression in older adults
- The effect of gender on the pharmacological management of depression
- The pharmacological management of psychotic depression
- The pharmacological management of atypical depression
- The pharmacological and physical management of seasonal pattern depression (major depression with a seasonal pattern)
- Antidepressant discontinuation symptoms
- The cardiotoxicity of antidepressants
- Depression, suicide and antidepressants
- Dosage issues

This chapter updates reviews the effects of sex on the effects of antidepressants, antidepressant discontinuation symptoms, cardiotoxicity, and antidepressants and suicide. It includes a new review of treatments for seasonal pattern major depression (seasonal affective disorder) included since this diagnosis was added to the scope of the updated guideline.

The section on the management of depression in older adults was not updated since there are few new data in older adults which indicate that the existing recommendations should be amended. In addition, since the previous guideline, a separate guideline has been developed specifically for depression in people with chronic physical health problems which covers the issues relevant to many older people with depression (NICE, in preparation).

The section on psychotic depression was not updated and the recommendations left unchanged. The review of atypical depression was also not updated. However, the GDG felt that the previous recommendations should be removed since there was no reason why treatment for people whose depression had atypical features should not follow that for those with major depression. The review of low-dose versus high-dose TCAs was not updated.

9.2 The pharmacological management of depression in older adults

Introduction
Depression is the most common mental health problem of later life affecting approximately 15% of older people (Beekman et al., 1999). Untreated it shortens life and increases healthcare costs, as well as adding to disability from medical illnesses, and is the leading cause of suicide amongst older people (Lebowitz et al., 1997). Most depression in older adults is treated in primary care (Plummer et al., 1997) but there is evidence of poor detection (ibid.) and sub-optimal treatment (Iliffe et al., 1991). In this population the monitoring of self-harm is particularly important. It is also very important to educate the patient and caregivers about depression and involve them in treatment decisions. Older adults are at risk of co-existing physical disorders, sensory deficits and other disabilities and, therefore, medication needs to be carefully monitored in these groups.

The efficacy of antidepressants in older adults has been summarised in a Cochrane systematic review (Wilson et al., 2001). There is some evidence that older people take longer to recover than younger adults and adverse events need to be carefully monitored for, since they might substantially affect function in a vulnerable individual.

There are a variety of potential differences in older adults in terms of absorption and metabolism of drugs and increased potential for interaction with other drugs. The maxim is, therefore, to start low and increase slowly but it is clear that much more research involving older patients with depression is required on this and other points.

It was possible to review the following pharmacological strategies for the treatment of depression in older adults:

- Use of individual antidepressants: amitriptyline, TCAs as a group, SSRIs, phenelzine, mirtazapine, venlafaxine and St John’s wort (studies were also available for reboxetine but, since this drug is not licensed for the treatment of depression in older adults, this drug is not reviewed)
- Augmentation of an antidepressant with lithium
- Strategies for relapse prevention.

**Use of individual antidepressants in the treatment of depression in older adults**

Studies considered for review

This review brings together studies from other reviews undertaken for this guideline where more than 80% of study participants were aged 65 years and over. A separate systematic search of the literature was not undertaken and, therefore, studies undertaken with elderly populations using drugs not reviewed for this guideline are not included.

In all, 15 studies from other reviews of individual antidepressants enrolled participants who were at least 60 years of age (COHN1990, DORMAN1992, FEIGHNER1985A, GEORGOTAS86, GERETSEGGER95, GUILLIBERT89, HARRER99, HUTCHINSON92, LAPIA1992, MAHAPATRA97, PELICIER1993, PHANJOO1991, RAHMAN1991, SCHATZBERG02, SMERALD1998). Ten studies were sourced from the review of SSRIs, two from venlafaxine and one each from mirtazapine, phenelzine and St John’s wort. Studies were included provided the mean dose achieved was at least half the ‘standard’ adult dose. Efficacy data were available from up to 1083 patients, and tolerability data from up to 1620 patients.
All included studies were published between 1985 and 2002. Two were classified as inpatient, eight as outpatient and one as primary care. In four, participants were either from mixed sources or it was not possible to determine the source. Studies ranged from five to eight weeks long.

8.2.2.2.2 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms in older adults:

- between amitriptyline and paroxetine (N = 2; n = 126; SMD = -0.1; 95% CI, -0.46 to 0.27)
- between SSRIs and alternative antidepressants (N = 8; n = 602; SMD = -0.01; 95% CI, -0.17 to 0.15)
- between venlafaxine and TCAs (N = 2; n = 202; SMD = 0.02; 95% CI, -0.26 to 0.29)
- between alternative antidepressants and TCAs (N = 6; n = 443; SMD = 0.00; 95% CI, -0.19 to 0.19)
- between St John’s wort and fluoxetine (N = 1; n = 149; SMD = -0.04; 95% CI, -0.36 to 0.28)
- between mirtazapine and paroxetine (N = 1; n = 254; SMD = -0.12; 95% CI, -0.37 to 0.13).

There is insufficient evidence to determine if there is a clinically significant difference in older adults on increasing the likelihood of achieving a 50% reduction in depression symptoms between:

- amitriptyline and paroxetine
- venlafaxine and TCAs
- alternative antidepressants and TCAs
- St John’s wort and fluoxetine
- mirtazapine and paroxetine.

There is evidence suggesting that there is no clinically significant difference between mirtazapine and paroxetine on increasing the likelihood of achieving remission in older adults (N = 1, n = 254; RR = 0.87; 95% CI, 0.73 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference in older adults on increasing the likelihood of achieving remission:

- between phenelzine and nortriptyline
- alternative antidepressants and TCAs.

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring mirtazapine over paroxetine on reducing the likelihood of older adults leaving treatment early due to side effects (N = 1, n = 254; RR = 0.57; 95% CI, 0.34 to 0.94).

There is evidence suggesting that there is no clinically significant difference between alternative antidepressants and TCAs on reducing the likelihood of older adults reporting adverse effects (N = 7, n = 581; RR = 0.89; 95% CI, 0.79 to 1.02).
There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of older adults leaving treatment early between:

- amitriptyline and SSRIs (N = 3; n = 422; RR = 0.89; 95% CI, 0.7 to 1.12)
- SSRIs and alternative antidepressants (N = 10; n = 1,115; RR = 0.96; 95% CI, 0.82 to 1.13)
- alternative antidepressants and TCAs (N = 10; n = 1058; RR = 0.97; 95% CI, 0.83 to 1.13).

There is evidence suggesting that there is no clinically significant difference between SSRIs and alternative antidepressants on reducing the likelihood of older adults leaving treatment early due to side effects (N = 10; n = 1154; RR = 1; 95% CI, 0.81 to 1.23).

There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of older adults reporting adverse events between:

- SSRIs and alternative antidepressants (N = 8; n = 717; RR = 0.95; 95% CI, 0.85 to 1.05)
- phenelzine and nortriptyline (N = 1; n = 60; RR = 0.97; 95% CI, 0.87 to 1.09)
- mirtazapine and paroxetine (N = 1, n = 254; RR = 0.97; 95% CI, 0.86 to 1.09).

There is insufficient evidence to determine if there is a clinically significant difference between other drug comparisons on other tolerability measures.

**Effect of setting on treatment efficacy and tolerability**

There is evidence suggesting that there is no clinically significant difference between SSRIs and TCAs on reducing depression symptoms in older inpatients (N = 2; n = 95; SMD = –0.07; 95% CI, –0.48 to 0.33).

There is insufficient evidence to determine any difference on any efficacy measure in older outpatients or patients in primary care.

There is some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline on reducing the likelihood of older adults in primary care reporting adverse effects (N = 1; n = 90; RR = 0.55; 95% CI, 0.35 to 0.86).

There is insufficient evidence to determine any difference on tolerability measures for any other patient setting.

**Augmentation of an antidepressant with lithium in older adults**

**Studies considered for review**

In the review of lithium augmentation all participants in one study (JENSEN1992) were aged 65 years or over. This was of inpatients, and compared nortriptyline (25 to 100 mg, median = 75 mg) plus lithium with nortriptyline (50 to 100 mg, median = 75 mg) plus placebo.

**8.2.2.3.2 Evidence statements**

**Effect of treatment on efficacy outcomes**

There is some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on increasing the
Depression in adults (update): full guideline DRAFT (February 2009)

likelihood of achieving remission in older adults (N = 1; n = 44; RR = 2.28; 95% CI, 1.09 to 4.78).

Acceptability and tolerability of treatment
There is some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on reducing the likelihood of older adults leaving treatment early (N = 1; n = 44; RR = 5.02; 95% CI, 1.26 to 20.07).

There is insufficient evidence to determine if there is a clinically significant difference between nortriptyline plus lithium and nortriptyline alone on reducing the likelihood of older adults leaving treatment early due to side effects (N = 1; n = 44; RR = 5.48; 95% CI, 0.72 to 41.82).

Relapse prevention in older adults

Studies considered for review
Five studies looked at relapse prevention in older adults (all at least 65 years of age or with a mean age of 65 years) (ALEXOPOULOS2000, COOK1986, GEORGOTAS1989, KLYSNER2002, WILSON2003), one in patients in primary care (WILSON2003) and four in outpatients (ALEXOPOULOS00, COOK1986, GEORGOTAS1989, KLYSNER2002).

8.2.2.4.2 Evidence statements
In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo there is strong evidence suggesting that there is a clinically significant difference favouring continuing treatment with antidepressants over discontinuing antidepressants on reducing the likelihood of relapse in elderly patients (N = 5; n = 345; RR = 0.55; 95% CI, 0.43 to 0.71).

Where there was sufficient evidence, there was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

Clinical summary
There is no difference in the efficacy of the various antidepressants for which studies have been undertaken in older adults. There is also no evidence of differences in acceptability. There is no evidence that there is a difference by setting, apart from in primary care, where fewer patients taking paroxetine report adverse events compared with those taking amitriptyline.

With regard to augmenting an antidepressant with lithium, elderly patients appear to be more likely to achieve remission without the addition of lithium. These patients are also less likely to leave treatment early.

It appears to be worthwhile continuing pharmacological treatment in elderly patients with multiple depressive episodes in order to avoid relapse.

These results are similar to those found in the reviews of studies for all adult patients elsewhere in this guideline.
From evidence to recommendation

The review of pharmacological treatments for older adults was not updated since there are few new data, and the overall conclusions in the previous guideline was that management of older adults should follow general principles. These were based on the fact that older people tend to metabolise drugs more slowly and are more likely to be taking concomitant medication and to be in poorer physical health than younger people. These recommendations are unchanged. However, they have been amended to bring them up to date with current NICE style. Since the publication of previous guideline, a guideline on the management of dementia has been published (NICE-SCIE CG042, 2006). This covers the management of comorbid depression and recommendations relating to this topic have been removed.

9.2.1 Clinical practice recommendation

9.2.1.1 When prescribing antidepressants for older adults practitioners should:

- prescribe at an age-appropriate dose taking into account the impact of age, general physical health and concomitant medication on pharmokinetics and pharmodynamics
- carefully monitor for side effects.

9.3 The effect of sex on antidepressant choice

Introduction

Although the female preponderance in the prevalence of unipolar depression has been well established (Weissman et al., 1993) relatively little attention has been paid to gender differences in treatment response to antidepressant medication. A meta-analysis of 35 studies published between 1957 and 1991 that reported imipramine response rates separately by sex reported that men responded more favourably to imipramine than did women (Hamilton et al., 1996). Some studies since then have suggested that younger women may respond preferentially to SSRIs over noradrenaline reuptake inhibitors (TCAs, maprotiline, reboxetine) with predominantly no difference found for men (Kornstein et al, 2000; Joyce et al., 2002; Baca et al., 2004; Martenyi et al., 2001; Berlanga & Flores-Ramos, 2006). This may be accounted for by a poorer tolerability of TCAs in younger women (Kornstein et al, 2000; Joyce et al., 2002; Baca et al., 2004). Results are inconsistent as to whether men respond better than women to TCAs (Quitkin et al., 2001). A study which compared tricyclic antidepressants and monoamine oxidase inhibitors found that in patients with atypical depression and associated panic attacks, women showed a more favourable response to MAOIs and men to tricyclic antidepressants (Davidson & Pelton, 1986).

However, the data are not consistent, and several studies have failed to show any significant effect of sex on antidepressant response. For example, when SSRIs were compared with with clomipramine in inpatients (Hildebrandt et al., 2003), and no effect of sex has been found with venlafaxine (Hildebrandt et al., 2003), duloxetine (Kornstein et al., 2006), and amfebutamone (bupropion) (Papakostas et al., 2007a). A large observational study of sertraline treatment in over 5,000 patients failed to find a clinically relevant effect of sex on response to treatment (Thiels et al., 2005).
Taken as a whole, no convincing data showing differential benefits for antidepressants based on sex have accrued since the previous guideline, the guideline development group considered that the previous recommendations should be removed from the guideline update.

9.3.1 Clinical practice recommendation

9.3.1.1 Practitioners should not routinely vary the treatment strategies for depression described in this guideline either by depression sub-type (e.g. atypical depression or seasonal depression) or personal characteristics (e.g. sex, ethnicity) as there is no convincing evidence to support such action.53

9.4 The pharmacological management of psychotic depression

9.4.1 Introduction

Major depression with psychotic features is a disorder with considerable morbidity and mortality. In the epidemiologic catchment area study (Johnson et al., 1991), 14.7% of patients who met the criteria for major depression had a history of psychotic features. The prevalence is higher in samples of elderly patients. The disorder is often not diagnosed accurately because the psychosis may be subtle, intermittent or concealed. There has been a long-standing debate as to whether major depression with psychotic features is a distinct syndrome or represents a more severe depressive subtype. The weight of evidence suggests that severity alone does not account for the differences in symptoms, biological features and treatment response (Rothschild, 2003). The systematic study of major depression with psychotic features has been limited by the fact that the disorder does not exist as a distinct diagnostic subtype in DSM-IV and because of the difficulties in enrolling such patients in research studies. As a result there are few controlled studies on the acute treatment of psychotic depression and no long-term maintenance studies. There is some evidence that patients with major depression with psychotic features exhibit more frequent relapses or recurrences than patients with non-psychotic depression though not all studies are in agreement (see Rothschild, 2003). Patients with major depression with psychotic features demonstrate more severe psychomotor disturbance more frequently than patients without psychosis.

Studies considered for review

Twenty studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985, ZANARDI1996, ZANARDI2000) and 14 of which did not, mainly because too many participants had been diagnosed with bipolar depression and, therefore, fell outside the inclusion criteria set by the GDG.

53 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
Four studies (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985) looked at augmenting an antidepressant with an antipsychotic and two (ZANARDI1996, ZANARDI2000) compared a single antidepressant with another. The following comparisons were possible:

- Amitriptyline plus perphenazine versus amoxapine
- Nortriptyline plus perphenazine versus nortriptyline plus placebo

Four-armed trial (BELLINI1994).

- Amitriptyline plus perphenazine versus amitriptyline
- Desipramine plus haloperidol versus desipramine plus placebo
- Fluvoxamine plus haloperidol versus fluvoxamine plus placebo
- Paroxetine versus sertraline
- Fluvoxamine versus venlafaxine.

In comparisons involving antipsychotic augmentation, efficacy data were available from up to 103 participants and tolerability data from up to 87 participants. In comparisons comparing single antidepressants, both efficacy and tolerability data were available from up to 60 participants. All included studies were published between 1985 and 2001 and were between four days and 16 weeks (mean = 7.17 weeks).

All studies were of inpatients, and in one all patients were at least 50 years of age (mean 71) (MULSANT2001). Participants had a diagnosis of major depressive disorder with psychotic features. In two studies (ANTON1990, ZANARDI2000) up to 25% (the limit allowed in the inclusion criteria set by the GDG is 15%) of participants were diagnosed with bipolar disorder. Two sets of analyses were performed including and excluding these two studies. There was no difference in results, so statements from the analysis excluding these studies are presented below.

Evidence statements

Effect of treatment on efficacy

There is some evidence suggesting that there is a clinically significant difference favouring sertraline over paroxetine on increasing the likelihood of achieving remission as measured by the HRSD in patients with psychotic depression (N = 1; n = 32; RR = 2.83; 95% CI, 1.28 to 6.25).

There is insufficient evidence on any efficacy measure to determine if there is a clinically significant difference between a TCA plus an antipsychotic and either amoxapine or a TCA in patients with psychotic depression.

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference on the acceptability of treatment between:

- perphenazine augmentation of a tricyclic antidepressant and tricyclic monotherapy
- paroxetine and sertraline.

Clinical summary

There is no good quality evidence for pharmacological treatments of psychotic depression. However, there are practical problems in recruiting sufficient numbers of
patients with psychotic depression and, therefore, practitioners may wish to consider lower levels of evidence.

9.4.2 Clinical practice recommendations

9.4.2.1 For people with psychotic depression, augmenting the current treatment plan with antipsychotic medication should be considered, although the optimum dose and duration of treatment are unknown. 54

9.5 The pharmacological management of atypical depression

Introduction
Depression with atypical features is described in DSM-IV (APA, 1994). The introduction of a formally defined type of depression with atypical features was in response to research and clinical data indicating that patients with atypical depression have specific characteristics. The classical atypical features are over-eating and over-sleeping (sometimes referred to as reverse vegetative symptoms). The syndrome is also associated with mood reactivity, leaden paralysis and a long-standing pattern of interpersonal rejection sensitivity. In comparison with major depressive disorder without atypical features, patients with atypical depression are more often female, have a younger age of onset and a more severe degree of psychomotor slowing. Co-existing diagnoses of panic disorder, substance misuse and somatisation disorder are common. The high incidence and severity of anxiety symptoms in these patients increases the likelihood of their being misclassified as having an anxiety disorder. The major treatment implication of atypical depression is that patients are said to be more likely to respond to a monoamine oxidase inhibitor than to tricyclic drugs. However, the significance of atypical features remains controversial as does the preferential treatment response to monoamine oxidase inhibitors. The absence of specific diagnostic criteria has limited the ability to assess the aetiology, prevalence and validity of the condition.

Studies considered for review
This section brings together studies from other reviews undertaken for the previous guideline where participants were diagnosed with atypical depression. A separate systematic search of the literature was not undertaken and, therefore, studies undertaken with atypical depression using drugs not reviewed for this guideline are not included. No new studies were found in the update search for the guideline update.

In all, three studies from other reviews were of atypical depression (MCGRATH2000, PANDE1996, QUITKIN1990). Two came from the review of phenelzine and one from the review of SSRIs. Data were available to look at the efficacy of phenelzine compared with imipramine/desipramine or with fluoxetine, and fluoxetine compared with imipramine. But there was only tolerability data available for phenelzine compared with fluoxetine. Efficacy data were available from up to 334 patients, and tolerability

54 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
data from up to 40 patients. All included studies were published between 1990 and 2000. Two were classified outpatient studies and in the other it was not possible to determine the source.

**Evidence statements**

**Effect of treatment on efficacy**

In people with atypical depression there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over other antidepressants (imipramine/desipramine and fluoxetine) on increasing the likelihood of achieving a 50% decrease in depression symptoms by the end of treatment as measured by the HRSD (N = 2; n = 232; RR = 0.69; 95% CI, 0.52 to 0.9).

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between phenelzine and other antidepressants on:

- increasing the likelihood of patients achieving remission by the end of treatment as measured by the HRSD (N = 2; n = 232; Random effects RR = 0.83; 95% CI, 0.39 to 1.75)
- reducing depression symptoms as measured by the HRSD (N = 2; n = 232; Random effects SMD = –0.31; 95% CI, –0.88 to 0.26).

In a sub-analysis by antidepressant class, there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs (imipramine/desipramine) on:

- increasing the likelihood of patients achieving a 50% decrease in depression symptoms by the end of treatment as measured by the HRSD (N = 1; n = 192; RR = 0.68; 95% CI, 0.52 to 0.9)
- increasing the likelihood of patients achieving remission by the end of treatment as measured by the HRSD (N = 1; n = 192; RR = 0.65; 95% CI, 0.49 to 0.87)
- reducing depression symptoms as measured by the HRSD (N = 1; n = 192; WMD = –3.15; 95% CI, –4.83 to –1.47).

Compared with SSRIs (fluoxetine), there is evidence suggesting that there is no clinically significant difference between phenelzine and fluoxetine on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; n = 40; WMD = 0.20; 95% CI, –2.11 to 2.51).

There is insufficient evidence to determine if there is a clinically significant difference between phenelzine and fluoxetine, or between fluoxetine and TCAs on any other efficacy measure.

**Acceptability and tolerability of treatment**

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between phenelzine and fluoxetine on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

**Clinical summary**

In patients with atypical depression there is some evidence suggesting a clinical advantage for phenelzine over TCAs (imipramine/desipramine) in terms of achieving remission and response. However, compared with SSRIs (fluoxetine), there is evidence
of no difference on mean endpoint scores, and insufficient evidence on other outcome measures. There is insufficient evidence for the acceptability and tolerability of any antidepressant.

From evidence to recommendations

The previous guideline recommended treatment with an SSRI for people with atypical depression. Since this is the treatment of choice for all people with depression, the guideline group decided to remove the recommendation from the updated guideline. They also considered that the other recommendations for treating atypical depression were adequately covered elsewhere in the guideline (cautions about the use of phenelzine, and referring to mental health specialist), and that no special management of people with atypical depression could be recommended.

9.5.1 Clinical practice recommendations

9.5.1.1 Practitioners should not routinely vary the treatment strategies for depression described in this guideline either by depression sub-type (e.g. atypical depression and seasonal depression) or personal characteristics (e.g. sex, ethnicity) as there is no convincing evidence to support such action.

9.6 The management of major depression with a seasonal pattern

Introduction

The term seasonal affective disorder (depression with a seasonal pattern), introduced by Rosenthal and colleagues (1984) to describe recurrent depressions that occur annually at the same time each year, includes bipolar depression but most sufferers have recurrent unipolar depression (70-80%). Winter depression with a seasonal pattern is far more common than summer depression with a seasonal pattern. DSM-IV includes criteria for a seasonal pattern for depressive episodes whereas only provisional criteria are given in the research version of ICD-10. The characteristic quality of major depression with a seasonal pattern is that symptoms usually present during the winter and remit in the spring. The symptoms of depression with a seasonal pattern do not clearly delineate it from other types of depression but in reported samples decreased activity was nearly always present and atypical depressive symptoms were common, particularly increased sleep, weight gain and carbohydrate craving.

Depression with a seasonal pattern as a separate diagnosis has been less accepted in Europe than North America, and an alternative view is that major depression with a seasonal pattern is an extreme form of a dimensional ‘seasonality trait’ rather than a specific diagnosis with so called ‘subsydromal major depression with a seasonal pattern’ appearing common. Nevertheless there are some patients with recurrent major depression who experience a seasonal pattern to their illness, at least for a time. There also appear to be people who experience seasonal fluctuations in mood that do not reach criteria for major depression.
The hypothesis that light therapy (ie increasing the amount or duration of light exposure) might be an effective treatment is based on the presumption that SSAD is caused by a lack of light in the winter months. There have subsequently been a number of controlled studies and meta-analyses (eg Golden et al, 2005) which have tended to conclude that light therapy is effective. There has been little research into other treatments in patients with depression with a seasonal pattern.

The electronic databases searched for published trials are given in Table 77. Details of the search strings used are in appendix 8.

### Table 77: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008; January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression with a seasonal pattern according to DSM, ICD or similar criteria, or seasonal affective disorder according to Rosenthal’s (ref) criteria or subsyndromal major depression with a seasonal pattern as indicated by score on seasonal depression scale</td>
</tr>
<tr>
<td>Treatments</td>
<td>Light therapy, dawn simulation, antidepressants, psychological therapies, other physical treatments</td>
</tr>
</tbody>
</table>

**9.6.1 Light therapy for depression with a seasonal pattern**

Depression with a seasonal pattern was not included in the scope of the original guideline. Light therapy, which has been developed as a treatment specifically for major depression with a seasonal pattern, was therefore not reviewed, but has been included here as an additional review for the updated guideline. For this review both published and unpublished randomised controlled trials were sought which investigated light therapy in patients diagnosed with major depression with a seasonal pattern or subsyndromal major depression with a seasonal pattern. There are a range of methods for administering light therapy, this review included a range of light treatments such as a light box, light room or visor and dawn simulation. Trials which compared a light treatment to a control condition, another light treatment or to light administered at different times of day were included in this review.

A special advisor was consulted regarding a number of issues for this review (see Appendix 3). He advised the GDG that 5,000 lux hours per day is a reasonable minimum dose for light box treatment, but that a minimum effective dose of light administered by a light visor has not yet been established. For the control light condition a placebo light of not more than 300 lux is appropriate. He suggested that a minimum trial duration of a week would be reasonable for evaluating the efficacy of light treatment. His advice was also sought regarding dawn simulation, he suggested that it would be informative to include this type of light treatment in the review and that a simulation of around an hour and a half peaking at 250 lux is an appropriate minimum, with a control condition of a light of less than 2 lux.
Studies considered for review

In total, 61 trials were found from searches of electronic databases. Of these, 20 were included and 41 were excluded. The most common reasons for exclusion were that papers were not RCTs or participants did not have a diagnosis of depression with a seasonal pattern or minor (subsyndromal) depression with a seasonal pattern. In addition, studies which used a cross-over design (where participants serve as their own controls by receiving both treatments) were not used unless pre-crossover data were available.

The studies which were found by the search and included in this review varied considerably in methodology. The intensity and duration of light, time of day and mode of administration of light, and the comparison conditions were different across studies. A range of outcomes were reported by the included studies, including the HRSD (termed ‘typical’ depression rating scale to distinguish it from scales measuring depression with a seasonal pattern symptoms), and scales adapted for measuring symptoms in depression with a seasonal pattern. These included the SIGH-major depression with a seasonal pattern which combines the HRSD with an additional 8 items relevant to depression with a seasonal pattern. Some studies report the 8 additional items separately. Both typical and atypical symptoms were measured using clinician- and self-rated scales. All data were extracted and can be seen on forest plots and in the full evidence profiles. Only data for the SIGH-major depression with a seasonal pattern (clinician and self-rated) are presented here.

Data were available to compare light therapy with a range of control conditions including waitlist, attentional controls and active treatment controls. In addition administration of light in the morning versus evening was compared and dawn simulation was compared with attentional control and with bright light. One study included a combination treatment of light and CBT and one trial reported on light therapy for relapse prevention. Summary study characteristics of the included studies are in Table 78 and Table 79 with full details in Appendix 17 which also includes details of excluded studies.

<table>
<thead>
<tr>
<th>Table 78 Summary study characteristics of light therapy studies versus control and morning light versus afternoon/evening light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light versus waitlist control</td>
</tr>
<tr>
<td>No. trials (Total participants)</td>
</tr>
<tr>
<td>N/% female</td>
</tr>
<tr>
<td>Mean age</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Light therapy</td>
</tr>
<tr>
<td>Lux hours/day</td>
</tr>
<tr>
<td>Comparator(s)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>(1) waitlist</td>
</tr>
<tr>
<td>(2) waitlist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of treatment (days)</th>
<th>(1) 21 (2) 42</th>
<th>(1) 28 (2) 28 (3) 14 (4) 14 (5) 7 (6) 21 (7) 14 (8) 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) light box used between 12-5pm (2) Fluorescent light box used within 1hr of bedtime (3) Light box 2-3 hours before bedtime</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 79 Summary study characteristics of dawn simulation and relapse prevention studies

<table>
<thead>
<tr>
<th>Dawn simulation versus attentional control</th>
<th>Light versus dawn simulation</th>
<th>Relapse prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>3 RCTs (139)</td>
<td>2 RCTs (112)</td>
</tr>
<tr>
<td>Study IDs</td>
<td>(1) AVERY1993 (2) AVERY2001 (3) TERMAN2006</td>
<td>(1) AVERY2001 (2) TERMAN2006</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 27/70 (2) 62/87 (3) 50/79</td>
<td>(1) 64/88 (2) 48</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 35 (2) 41 (3) 40</td>
<td>(1) 41 (2) 40</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) major depression with a seasonal pattern (Rosenthal) (2) MD or bipolar with seasonal pattern (DSM-IV) (3) MD with seasonal pattern (DSM-III-R)</td>
<td>(1) MD or bipolar with seasonal pattern (DSM-IV) (2) MD with seasonal pattern (DSM-III-R)</td>
</tr>
<tr>
<td>Light therapy</td>
<td>(1) gradual dawn simulation over 2hrs (2) gradual dawn simulation over 1.5hrs (3) gradual dawn simulation over 3.5hrs</td>
<td>(1) Light box (2) Light box</td>
</tr>
<tr>
<td>Lux hours/day</td>
<td>(1) 250 lux peak intensity (2) 250 lux peak intensity (3) 250 lux peak intensity</td>
<td>(1) 5000 (2) 10000</td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) rapid dim 0.2 lux dawn</td>
<td>(1) gradual dawn (1a) no treatment</td>
</tr>
</tbody>
</table>
Bright light versus waitlist or attentional control

Compared with waitlist control, bright light (either light room or light box) shows a strong effect on symptoms in depression with a seasonal pattern although there are few studies. Compared with attentional controls, such as deactivated negative ion generator, dim red light, and sham light boxes, bright light (either via light box or light visor) shows a small effect on symptoms in depression with a seasonal pattern which was not statistically significant. See Table 80 for the summary evidence profile and Appendix 16 for the full profile.

Table 80 Summary evidence profile for bright light versus waitlist or attentional controls

<table>
<thead>
<tr>
<th></th>
<th>Bright light vs waitlist control</th>
<th>Bright light vs attentional control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.95 (0.21 to 4.32) (7.1% vs 7.5%)</td>
<td>RR 0.88 (0.50 to 1.54) (13.4% vs 14.5%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=45</td>
<td>K=6; n=288</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 01.01</td>
<td>Pharm major depression with a seasonal pattern: 02.01</td>
</tr>
<tr>
<td>Reported side effects</td>
<td>RR 0.98 (0.73 to 1.32) (55.6% vs 58.3%)</td>
<td>Low</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=81</td>
<td>K=8; n=300</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 02.03</td>
<td>Pharm major depression with a seasonal pattern: 01.04</td>
</tr>
<tr>
<td>Clinician-rated: major depression with a seasonal pattern depression scores at endpoint (SIGH-major depression with a seasonal pattern)</td>
<td>WMD -10.4 (-15.99 to -4.81)</td>
<td>WMD -3.07 (-6.71 to 0.58)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=31</td>
<td>K=8; n=300</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 01.04</td>
<td>Pharm major depression with a seasonal pattern: 01.04</td>
</tr>
<tr>
<td>Self-rated: major depression with a seasonal pattern depression scores at endpoint</td>
<td>WMD -12.8 (-18.52 to -7.08)</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Bright light versus active treatment control

There were data to compare light therapy with group CBT, light therapy plus CBT, and dim light plus fluoxetine. There was also a study comparing light therapy plus St John’s wort with dim light plus St John’s wort.

Compared with group CBT (tailored to depression with a seasonal pattern) bright light therapy was no better in terms of reducing depressive symptoms in depression with a seasonal pattern, although the effect size is not statistically significant and was graded low quality. However, more participants achieved remission with bright light therapy than with group CBT (52% compared with 37.5%), although the result is not statistically significant. Similarly, light therapy appeared to be more acceptable group CBT with fewer people leaving treatment early (8% compared with 16.7%) although the effect size is not statistically significant. Treatment lasted for 6 weeks.

Combination treatment (bright light plus CBT) was more effective than light therapy alone on both the SIGH-major depression with a seasonal pattern and the BDI, although the effect sizes were not statistically significant. Roughly equal numbers of participants left treatment early.

There appeared to be little difference between bright light therapy and fluoxetine (20mg) on efficacy outcomes (both treatments given with a sham treatment mimicking the other). Treatment was given for 8 weeks.

There was no evidence for the efficacy of light therapy combined with St John’s wort compared with a sham light condition plus St John’s wort. There was only a single small 4-week study (n = 20).

See Table 81 for the summary evidence profile and Appendix 16 for the full profile.

<table>
<thead>
<tr>
<th>endpoint (SIGH-major depression with a seasonal pattern-SR)</th>
<th>Quality</th>
<th>Number of studies; participants</th>
<th>Forest plot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>K=1; n=48</td>
<td>Pharm major depression with a seasonal pattern: 01.03</td>
</tr>
<tr>
<td>Non-remission (based on SIGH-major depression with a seasonal pattern-SR)</td>
<td>RR 0.53 (0.38 to 0.74) (47.6% vs 90%)</td>
<td>RR 0.89 (0.66 to 1.2) (56.3% vs 61.3%)</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=82</td>
<td>K=6; n=336</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 01.10</td>
<td>Pharm major depression with a seasonal pattern: 01.08</td>
<td></td>
</tr>
</tbody>
</table>
Table 81 Summary evidence profile for bright light versus active treatment control

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Light box vs group CBT</th>
<th>Light box vs light box + group CBT</th>
<th>Light box + placebo pill vs dim light box + fluoxetine</th>
<th>Light box + St John’s wort vs dim light + St John’s wort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.53 (0.12 to 2.31) (8% vs 16.7%)</td>
<td>RR 0.92 (0.17 to 4.91) (8% vs 8.7%)</td>
<td>RR 1.5 (0.65 to 3.44) (17.6% vs 11.8%)</td>
<td>Not pooled (zero dropout rate) (0% vs 0%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=49</td>
<td>K=2; n=48</td>
<td>K=2; n=138</td>
<td>K=1; n=20</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 03.01</td>
<td>Pharm light 04.01</td>
<td>Pharm light 03.01</td>
<td>Pharm light 03.01</td>
</tr>
<tr>
<td>Reported side effects</td>
<td>N/R</td>
<td>RR 1.03 (0.82 to 1.29) (77.1% vs 75%)</td>
<td>N/R</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 03.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician-rated (major depression with a seasonal pattern) depression scores at endpoint</td>
<td>WMD -0.2 (-6.5 to 6.1) (SIGH-major depression with a seasonal pattern)</td>
<td>WMD 4.2 (-0.52 to 8.92) (SIGH-major depression with a seasonal pattern)</td>
<td>WMD -0.49 (-3.72 to 2.74) (SIGH-major depression with a seasonal pattern)</td>
<td>SMD -0.32 (-1.2 to 0.57) (HRSD)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=31</td>
<td>K=1; n=31</td>
<td>K=2; n=136</td>
<td>K=1; n=20</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 03.05</td>
<td>Pharm light 04.03</td>
<td>Pharm light 03.05</td>
<td>Pharm light 03.06</td>
</tr>
<tr>
<td>Self-rated: (major depression with a seasonal pattern) depression scores at endpoint</td>
<td>WMD -0.7 (-7.16 to 5.76) (BDI)</td>
<td>SMD 2.3 (-2.47 to 7.07) (BDI)</td>
<td>WMD -1.6 (-5.68 to 2.48) (BDI)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=31</td>
<td>K=1; n=31</td>
<td>K=1; n=96</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 03.08</td>
<td>Pharm light 04.06</td>
<td>Pharm light 03.08</td>
<td></td>
</tr>
<tr>
<td>Non-remission (based on SIGH-major depression with a seasonal pattern-5R)</td>
<td>RR 0.77 (0.46 to 1.28) (48% vs 62.5%)</td>
<td>RR 2.22 (0.92 to 5.32) (48% vs 21.7%)</td>
<td>RR 0.92 (0.67 to 1.27) (50% vs 54.4%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=49</td>
<td>K=2; n=48</td>
<td>K=2; n=136</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 01.09</td>
<td>Pharm light 04.07</td>
<td>Pharm major depression with a seasonal pattern: 01.09</td>
<td></td>
</tr>
</tbody>
</table>

N/R = not reported

Morning light versus afternoon/evening light

Three studies compared light therapy administered in the morning compared with light therapy in the afternoon or evening, one of which was in participants with subsyndromal major depression with a seasonal pattern. There were no significant differences in outcome measures for those given light therapy in the morning.

Depression in adults (update): full guideline DRAFT (February 2009)
compared with those given light therapy in the afternoon or evening. See Table 82 for the summary evidence profile and 615 for the full profile.

### Table 82 Summary evidence profile for morning light versus evening light

<table>
<thead>
<tr>
<th></th>
<th>Overall results</th>
<th>Sub-syndromal major depression with a seasonal pattern only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.98 (0.41 to 2.35) (12.1% vs 12.5%)</td>
<td>Not pooled (0% vs 0%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=130</td>
<td>K=1; n=31</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 05.01</td>
<td>Pharm light 05.01</td>
</tr>
<tr>
<td>Reported side effects</td>
<td>RR 0.47 (0.05 to 4.65) (6.3% vs 13.3%)</td>
<td>RR 0.47 (0.05 to 4.65) (6.3% vs 13.3%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=31</td>
<td>K=1; n=31</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 05.03</td>
<td>Pharm light 05.03</td>
</tr>
<tr>
<td>Clinician-rated: major depression with a seasonal pattern depression scores at endpoint</td>
<td>WMD -1.38 (-5.49 to 2.73) (SIGH-major depression with a seasonal pattern)</td>
<td>WMD 0.6 (-3.89 to 5.09) (SIGH-major depression with a seasonal pattern)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=68</td>
<td>K=1; n=30</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 05.04</td>
<td>Pharm light 05.04</td>
</tr>
<tr>
<td>Self-rated: depression scores at endpoint</td>
<td>WMD -0.9 (-4.66 to 2.86) (BDI)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=65</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 05.07</td>
<td></td>
</tr>
<tr>
<td>Non-remission (based on SIGH-major depression with a seasonal pattern-SR)</td>
<td>RR 1.28 (0.43 to 3.79) (54% vs 54.2%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=98</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 05.08</td>
<td></td>
</tr>
</tbody>
</table>

### Dawn simulation versus attentional control or light therapy

Three studies compared dawn simulation with an attentional control. There was some evidence that dawn simulation improved depression symptoms but it was not statistically significant and was not supported by other outcomes including the major depression with a seasonal pattern subscale. Similarly, there was no evidence of
superiority of dawn simulation over regular light therapy. See Table 83 for the summary evidence profile and Appendix 16 for the full profile.

**Table 83 Summary evidence profile for dawn simulation studies**

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Dawn simulation vs attentional control</th>
<th>Light therapy vs dawn simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.33 (0.05 to 2.22) (2.9% vs 14.1%)</td>
<td>RR 3.72 (0.62 to 22.22) (8.9% vs 1.8%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=141</td>
<td>K=2; n=112</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 06.01</td>
<td>Pharm light 07.01</td>
</tr>
<tr>
<td>Reported side effects</td>
<td>RR 5.57 (0.77 to 40.26) (42.9% vs 7.7%)</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=27</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 06.04</td>
<td></td>
</tr>
<tr>
<td>Clinician-rated: depression scores at endpoint</td>
<td>SMD -0.33 (-1.62 to 0.15) (HRSD)</td>
<td>WMD -0.9 (-4 to 2.2) (HRSD)</td>
</tr>
<tr>
<td></td>
<td>WMD -2.20 (-7.52 to 3.11) (major depression with a seasonal pattern subscale)</td>
<td>WMD -1.8 (-6.98 to 3.38) (major depression with a seasonal pattern subscale)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate (HRSD)</td>
<td>Very low (HRSD)</td>
</tr>
<tr>
<td></td>
<td>Very low (major depression with a seasonal pattern subscale)</td>
<td>Low (major depression with a seasonal pattern subscale)</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=73</td>
<td>K=1; n=45</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 06.05</td>
<td>Pharm light 07.06/07</td>
</tr>
<tr>
<td>Self-rated: depression scores at endpoint</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-remission (based on SIGH-major depression with a seasonal pattern)</td>
<td>RR 0.9 (0.61 to 1.32) (44.6% vs 50%)</td>
<td>RR 1.19 (0.70 to 2.00) (53.6% vs 44.6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=114</td>
<td>K=2; n=112</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm light 06.07</td>
<td>Pharm light 07.04</td>
</tr>
</tbody>
</table>

**Prevention of future episodes using light therapy**

One study compared bight light therapy with a control treatment and with no treatment as relapse prevention in people who had a history of depression with a seasonal pattern but had not yet developed symptoms. This showed that those
receiving light therapy were less likely to develop depression symptoms compared with those receiving no treatment. However, those using the infrared light visor were less likely to develop depression symptoms than those using the bright white light visor. Neither finding was statistically significant. See Table 84 for the summary evidence profile and Appendix 16 for the full profile.

### Table 84 Summary evidence profile for relapse prevention using bright light

<table>
<thead>
<tr>
<th></th>
<th>Bright white light visor vs no treatment control</th>
<th>Bright white light visor vs infrared light visor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leaving treatment early</strong></td>
<td>RR 2.22 (0.29 to 17.27) (22.2% vs 10%)</td>
<td>RR 1.53 (0.35 to 5.13) (22.2% vs 16.7%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=28</td>
<td>K=1; n=36</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm light 08.01</td>
<td>Pharm light 08.01</td>
</tr>
<tr>
<td><strong>Reported side effects</strong></td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse (BDI &gt; 13 for 2 consecutive weeks)</strong></td>
<td>RR 0.62 (0.36 to 1.09) (50% vs 80%)</td>
<td>RR 2.25 (0.84 to 5.99) (50% vs 22.2%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=28</td>
<td>K=1; n=28</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm light 08.02</td>
<td>Pharm light 08.02</td>
</tr>
</tbody>
</table>

**Clinical summary for light therapy**

Although there are a large number of studies that address the efficacy of light treatment in people with depression that follows a seasonal pattern, these studies are difficult to interpret due to methodological differences. The doses and colours of light, methods of delivery, comparator treatments, and clinical populations included in studies are diverse. While bright light is clearly more effective than waitlist control, it is unclear if this is more than a placebo effect (see earlier section on the placebo effect). Studies that compare bright light against other treatments that are not known to be effective give equivocal results. There are too few data relating to active controls to determine non-inferiority, and few systematic data relating to side effects. In clinical practice, where bright light is used, a minimum daily dose of 5,000 lux administered in the morning during the winter months is the most common treatment strategy. The most common side effect seen is mild agitation.

### 9.6.2 Other therapies for depression with a seasonal pattern

**Studies considered for review**

In total, 14 trials of interventions other than bright light were found, mostly of antidepressants, of which 5 met inclusion criteria for a review of acute-phase treatment, 1 for a review of continuation treatment in people who had responded to open-label treatment, and 3 (published in the same paper) for a review of prevention in
people with a history of depression with a seasonal pattern. See Table 85 for summary study characteristics.
Table 85 Summary study characteristics for interventions other than bright light for major depression with a seasonal pattern

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Acute phase treatments</th>
<th>Continuation treatment</th>
<th>Prevention treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) LAM1995</td>
<td>4 RCTs</td>
<td>1 RCTs</td>
<td>3 RCTs</td>
</tr>
<tr>
<td>(2) LINGJAERDE1993</td>
<td>(3) MOSCOVITCH2004</td>
<td>(4) PARTONEN1996</td>
<td>(5) TERMAN1995</td>
</tr>
<tr>
<td>(1) SCHLAGER1994*</td>
<td>(1) MODELL2005 study 1</td>
<td>(2) MODELL2005 study 1</td>
<td>(3) MODELL2005 study 1</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 68/66</td>
<td>(1) 23 (not available)</td>
<td>(1) 23 (not available)</td>
</tr>
<tr>
<td>(2) 34/74</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(3) 187/78</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(4) 32/66</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>(5) 25/88</td>
<td>(5)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 36</td>
<td>(1) Not given</td>
<td>(1) Not given</td>
</tr>
<tr>
<td>(2) 43</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(3) 40</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(4) 44</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>(5) 38</td>
<td>(5)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>(1) Recurrent major depressive episodes with seasonal pattern</td>
<td>(1) Responders to initial treatment for recurrent major depressive episodes with seasonal pattern</td>
<td>(1)</td>
</tr>
<tr>
<td>(2) Mood disorder with seasonal pattern</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(3) 79% major depression with seasonal pattern; 13% depression NOS with seasonal pattern; 7% bipolar disorder with seasonal pattern; 2% bipolar disorder NOS with seasonal pattern</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(4) 100% major depressive disorder; 18% mood disorder with seasonal pattern</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>(5) major depression with a seasonal pattern, major depressive disorder with seasonal pattern, or bipolar disorder NOS with seasonal pattern - % not clear</td>
<td>(5)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>(1) Fluoxetine 20mg</td>
<td>(1) Propanolol 33mg</td>
<td>(1) Propanolol 33mg</td>
</tr>
<tr>
<td>(2) Moclobemide 400mg</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>(3) Sertraline 50-200mg</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(4) Moclobemide 300-450mg</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(2) High density negative ions</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>(1) Placebo</td>
<td>(1) Placebo</td>
<td>(1) Placebo</td>
</tr>
<tr>
<td>(2) Placebo</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(3) Placebo</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(4) Fluoxetine 20-40mg</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>(5) Low density negative ions</td>
<td>(5)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Length of treatment (days)</td>
<td>(1) 5 weeks</td>
<td>(1) 2 weeks</td>
<td>(1) 2 weeks</td>
</tr>
<tr>
<td>(2) 3 weeks</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>(3) 8 weeks</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>(4) 6 weeks</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
</tbody>
</table>
NOS = not otherwise specified; *continuation trial

Acute-phase treatments

The data for acute-phase treatment comparing antidepressants with placebo were largely inconclusive, although on one outcome (response) there appeared to be little difference. Acceptability and tolerability data were inconclusive. There was no evidence to suggest a difference between moclobemide and fluoxetine, which was the only head-to-head evidence available. There was some evidence to suggest that high density ions were more effective than low density ions, although there was only one study. See Table 86.

Table 86 Summary evidence profile for acute-phase treatments (not light therapy) for major depression with a seasonal pattern

<table>
<thead>
<tr>
<th></th>
<th>Antidepressants versus placebo</th>
<th>Antidepressants versus antidepressants</th>
<th>High ion density v Low ion density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response (based on SIGH-major depression with a seasonal pattern)</td>
<td>RR 0.82 (0.63 to 1.05) (44.2% vs 54%)</td>
<td>N/R</td>
<td>RR 0.49 (0.24 to 1) (41.7% vs 84.6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=255</td>
<td>K=1; n=25</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 09.01</td>
<td>Pharm major depression with a seasonal pattern: 12.01</td>
<td></td>
</tr>
<tr>
<td>Clinician-rated: depression scores at endpoint SIGH-major depression with a seasonal pattern</td>
<td>SMD -0.11 (-0.65 to 0.42)</td>
<td>Moclobemide v Fluoxetine: WMD -1.6 (-7.01 to 3.81)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=99</td>
<td>K=1; n=29</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 09.02</td>
<td>Pharm major depression with a seasonal pattern: 11.02</td>
<td>N/R</td>
</tr>
<tr>
<td>Self-rated: depression scores at endpoint BDI</td>
<td>WMD -1.7 (-6.53 to 3.13)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 09.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 0.7 (0.16 to 3.05) (18.3% vs 20.5%)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 10.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Leaving treatment early due to side effects

<table>
<thead>
<tr>
<th>Quality</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=289</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 10.04</td>
</tr>
</tbody>
</table>

N/R = not reported

Continuation treatment and prevention of future episodes

One small study compared the β-blocker, propanolol, with placebo for people who had responded to previous open treatment. This showed that depression symptoms in those continuing treatment remained lower compared with those switched to placebo. Another 3 trials compared bupropion with placebo to prevent episodes in people with a history of depression. Treatment started before the onset of winter and continued until early spring. There was a statistically significant reduction in the number of recurrences amongst those taking bupropion compared with the rate in those taking placebo. See Table 87.

Table 87 Summary evidence profile of continuation treatment and prevention of future episode for people with major depression with a seasonal pattern

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Continuation treatment: Propanolol v Placebo</th>
<th>Prevention: Bupropion vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAMD-21: WMD -7 (-11.24 to -2.76)</td>
<td>Recurrence: RR 0.58 (0.46 to 0.72) (17% vs 29.5%)</td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=23</td>
<td>K=3; n=1061</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm major depression with a seasonal pattern: 13.01</td>
<td>Pharm major depression with a seasonal pattern: 14.01</td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 2.57 (0.12 to 57.44) (7.7% vs 0%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=24</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N/R = not reported

Clinical summary

There was a lack of evidence for the effectiveness of antidepressants in the treatment of major depression with a seasonal pattern once symptoms had begun but evidence for a prophylactic effect of starting treatment before symptoms start and continuing until early spring.

9.6.3 From evidence to recommendations

The evidence for light therapy for major depression with a seasonal pattern is still poorly developed, with many trials comparing different elements of treatment, including time of day, level of light, and length of treatment. There is little evidence for the efficacy of bright light in the treatment of major depression with a seasonal pattern compared with placebo treatment. The evidence for other treatments is sparse. Evidence is lacking that antidepressants are effective once symptoms have begun, but they may be worthwhile as prophylactics. Depression with a seasonal pattern should following the guidance for major depressive disorder elsewhere in this guideline.
9.7 Clinical practice recommendations

9.7.1.1 Practitioners should not routinely vary the treatment strategies for depression described in this guideline either by depression sub-type (for example, atypical depression and seasonal depression) or personal characteristics (for example, sex, ethnicity) as there is no convincing evidence to support such action.

9.7.1.2 Practitioners should advise people with winter depression that follows a seasonal pattern and who wish to try light treatment in preference to antidepressant or psychological treatment that the evidence for the efficacy of light therapy is uncertain.

9.7.1.3 Research Recommendation

What is the efficacy of light therapy compared with antidepressants for mild to moderate depression with a seasonal pattern?

This question should be answered using a randomised controlled trial design in which mild to moderately ill people suffering from depression with a seasonal pattern (seasonal affective disorder) receive light therapy or an SSRI antidepressant in a partially placebo-controlled design. The doses of both light and SSRI should be at accepted or proposed therapeutic levels and there should be an initial phase over a few weeks in which a plausible placebo treatment is administered followed by randomisation to one of the active treatments. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects and mediators and moderators of response should be investigated.

Why this is important
Although the status of season depression as a separate entity is not entirely clear surveys have consistently reported a high prevalence of seasonal (predominantly winter) depression in the UK. This reflects a considerable degree of morbidity for sufferers predominantly in the winter months. Light therapy has been proposed as a specific treatment for winter depression but only small inconclusive trials have been carried out from it is not possible to tell from them whether either light therapy or antidepressants are effective in its treatment. Clarification or whether and to what degree treatments are effective would help to inform the decisions that people with seasonal depression and healthcare professionals have to make about the treatment of winter depression.

9.8 Dosage issues

9.8.1 Low-dose versus high-dose TCAs

There is controversy over whether the existing recommended dosages for TCAs (100 mg/day, Bollini et al., 1999) are too high. Some GPs are criticised for prescribing at doses that are too low, and evidence for dosing levels has not been established (Furukawa et al., 2002a). This review compares the efficacy and tolerability of low and
high doses of TCAs. Low doses were those where the mean dose achieved was less than the equivalent of 100 mg of amitriptyline.

### 9.8.2 Studies considered for review

The GDG used an existing review (Furukawa et al., 2002a) as the basis for this review. The original review included 38 studies of which 33 did not meet the inclusion criteria set by the GDG, mainly because of inadequate diagnosis of depression. Therefore, five trials (BURCH1988, DANISH1999, ROUILLON1994, SIMPSON1988, WHO1986) are included in this review providing data from up to 222 participants.

All included studies were published between 1988 and 1999 and were between four and eight weeks long (mean = six weeks). One study was of inpatients and two of outpatients, with none in primary care. Patients in one study were from mixed sources (DANISH1999). It was not possible to discern setting in WHO1986. No study included all elderly participants or those whose depression has atypical features. Study inclusion criteria ensured a minimum HRSD score at baseline of between 16 and 22 or a MADRS score of 15.

Data were available to compare low doses with high doses of clomipramine, amitriptyline, trimipramine and imipramine. Data were also available to compare low-dose clomipramine with placebo.

Mean low dose was 60.8 mg (total range 25 mg to 75 mg) and mean high dose was 161.9 mg (total range 75 mg to 200 mg) (low-dose versus high-dose studies).

### 9.8.3 Evidence statements

**Effect of treatment on efficacy**

There is evidence suggesting that there is no clinically significant difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving remission by the end of treatment (N = 3; n = 222; RR = 0.99; 95% CI, 0.84 to 1.16).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms or on reducing depression symptoms as measured by the HRSD.

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and placebo on reducing depressive symptoms by the end of treatment as measured by the MADRS or on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD.

**Acceptability and tolerability of treatment**

There is some evidence suggesting that there is a clinically significant difference favouring low-dose TCAs over high-dose TCAs on leaving the study early due to side effects (N = 1; n = 151; RR = 0.35; 95% CI, 0.16 to 0.78).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and high-dose TCAs on reducing the likelihood of patients leaving treatment early.
9.8.4 Clinical summary

There is no clinically significant difference on achieving response between low-dose TCAs (mean dose = 60.8 mg) and therapeutic dose TCAs (mean dose = 161.9 mg). Of the four studies that compared low-dose TCA with high-dose TCA, two reported completer data only. Patients receiving a low-dose TCA were less likely to leave treatment early due to side effects.

9.8.5 From evidence to recommendations

This review was not updated by the guideline development group and the recommendation to maintain a low-dose TCA in people whose depression had responded was retained. However, the recommendation to monitor outcomes and increase dose depending on efficacy and side effects was removed since the points made are adequately covered by other recommendations in the guideline.

9.9 Clinical practice recommendation

5.9.1.1 People who start on low-dose tricyclic antidepressants and who have a clear clinical response can be maintained on that dose with careful monitoring. 55

Introduction

Although antidepressants are not associated with tolerance and craving, such as are experienced when withdrawing from addictive substances such as opiates or alcohol, some patients experience symptoms when stopping antidepressants or reducing the dose. In this guideline they are referred to as discontinuation symptoms.

Discontinuation symptoms can be broadly divided into 6 groups; affective (eg irritability), gastrointestinal (eg nausea), neuromotor (eg ataxia), vasomotor (eg sweating), neurosensory (eg paraesthesia), and other neurological (eg dreaming; Delgrado et al, 2006). They may be new or hard to distinguish from some of the original symptoms of the underlying illness. By definition they must not be attributable to other causes. They are experienced by at least a third of patients (Lejoyeux et al., 1996; MHRA, 2004) and are seen to some extent with all antidepressants (Taylor et al, 2006). Of the commonly used antidepressants, the risk of discontinuation symptoms seems to be greatest with paroxetine, venlafaxine and amitriptyline (Taylor et al, 2006).

The onset is usually within five days of stopping treatment, or occasionally during taper or after missed doses (Rosenbaum et al., 1998; Michelson et al., 2000). This is influenced by a number of factors, which may include a drug’s half-life. Symptoms can vary in form and intensity and occur in any combination. They are usually mild and self-limiting, but can occasionally be severe and prolonged, particularly if withdrawal is abrupt. Some symptoms are more likely with individual drugs, for example

55 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
dizziness and electric shock like sensations with SSRIs, and sweating and headache with TCAs (Lejoyeux et al., 1996; Haddad, 2001).

Factors affecting the development of discontinuation symptoms

Although anyone can experience discontinuation symptoms, the risk is increased in those prescribed short half-life drugs (Rosenbaum et al., 1998), such as paroxetine and venlafaxine (Hindmarch et al., 2000; Fava et al., 1997; MHRA, 2004). They can also occur in patients who do not take their medication regularly. Two-thirds of patients prescribed antidepressants skip a few doses from time to time (Meijer et al, 2001). The risk is also increased in those who have been taking antidepressants for eight weeks or longer (Haddad, 2001); those who developed anxiety symptoms at the start of antidepressant therapy (particularly with SSRIs); those receiving other centrally acting medication (eg antihypertensives, antihistamines, antipsychotics); children and adolescents; and those who have experienced discontinuation symptoms before (Lejoyeux & Ades, 1997; Haddad, 2001).

Discontinuation symptoms may also be more common in those who relapse on stopping antidepressants (Zajecka et al., 1998; Markowitz et al., 2000).

Clinical relevance

The symptoms of a discontinuation reaction may be mistaken for a relapse of illness or the emergence of a new physical illness (Haddad, 2001) leading to unnecessary investigations or reintroduction of the antidepressant. Symptoms may be severe enough to interfere with daily functioning. Another point of clinical relevance is that patients who experience discontinuation symptoms may assume that this means that antidepressants are addictive and not wish to accept further treatment. It is very important to counsel patients before, during and after antidepressant therapy about the nature of this syndrome.

How to avoid discontinuation symptoms

Although it is generally advised that antidepressants (except fluoxetine) should be discontinued over a period of at least 4 weeks, preliminary data suggest that it may be the half-life of the antidepressant rather than the rate of taper that ultimately influences the risk of discontinuation symptoms (Tint et al, 2008). When switching from one antidepressant to another with a similar pharmacological profile, the risk of discontinuation symptoms may be reduced by completing the switch as quickly as possible (a few days at most). A different approach may be required at the end of treatment where a slower taper is likely to be beneficial. The half-life of the drug should be taken into account. The end of the taper may need to be slower as symptoms may not appear until the reduction in the total daily dosage of the antidepressant is substantial. Patients receiving MAOIs may need dosage to be tapered over a longer period. Tranylcypromine may be particularly difficult to stop. It is not clear if the need for slow discontinuation of MAOIs, and particularly tranylcypromine, is due to the discontinuation syndrome or the loss of other neurochemical effects of these drugs. Since it is not possible to disentangle these phenomena, the clinical advice is that patients on MAOIs and those at risk patients (see above) need a slower taper (Haddad, 2001).

Many patients experience discontinuation symptoms despite a slow taper. For these patients, the option of abrupt withdrawal should be discussed. Some may prefer a short period of intense symptoms over a prolonged period of milder symptoms.
How to treat

There are no systematic randomised studies in this area. Treatment is pragmatic. If symptoms are mild, reassure the patient that these symptoms are not uncommon after discontinuing an antidepressant and that they will pass in a few days. If symptoms are severe, reintroduce the original antidepressant (or another with a longer half-life from the same class) and taper gradually while monitoring for symptoms (Lejoyeux & Ades, 1997; Haddad, 2001).

From evidence to recommendations

Since the previous guideline, the evidence base regarding for discontinuation symptoms with antidepressants is largely unchanged. Practitioners should ensure that they discuss the issue fully with patients, and consider prescribing antidepressants which are not associated with discontinuation symptoms, particularly for patients who have had previous experience of these. The previous recommendations are therefore retained, but rewritten to fit the updated NICE style.

9.9.1.2 When prescribing antidepressant medication prescribers should explore any concerns the person may have about taking medication, and provide a full explanation of the reasons for prescribing, including:

- the delay in development of the full antidepressant effect
- the importance of taking medication as prescribed and the need to continue treatment after remission
- information on any potential side effects
- the potential for interactions with other medications
- the risk of discontinuation symptoms and how these can be minimised, particularly with shorter half-life drugs, such as paroxetine and venlafaxine
- the fact that physical dependence does not occur with antidepressants.

Written information appropriate to the person’s needs should be made available.

9.9.1.3 Discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug but are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly.

9.9.1.4 Practitioners should normally gradually reduce the doses of the drug over a 4-week period although some people may require longer periods. This is not required with fluoxetine because of its long half-life.

9.9.1.5 If discontinuation symptoms occur, practitioners should;

- monitor symptoms and reassure the person if symptoms are mild
• inform the person that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms.

• consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) and reduce gradually while monitoring symptoms if symptoms are severe.

9.10 The cardiotoxicity of antidepressants

Consistent associations between depression and cardiovascular morbidity and mortality have been identified (Glassman & Shapiro, 1998). Depression is a significant independent risk factor for both first myocardial infarction and cardiovascular mortality with an adjusted relative risk in the range of 1.5 to 2 (Ford et al., 1998). In patients with ischaemic heart disease, depression has been found to be associated with a three- to four-fold increase in cardiovascular morbidity and mortality (Carney et al., 1997). The prevalence of major depression in patients with coronary heart disease is approximately 20% (Glassman et al., 2002).

In view of the above associations and factors it is important to use antidepressant drugs that either reduce or do not increase the cardiovascular risk of the condition itself and to establish a safe and effective treatment strategy for depressed patients with heart disease. There is evidence that adequate treatment of depression appears either to lower (Avery & Winokur, 1976) or not to change (Pratt et al., 1996) the risk of heart disease. However, two large-scale follow-up studies have shown an increase in myocardial infarction in users of antidepressants with an average odds ratio of 5.8 (Penttinen & Valonen, 1996; Thorogood et al., 1992). Recently a similar association has been identified in the UK for dothiepin/dosulepin (Hippsley-Cox et al., 2001).

However, these studies do not distinguish between the effects of drugs and the condition itself. Thus it is necessary to look at the effects of antidepressants on cardiovascular function and what trials are available (Roose, 2003).

9.10.1 Tricyclic antidepressants

Sinus tachycardia, postural hypotension and episodic hypertension are side effects frequently observed. ECG changes are frequent, such as lengthening of the QT, PR and QRS intervals relating to alterations in AV conduction and repolarisation (Roose et al., 1989). These effects are due to the wide-ranging pharmacological actions of TCAs that are not correlated with recognised mechanisms of antidepressant action. In healthy patients such changes may be asymptomatic or clinically unimportant, but in those with heart disease they may lead to significant morbidity and mortality (Glassman et al., 1993). For example, prolonged increased heart rate (mean 11%, Roose & Glassman, 1989) could have a major impact in terms of cardiac work (Roose, 2003). In patients with left ventricular impairment on TCAs, orthostatic hypotension is three to seven times more common and potentially clinically harmful (Glassman et al., 1993). The TCA induced prolongation of conduction may be clinically unimportant in healthy patients, but can lead to complications in those with conduction disease, in particular bundle branch block, and these can be severe in 20% of subjects (Roose et al., 1987). TCAs may be regarded as Class I arrhythmic drugs. Evidence suggests that this class of
drug is associated with an increase in mortality in post-infarction patients and in patients with a broader range of ischaemic disease, probably because they turn out to be arrhythmogenic when cardiac tissue becomes anoxic. Overdose of TCAs or elevated plasma levels as a result of interactions with other drugs, liver disease and age is associated with serious hypotension and atrial and ventricular arrhythmias may arise even to the extent of complete AV block, which in a number of cases may be fatal (deaths from TCAs represent 20% of overdose deaths; Shah et al., 2001).

9.10.2 Individual tricyclics
The tertiary amine tricyclics (amitriptyline, imipramine and clomipramine) have more cardiovascular effects than the secondary amine tricyclics (e.g. nortriptyline). The last drug has been shown to have less postural hypotension and, therefore, may be considered in those with cardiovascular disease and in the elderly in whom postural hypotension can be very hazardous. There is evidence (although not from an RCT) that lofepramine is safer in overdose than other tricyclics (Lancaster & Gonzalez, 1989). It is thought that lofepramine blocks the cardiotoxic effects of the main metabolite desipramine. Dothiepin/dosulepin has marked toxicity in overdose in uncontrolled studies (Henry & Antao, 1992; Buckley et al., 1994).

Selective serotonin reuptake inhibitors
Depression in untreated populations has been demonstrated to increase cardiovascular morbidity and mortality. SSRIs appear to reduce that risk, since two studies have reported no difference in cardiovascular risk between SSRI-treated depressed patients and non-treated non-depressed controls (Cohen et al., 2000; Meier et al., 2001). Recently Sauer et al. (2001) compared the rate of MI in patients on an SSRI with those on no antidepressants. The SSRI-treated patients had a significantly lower rate of MI than did the non SSRI-treated patients. Multiple studies (Roose, 2001) reveal no clinically significant effects of SSRIs on heart rate, cardiac conduction or blood pressure (see further details below). Studies of depressed patients with and without ischaemic heart disease have documented increased platelet activation and aggregation, which potentially contributes to thrombus formation (Musselman et al., 1998). Treatment with SSRIs normalises elevated indices of platelet activation and aggregation seen in non-treated patients with depression and IHD. There is evidence that this effect occurs at relatively low doses and before the antidepressant effect (Pollock et al., 2000). However, the effects on platelet serotonin are not always advantageous: SSRIs increase the probability of having a serious GI bleed, particularly in the very old (Walraven et al., 2001).

9.10.3 Individual drugs
Citalopram
The cardiac safety of citalopram has been studied in prospective studies in volunteers and patients and in retrospective evaluations of all ECG data from 40 clinical trials (1789 citalopram-treated patients) (Rasmussen et al., 1999). The only effect of citalopram was the reduction in heart rate (of eight beats per minute) but no other ECG change. There have been case reports of bradycardia with citalopram (Isbister et al., 2001) and a low frequency of hypotension and arrhythmias including left bundle branch block (Mucci, 1997).

Fluoxetine
In a seven-week open trial of older adults with cardiac disease, Roose et al. (1998b) showed that fluoxetine caused no major cardiovascular change. Strik et al. (2000) showed that fluoxetine was safe in 27 patients with recent myocardial infarction (more than three months since the myocardial infarction) and there was no change in cardiovascular indices in these patients compared with placebo. However, fluoxetine did not demonstrate clinical efficacy in this group compared with placebo (n = 54; WMD = –2.50, 95% CI, –5.64 to 0.64). It is noteworthy that fluoxetine has significant potential to interact with drugs commonly used in the management of heart disease (Mitchell, 1997).

Fluvoxamine

Fluvoxamine has not been found to be associated with cardiovascular or ECG changes (Hewer et al., 1995). Fluvoxamine appears to be safe in overdose (Garnier et al., 1993). Cardiotoxicity was not a serious problem; sinus bradycardia requiring no treatment was noted in a few cases.

Paroxetine

20 mg to 30 mg paroxetine daily was compared with nortriptyline (dose adjusted to give plasma concentrations of 80 to 120 mg/ml) in a double-blind study of 41 patients with MDD and IHD (Roose et al., 1998a). Paroxetine was not associated with clinically significantly sustained changes in heart rate, blood pressure or conduction intervals whereas nortriptyline caused ‘clinically significant’ changes in these measures and ‘more serious cardiac events’.

Sertraline

Three-hundred-and-sixty-nine patients with either unstable angina (26%) or recent (within 30 days) MI (74%) were randomised to receive either placebo or sertraline (flexible dose, 50 mg to 200 mg per day in a randomised double-blind trial) (Glassman et al., 2002). Sertraline had no significant effect on left ventricular function compared with placebo or on a range of clinical or laboratory investigations. The incidence of severe cardiovascular events was 14.5% with sertraline numerically, but not significantly, less than placebo at 22.4%.

There was no overall difference between sertraline and placebo in terms of antidepressant response in all patients studied. However, in more severely depressed patients (HRSD >=18 and at least two previous depressive episodes), there was some evidence of a greater decrease in depression symptoms in those on SSRIs compared with those on placebo (n = 90; WMD= –3.4, 95% CI, –6.47 to –0.3356). However, this study and others in the field are not adequately powered or of sufficient length to determine cardiovascular morbidity or mortality in the longer term.

9.10.4 Overdose

In contrast to the TCAs, the SSRIs, if taken alone, are only rarely lethal in overdose (Barbey & Roose, 1998; Goeringer et al., 2000). Deaths have occurred when citalopram has been ingested in very high doses (Ostrom et al., 1996). However, other studies, whilst reporting complications with high-dose citalopram overdoses, have not reported deaths (Personne et al., 1997b; Grundemar et al., 1997). The mechanisms of the deaths reported by Ostrom et al. (1996) are not clear. There is some evidence that high-
dose citalopram overdoses have been associated with ECG abnormalities (Personne et al., 1997a) and QTc prolongation (Catalono et al., 2001). However, Boeck et al. (1982) did not report cardiotoxicity with high-dose citalopram in the dog, and in the deaths reported by Ostrom et al. (1996) levels of the potentially cardiotoxic metabolite were low. Another potential mechanism of toxicity is that high-dose citalopram overdoses induce seizures and this has been shown in animals (Boeck et al., 1982) and man (Grundemar et al., 1997; Personne et al., 1997a). Glassman (1997) suggested that all high dose SSRI overdoses were a cause for concern and advised prudence over the prescription of large amounts of tablets.

9.10.5 Other drugs

Lithium

Lithium has a number of cardiac effects and they can be of clinical significance in patients with heart disease, the elderly, those with higher lithium levels, hypokalaemia and when lithium is used with other drugs such as diuretics, hydroxyzine and tricyclic antidepressants (Chong et al., 2001). Common, often subclinical, effects of lithium include the ‘sick sinus’ syndrome, first degree heart block, ventricular ectopics, flattened T-waves and increased QT dispersion (Reilly et al., 2000), but adverse clinical outcomes are rare. Caution and periodic ECG monitoring is advised in those at risk or with cardiac symptoms.

Mianserin

Cardiac effects with mianserin are rare (Peet et al., 1977; Edwards & Goldie, 1983; Jackson et al., 1987) although there have been some reports of bradycardia and complete heart block in overdose (Haefeli et al., 1991; Hla & Boyd, 1987) and, rarely, bradycardia at therapeutic doses (Carcone et al., 1991). Bucknall et al. (1988) showed that mianserin was well tolerated in most, but not all, cardiac patients.

Mirtazapine

No significant cardiovascular effects from mirtazapine have been noted (Nutt, 2002). It appears to have a benign safety profile in overdose (Velazquez et al., 2001).

Moclobemide

Moclobemide is not associated with any significant cardiovascular effects (Fulton & Benfield, 1996) and there are no reports of death in overdose with moclobemide as the sole agent.

Phenelzine

Phenelzine causes marked postural hypotension particularly in the early weeks of treatment and it is associated with a significant bradycardia. It does not cause conduction defects (McGrath et al., 1987a). Its fatal toxicity index in overdose appears to be less than most tricyclics (Henry & Antao, 1992). There is no data on the safety or clinical efficacy of phenelzine in patients with ischaemic heart disease.

Reboxetine

No specific clinical or ECG abnormalities have been noted with reboxetine (Fleishaker et al., 2001) and it has relative safety in overdose.

Trazodone

Trazodone is generally believed to have low cardiotoxicity, although there have been some reports of postural hypotension and, rarely, arrhythmias (Janowsky et al., 1983).
Venlafaxine

No obvious laboratory or clinical cardiac changes have been found with venlafaxine in routine use (Feighner, 1995). There is evidence that in higher doses greater than 200 mg, hypertension occurs in a small but significant minority, and others have recommended regular blood pressure monitoring at and above this dose (e.g. Feighner, 1995). There is also evidence that in overdose (greater than 900 mg) venlafaxine is pro-convulsant compared with TCAs and SSRIs (Whyte et al., 2003) and has a higher fatal toxicity index in overdose than SSRIs (Buckley & McManus, 2002). The MHRA also raised concerns about the increased incidence of adverse cardio-vascular events and the use of venlafaxine in individuals with pre-existing cardio-vascular disease (MHRA, 2004).

9.10.6 Clinical practice recommendations regarding antidepressant cardiotoxicity

Recommendations about the prescription of antidepressants to people with chronic physical illnesses are in a separate guideline (Depression in Chronic Physical Health Problems, in preparation).

9.10.6.1 When prescribing drugs other than SSRIs, practitioners should take into account:

- the increased likelihood of the person with depression stopping treatment because of side effects with venlafaxine, duloxetine and TCAs, and the consequent need to increase the dose gradually
- the specific cautions, contraindications, and monitoring requirements for some drugs. For example, the possibility of exacerbation of hypertension with venlafaxine and duloxetine; the the risk of hypokalaemia with reboxetine; the need for haematological monitoring with mianserin. Consult the BNF for detailed information.
- that non-reversible MAOIs, such as phenelzine, should normally be prescribed only by specialist mental health professionals that dosulepin should not be initiated.

9.11 Depression, antidepressants and suicide

9.11.1 Introduction

The majority of patients with depression have at least episodic suicidal ideation often linked to general negativity and hopelessness. Two-thirds of people who attempt suicide are suffering from depression, and suicide is the main cause of the increased mortality of depression and is commonest in those with comorbid physical and mental illness. Suicidal behaviour also occurs with milder forms of depression. In a meta-analysis of 36 studies the lifetime prevalence of suicide has been reported to be 4% in hospitalised depressed patients, rising to 8.6% if hospitalised for suicidality. In mixed inpatient/outpatients populations the lifetime prevalence is 2.2% compared with less than 0.5% in the non-affectively ill population (Bostwick & Pankratz, 2000). Harris and Barraclough (1997) found a suicide risk of 12 times that expected in a cohort of patients with dysthymia (DSM-III (APA, 1980)

Therefore, the effective recognition and treatment of depression should lead to a fall in the overall suicide rate.
9.11.2 Suicidality and antidepressants

There is evidence for a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment (Jick et al., 2004). However, this must be put against recent data showing that the risk of clinically significant suicidal behaviour is highest in the month before starting antidepressants and declines thereafter (Simon et al., 2006). The highest rates of suicidal behaviour were seen in patients treated by psychiatrists but same pattern was also seen with psychological treatments and in primary care (Simon & Savarino, 2007). No temporal pattern of completed suicide was found in the six months after starting an antidepressant (Simon et al, 2006). No increase in suicide/suicide thoughts or attempts were seen with SSRIs compared with other antidepressants (Jick et al, 2004; Simon et al, 2006b).

It is therefore not clear from these naturalistic data to what extent suicidal thoughts or behaviour can be attributable to a direct result of taking an antidepressant (the effect was seen with all classes of antidepressant) as opposed to the timing of when help was sought. Two meta-analyses of RCTs (Gunnell et al., 2005; Fergusson et al., 2005) with 702 and 477 studies respectively and a large nested case-control study comparing new prescriptions of SSRIs and TCAs (Martinez et al., 2005) found no evidence of an increase in completed suicide with SSRIs but possible evidence of increased suicidal/self-harm behaviour with SSRIs compared with placebo (NNH 684 and 754 in the two meta-analyses). There was no overall difference between SSRIs and TCAs (Fergusson et al, 2005; Martinez et al, 2005) but Martinez et al. (2005) found some evidence for increased self-harm behaviour on SSRIs compared with TCAs in those under 19 years. A review by Möller et al (2008) concluded that all antidepressants carry a small risk of inducing suicidal thoughts and suicide attempts, in age groups below 25 years, the risk reducing further at the age of about 30–40 years.

There is a delay in noticeable improvement after starting antidepressants, and, just after initiation of treatment, mood remains low with prominent feelings of guilt and hopelessness, but energy and motivation can increase and may be related to the increased suicidal thoughts. A similar situation can arise with patients who develop akathisia or increased anxiety due to a direct effect of some SSRIs and related drugs and it has been hypothesized that this may increase the propensity to suicidal ideation and suicidal behaviour (Healey, 2003). Careful monitoring is therefore indicated when treatment is initiated with an antidepressant. Patients should be monitored regardless of the apparent severity of their depression.

A meta-analysis of observational studies (Barbui et al 2009) found that compared with depressed people who did not take antidepressants, adolescents receiving SSRIs had a significantly higher risk of suicide attempts and completed suicide. In contrast adults, especially older adults, had a significantly lower risk of suicide attempts and completed suicide. Ecological data has failed to find any link between SSRI use and higher completed suicide rates (Gibbons et al., 2005; Hall & Lucke, 2006), in fact it has been suggested that the overall reduction in suicide rate may be partly due to more effective treatment of depression with newer antidepressants. In particular, it has been argued that the significant reductions in suicide rates in Sweden, Hungary, the USA and Australia have been due to treatment with these drugs (Isacsson et al., 1997; Hall et al., 2003). However, a number of other factors may account for this trend including changing socio-economic circumstances, and demonstrating a causal link between
increased antidepressant prescription and falling suicide rates is not straightforward and has not been conclusively established (Gunnell & Ashby, 2004).

The use of antidepressants in the treatment of depression is also not without risk not least because of their toxicity in overdose. Antidepressants were involved in 18% of deaths from drug poisoning between 1993 and 2002 (Morgan et al, 2004), with TCAs, which are cardiotoxic in overdose (see section 8.2.9), accounting for 89% of these. This is equivalent to 30.1 deaths per million prescriptions. Dothiepin/dosulepin alone accounted for 48.5 deaths per million prescriptions (ibid). By contrast, over the same period, SSRIs accounted for around 6% of deaths by suicide, and other antidepressants, including venlafaxine, around 3%. This is equivalent to 1 and 5.2 deaths per million prescriptions respectively (ibid). Venlafaxine alone accounted for 8.5 deaths per million prescriptions. Morgan et al. (2004) showed an overall reduction in mortality rates over the time period studied, with a fall in rates related to TCAs, little change for SSRIs, but an increase for other antidepressants largely due to venlafaxine. These data are based on analyses of coroners’ records for England and Wales, and prescription data for drugs dispensed in England (regardless of the prescription’s country of origin). They may be subject to bias because indication is not recorded on prescriptions. Some antidepressants are licensed for conditions such as obsessive-compulsive disorder and post-traumatic stress disorder in addition to depression. Also, coroners record antidepressant information voluntarily and only if they consider the antidepressant contributed to the cause of death (ibid). Interpretation of these data is complicated by the possibility of differential prescribing, that is patients at high risk of suicide may have been prescribed different drugs from those at low risk, and the MHRA (2006) concluded that the increased rate seen with venlafaxine was partly, but not wholey, attributable to patient characteristics.

**From evidence to recommendations**

There is a small risk of inducing suicidal ideation in younger people starting antidepressants. Although the most recent data suggests the cut-off for this is around 25 years old, previous advice from the MHRA suggests the cut-off should be around 30. Practitioners should seek strategies to reduce risk as far as possible for people who are at increased risk of suicide, including prescribing drugs with relatively low toxicity and prescribing small amounts of drugs. They should refer people at high risk to specialist mental health services.

**9.12 Clinical practice recommendations**

9.12.1 A person with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically significant.
9.12.1.2 Where a person with depression presents considerable immediate risk to self or others, urgent referral to a specialist mental health service should be arranged.

9.12.1.3 When a person with depression is assessed to be at risk of suicide, practitioners should consider:
   - toxicity in overdose where an antidepressant is prescribed and when determining the quantity supplied at any one time; where necessary, implement strategies to limit the amount of drug available
   - the use of additional support such as more frequent direct or telephone contacts
   - referral to specialist mental health services.

9.12.1.4 Practitioners should advise patients of the potential for increased agitation, anxiety, suicidal ideation (and for people taking antidepressants, akathisia) in the initial stages of treatment. They should actively seek out these symptoms and ensure that the person with depression knows how to seek help promptly if these are at all distressing. In the event that a patient develops marked and/or prolonged agitation (or akathisia while taking an antidepressant), the treatment should be reviewed.

9.12.1.5 Consider toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. Be aware of the greater risk of death from overdose with tricyclic antidepressants (with the exception of lofepramine) and venlafaxine, than other equally effective drugs recommended for routine use in primary care.
10 The pharmacological management of depression which has not responded adequately to treatment

10.1 Introduction

Despite major developments in the management of mood disorders, in clinical practice the problem of incomplete, or lack of, response to treatment continues to be problematic. Numerous outcome studies have demonstrated that approximately one-third of patients treated for major depression do not respond satisfactorily to first-line antidepressant pharmacotherapy.

Follow-up observations reveal that a considerable number of patients have a poor prognosis with as many as 20% remaining unwell two years after the onset of illness (Keller et al., 1986). Even after multiple treatments, up to 10% of patients remain depressed (Nirenberg & Amsterdam, 1990). A range of studies suggests that between 10% and 20% of patients with major depressive disorder have a long-term poor outcome (Winokur et al., 1993; Lee & Murray, 1988).

It is difficult, however, to evaluate the true degree of poor response to treatment for major depressive disorder from these figures. Although poor response is relatively common in clinical practice, a major problem has been the inconsistent way in which it has been characterised and defined, limiting systematic research. In recent years there have been attempts to agree definitions of ‘treatment resistance’ in order to improved the characterisation of the phenomenon, although there is still disagreement on some of the items. The key parameters that have been used to characterise and define treatment resistance include the basic criteria used to specify the diagnosis, response to treatment, previous treatment trials and the adequacy of treatment (Nirenberg & Amsterdam, 1990). While it is important to be able to describe these parameters, as discussed in the introduction (Chapter 2) we have moved away from the term treatment resistant depression as used in the previous guideline. The term implies that there is natural cut-off at 2 antidepressant-treatment failures which is not supported by evidence; and the term may be taken by both clinicians and patients as a perjorative label. It does not take into account different degrees of improvement or stage of illness, psychosocial treatment and non-antidepressant augmenting agents are not easily incorporated. We have preferred to approach the problem of inadequate response from the direction of next-step treatment options rather than a category of patient.

10.1.1 Approach to the reviews

The major reviews undertaken for the previous guideline are represented, updated with new studies where these were available. Previously, studies had been categorised ‘treatment-resistant’ where participants had been recruited because their depression had not responded to two sequential antidepressant drugs prescribed in an adequate dose for an adequate duration of time, and ‘acute-phase non-responder’ where
participants’ depression had not adequately responded to one antidepressant. These
distinctions were not made in the present review, although the studies were coded for
the number of antidepressant courses ‘failed’ both historically and prospectively (for
example, H2P1 denotes that participants had inadequately responded to 2
antidepressants historically and one prospectively). In addition, studies of
augmentation strategies which had not recruited people specifically because their
depression had not responded to at least one previous treatment were removed from
the analyses. A few studies used an open-label design. Since there are relatively few
data on this topic, these were analysed separately and described narratively.

Table 88: Databases searched and inclusion/exclusion criteria for clinical
effectiveness of pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008, January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
</tbody>
</table>
| Population           | People with a diagnosis of depression according to DSM, ICD or similar
criteria whose depression has failed to respond to treatment |
| Treatments           | Any pharmacological or physical treatment |

In total, 11 new trials were found to supplement the previous reviews.

Data were available to examine the following next-step strategies:

- Increasing the dose
- Switching to another antidepressant
- Augmentation strategies including:
  - Another antidepressant
  - An antipsychotic
  - Lithium
  - An anticonvulsant
  - Pindolol
  - T3
  - Augmentation with other agents (atomoxetine, buspirone)
  - ECT57.

In addition, a narrative review of repetitive transcranial magnetic stimulation (rTMS)
and vagal nerve stimulation (VNS) were included.

There were no new data for some strategies (augmentation with lithium,
anticonvulsants, pindolol or benzodiazepines).

The above strategies were reviewed, as there was sufficient evidence to come to a
conclusion about efficacy and/or there is significant clinical usage of such strategies in
the UK. There is, however, a wide range of other strategies used where first-line

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57 This section updates the NICE Technology Appraisal on ECT (for depression only)
treatment has not been effective, for which either the evidence base is so weak or the clinical usage so low that the GDG did not include them in this review. Examples of these latter strategies include the use of stimulants or glucocorticoid antagonists either alone or to augment antidepressants.

Details of the available information about these strategies (e.g. case reports, open studies, expert opinion) can be found elsewhere (Bauer et al., 2002b; Price et al., 2001; Thase & Rush, 1997). These papers also include details of the pharmacological issues associated with these strategies. A wide variety of new treatments to augment antidepressants are being developed or are in pilot trial phase. These are beyond the scope of this review and details can be found elsewhere (Tamminga et al., 2002).

MAOIs have been used extensively in the management of ‘treatment-resistant’ depression for four decades but there is no randomised data on which to base recommendations. Most information and experience is with phenelzine. McGrath et al. (1987b) treated patients in a cross-over design with high doses of phenelzine (maximum 90 mg), imipramine (maximum 300 mg) or placebo and found that of the non-responders only four of the 14 patients responded to a tricyclic cross-over with 17 of the 26 patients responding to an MAOI cross-over. There was some evidence of a preferential response in treatment-resistant patients with atypical depression symptoms, but Nolen et al. (1988) subsequently showed that not only patients with atypical depressive symptoms but also patients with major depression and melancholia responded to MAOIs, in particular tranylcypromine. It does not appear that moclobemide has the same spectrum of efficacy in treatment resistance as the classical MAOIs. Nolen et al. (1994) switched patients with resistant depression stabilised on tranylcypromine to moclobemide. About 60% of the patients showed deterioration and one-third relapsed.

10.1.2 Increasing the dose

When depression does not respond adequately, a common treatment strategy is to increase the dose of the antidepressant within the licensed dosage range. There is little objective evidence to support higher response rates with increasing dose (within the licensed dosage range) for the majority of antidepressants, but this does not preclude the possibility of a beneficial effect being seen in individual patients. Any beneficial effect is likely to be at least partially determined by individual differences in hepatic metabolising enzymes.

Nine studies were found which compared drugs at different doses following lack of response to the initial dose (of which one was found in the update search (WHITMYER2007)), but only 2 included a treatment group that remained on the previous dose after an adequate trial of the initial treatment (see Table 89). Summary study characteristics of these 2 studies are in Table 90 (with full details in Appendix 17). Only one study (Licht et al, 2002) used a licensed dose for all patients in the initial phase, allowed adequate time to respond to this dose, and then randomised patients to remain on this dose or receive a higher dose.

<table>
<thead>
<tr>
<th>Table 89 Studies (RCTs) comparing antidepressants at different doses in people whose depression is resistant to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>StudyID</td>
</tr>
<tr>
<td>---------</td>
</tr>
</tbody>
</table>

Depression in adults (update): full guideline DRAFT (February 2009)
Fava1994
Fluoxetine 20mg 8 weeks
Fluoxetine high-dose 40-60mg
Fluoxetine + mianserin
Fluoxetine + lithium
No same dose group

Fava2002
Fluoxetine 20mg 8 weeks
Fluoxetine high-dose 40-60mg
Fluoxetine + desipramine
Fluoxetine + lithium
No same dose group

Licht2002
Sertraline 50mg 4 weeks then 100mg 2 weeks
Sertraline same-dose 100mg
Sertraline high-dose 200mg
Sertraline + mianserin
Allows comparison

Benkert1997
Maprotiline 100mg 3 weeks
Maprotiline same-dose 100mg
Maprotiline high-dose 150mg
Open-label phase too short

Benkert1997
Paroxetine 20mg 3 weeks
Paroxetine same-dose 20mg
Paroxetine high-dose 40mg
Open-label phase too short

Schweizer2001
Sertraline 50mg 3 weeks
Sertraline same-dose 50mg
Sertraline high-dose 150mg
Open-label phase too short

Dornseif1989
Fluoxetine 20mg 3 weeks
Fluoxetine same-dose 20mg
Fluoxetine high-dose 60mg
Open-label phase too short & high-dose fluoxetine dose too high

Schweizer1990
Fluoxetine 20mg 3 weeks
Fluoxetine same-dose 20mg
Fluoxetine high-dose 60mg
Open-label phase too short & high-dose fluoxetine dose too high

Whitmyer2007
Duloxetine 30mg or 60mg 6 weeks
Duloxetine 60mg
Duloxetine 120mg
Allows comparison, although some participants were on a sub-therapeutic dose during the open-label phase

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LICHT2002 H0P1</td>
<td>Sertraline 50mg 4 weeks then 100mg 2 weeks</td>
</tr>
<tr>
<td>WHITMYER2007 H0P1</td>
<td>Sertraline 200mg 6 weeks</td>
</tr>
</tbody>
</table>

There was evidence that increasing the dose led to small improvements in outcomes compared with continuing with the current dose, although these are not statistically significant. However, there are few randomised trials (see Table 91) for the summary evidence profile. The full profile is in Appendix 16.

Table 91 Summary evidence profile for dose-escalation following an inadequate treatment response

| Dose-escalation | Mean depression scores at SMD-0.11 (-0.29 to 0.08) |

Depression in adults (update): full guideline DRAFT (February 2009) Page 325 of 441
Clinical summary for dose escalation
There is little objective evidence that increasing the dose improves outcomes, although there are very few randomised studies. It is known that there are genetically determined differences in the activity of several hepatic enzymes that are involved in the metabolism of antidepressant drugs. Fast or extensive metabolisers may therefore need higher doses. Until further data are available, it is reasonable to consider increasing the dose of an antidepressant within the SPC recommended range, particularly where there has been a partial response and side effects are not problematic.

10.1.3 Switching strategies

Introduction
Approximately 20% to 30% of patients with depression fail to respond to the first antidepressant prescribed (assuming an adequate dose, duration of treatment and compliance with medication; Cowen, 1998). It is normal clinical practice at this point to increase the dose to the maximum tolerated (within licensed limits; see section 10.1.2) and, if there is still no or minimal response, to switch to an alternative antidepressant (Anderson et al., 2008). Most prescribers select an antidepressant from a different class to the ‘failed’ drug (Fredman et al., 2000). Randomised studies of switching are difficult to interpret as they either include patients who may be expected to fare poorly on one of the treatments (e.g. patients with atypical depression in a study with a MAOI and

<table>
<thead>
<tr>
<th>endpoint (clinician-rated)</th>
<th>Quality</th>
<th>Number of studies; participants</th>
<th>Forest plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>High</td>
<td>K=1;n=443</td>
<td>Pharm next-step 01.01</td>
</tr>
<tr>
<td>RR 0.8 (0.59 to 1.1)</td>
<td></td>
<td>(44.8% vs 54.5%)</td>
<td></td>
</tr>
<tr>
<td>Quality Low</td>
<td></td>
<td>K=2;n=452</td>
<td>Pharm next-step 01.03</td>
</tr>
<tr>
<td>Non-remission</td>
<td></td>
<td>K=2;n=452</td>
<td>Pharm next-step 01.02</td>
</tr>
<tr>
<td>RR 0.94 (0.83 to 1.06)</td>
<td></td>
<td>(67% vs 71.2%)</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>Moderate</td>
<td>K=2;n=452</td>
<td>Pharm next-step 01.04</td>
</tr>
<tr>
<td>RR 0.7 (0.48 to 1.04)</td>
<td></td>
<td>(15.7% vs 22.1%)</td>
<td></td>
</tr>
<tr>
<td>Quality Low</td>
<td></td>
<td>K=2;n=453</td>
<td>Pharm next-step 01.05</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td></td>
<td>RR 0.97 (0.45 to 2.11)</td>
<td></td>
</tr>
<tr>
<td>RR 0.97 (0.45 to 2.11)</td>
<td></td>
<td>(5.2% vs 5.4%)</td>
<td></td>
</tr>
</tbody>
</table>
TCA arm; McGrath et al., 1993) or employ a cross-over design (Thase et al., 1992; McGrath et al., 1993). Open studies, however, show that approximately 50% of patients who do not respond to their first treatment are likely to respond to the second antidepressant irrespective of whether it comes from the same class or a different one (Thase & Rush, 1997).

**Studies considered for review**

Altogether, 6 studies met inclusion criteria for the update, 3 of which were included in the previous guideline (2 in other reviews) (FERRERI2001; POIRIER99; THASE2002). Data were available to compare various switching strategies, including continuing with antidepressant treatment versus switching, comparison of switches to other single antidepressants, and comparison of switches to a single antidepressant versus switching to combinations of drugs. Data were available to compare continuing antidepressant treatment versus switching to olanzapine, but the GDG did not consider this relevant to clinical practice so the data are not reported (but are included in the forest plots for completeness).

Summary study characteristics of the included studies are in Table 92 with full details in Appendix 17 which also includes details of excluded studies.
### No. trials (Total participants)

<table>
<thead>
<tr>
<th>No. trials (Total participants)</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 RCTs</td>
<td>5 RCTs</td>
<td></td>
</tr>
</tbody>
</table>

### Study IDs

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) CORYA2006 H1P1</td>
<td>(1) CORYA2006 H1P1</td>
<td></td>
</tr>
<tr>
<td>(2) FERRERI2001 H0P1</td>
<td>(2) LENOX-SMITH2008 H1P0</td>
<td></td>
</tr>
<tr>
<td>(3) SHELTON2005 H1P1</td>
<td>(3) POIRIER99 H2P0</td>
<td></td>
</tr>
<tr>
<td>(4) SHELTON2005 H1P1</td>
<td>(4) SHELTON2005 H1P1</td>
<td></td>
</tr>
<tr>
<td>(5) THASE2002 H0P1</td>
<td>(5) THASE2002 H0P1*</td>
<td></td>
</tr>
</tbody>
</table>

### N/ % female

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 119/73</td>
<td>(1) 303/73</td>
<td></td>
</tr>
<tr>
<td>(2) 104/unclear</td>
<td>(2) 406/42</td>
<td></td>
</tr>
<tr>
<td>(3) 210/68</td>
<td>(3) 122/72</td>
<td></td>
</tr>
<tr>
<td>(4) 288/68</td>
<td>(4) 288/68</td>
<td></td>
</tr>
<tr>
<td>(5) 166/68</td>
<td>(5) 166/68</td>
<td></td>
</tr>
</tbody>
</table>

### Mean age (range if not available)

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 46</td>
<td>(1) 46</td>
<td></td>
</tr>
<tr>
<td>(2) Not given</td>
<td>(2) 46</td>
<td></td>
</tr>
<tr>
<td>(3) 42</td>
<td>(3) 21-62</td>
<td></td>
</tr>
<tr>
<td>(4) 42</td>
<td>(4) 42</td>
<td></td>
</tr>
<tr>
<td>(5) 21-65</td>
<td>(5) 21-65</td>
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</tbody>
</table>

### Treatment group 1

<table>
<thead>
<tr>
<th>Treatment group 1</th>
<th>Treatment group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Continuing venlafaxine</td>
<td>(1) Switching to fluoxetine</td>
</tr>
<tr>
<td>(2) Continuing fluoxetine</td>
<td>(2) Switching to mianserin</td>
</tr>
<tr>
<td>(3) Continuing nortriptyline</td>
<td>(3) Switching to fluoxetine</td>
</tr>
<tr>
<td>(4) Switching to fluoxetine + olanzapine</td>
<td>(4) Switch to venlafaxine</td>
</tr>
<tr>
<td>(5) Switch to venlafaxine</td>
<td>(5) Switch to imipramine</td>
</tr>
</tbody>
</table>

### Setting

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Unclear</td>
<td>(1) Unclear</td>
<td></td>
</tr>
<tr>
<td>(2) In/outpatients</td>
<td>(2) In/outpatients</td>
<td></td>
</tr>
<tr>
<td>(3) Unclear</td>
<td>(3) In/outpatients</td>
<td></td>
</tr>
<tr>
<td>(4) Unclear</td>
<td>(4) Unclear</td>
<td></td>
</tr>
<tr>
<td>(5) Outpatients</td>
<td>(5) Outpatients</td>
<td></td>
</tr>
</tbody>
</table>

### Length of treatment

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Continuing antidepressant treatment vs switching</th>
<th>Switching treatment(s) (comparison of drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 12 weeks</td>
<td>(1) 12 weeks</td>
<td></td>
</tr>
<tr>
<td>(2) 6 weeks</td>
<td>(2) 12 weeks</td>
<td></td>
</tr>
<tr>
<td>(3) 8 weeks</td>
<td>(3) 4 weeks</td>
<td></td>
</tr>
<tr>
<td>(4) 8 weeks</td>
<td>(4) 8 weeks</td>
<td></td>
</tr>
<tr>
<td>(5) 12 weeks</td>
<td>(5) 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

* participants in this study were randomised to both initial treatment and switching strategy and it is therefore analysed separately

### Continuing with antidepressant treatment versus switching

Data were available to compare continuing nortriptyline with switching to fluoxetine, continuing fluoxetine with switching to mianserin, and continuing venlafaxine with switching to fluoxetine. There was no evidence that either strategy was more effective, or more acceptable and tolerable. In addition, switching to an SSRI from an antidepressant of another class is unusual clinical practice. See Table 93 for the summary evidence profile. The full profile is in Appendix 16.

### Table 93 Summary evidence profile for continuing antidepressant treatment versus switching following inadequate response to treatment

<table>
<thead>
<tr>
<th>Mean depression scores at endpoint (self-rated)</th>
<th>Nortriptyline vs fluoxetine</th>
<th>Fluoxetine vs mianserin</th>
<th>Venlafaxine vs fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMD 1.05 (~1.31 to 3.41)</td>
<td>WMD 1.8 (~1.63 to 5.23)</td>
<td>WMD -2.03 (~5.22 to 1.16)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Number of studies; participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>K=1; n=210</td>
</tr>
<tr>
<td>Low</td>
<td>K=1; n=72</td>
</tr>
<tr>
<td>Low</td>
<td>K=1; n=119</td>
</tr>
</tbody>
</table>
Switching antidepressant treatment (comparison of strategies)

Data were available to compare the following switching strategies: switch to venlafaxine versus switch to an SSRI (citalopram or paroxetine); and switch to fluoxetine + olanzapine versus switch to fluoxetine. This part of the review updates the review of venlafaxine for treatment-resistant depression included in the previous guideline. There was no difference between the switching strategies for which data were available on any measure, other than on the number of people leaving treatment early because of side effects which favoured fluoxetine over fluoxetine plus olanzapine. Pooling the two RCTs in which non-responders were randomised to venlafaxine or an SSRI did not show a significant advantage to venlafaxine. One study in severely ill patients did suggest an advantage to venlafaxine in some outcomes as reported in the previous guideline but the latest study did not. A secondary analysis of the second study did however report an advantage to venlafaxine over ** but a secondary analysis of severely ill patients did significantly favour venlafaxine. Whether venlafaxine has an advantage in severely depressed patients is therefore undetermined. See Table 94 for the summary evidence profile. The full profile is in Appendix 16.

One study randomised to both initial treatment and switching strategy, and this was analysed separately. It showed no statistically significant advantage for either strategy (sertraline to imipramine or imipramine to sertraline), although there was an advantage for those starting on imipramine and switching to sertraline following inadequate response (see Appendix 16 for data).
Table 94 Summary evidence profile for switching antidepressant treatment (comparison of strategies) following inadequate antidepressant response

<table>
<thead>
<tr>
<th></th>
<th>Venlafaxine vs SSRIs</th>
<th>Fluoxetine + olanzapine vs fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean depression scores at endpoint (self-rated)</td>
<td>WMD -0.5 (2.09 to 1.09)</td>
<td>WMD -1.13 (-3.22 to 0.97)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=526</td>
<td>K=2; n=591</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 03.02</td>
<td>Pharm next-step 03.04</td>
</tr>
<tr>
<td>Non-response</td>
<td>RR 0.91 (0.73 to 1.14) (61.6% vs 65.5%)</td>
<td>RR 0.88 (0.74 to 1.05) (47% vs 40.6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=519</td>
<td>K=2; n=591</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 03.01</td>
<td>Pharm next-step 03.04</td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.91 (0.67 to 1.24) (52.2% vs 54.5%)</td>
<td>RR 1 (0.69 to 1.47) (5.37% vs 34.2%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=519</td>
<td>K=2; n=591</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 03.01</td>
<td>Pharm next-step 03.04</td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 1.19 (0.85 to 1.67) (22.2% vs 18.7%)</td>
<td>RR 1.12 (0.79 to 1.59) (23.1% vs 19.8%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=529</td>
<td>K=2; n=591</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 03.03</td>
<td>Pharm next-step 03.04</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 1.17 (0.58 to 2.36) (6.1% vs 5.2%)</td>
<td>RR 2.41 (1.07 to 5.43) (10% vs 3.5%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=529</td>
<td>K=2; n=591</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 03.03</td>
<td>Pharm next-step 03.04</td>
</tr>
</tbody>
</table>

In addition to the blinded RCTs that were included in the meta-analyses, the search yielded two large open randomised studies. In the first, non-responders to a single antidepressant were randomised to receive venlafaxine or another antidepressant (Baldomero et al, 2005), and in the second, non-responders to citalopram were randomised to switch to another antidepressant or receive an augmenting drug; those who did not remit were further randomised (Star D).

In the first large 24-week open-label study (Baldomero et al, 2005), 3502 outpatients with major depressive disorder, minor depression (8.7%) and dysthymia (16%) whose depressive symptoms (HRSD scores above 17) had not responded to treatment with an antidepressant (most commonly an SSRI) for at least 4 weeks, 1830 people were randomised to venlafaxine XR (mean dose 164mg) and 1672 to other antidepressants (different to that used in earlier treatment and including fluoxetine (17%), paroxetine (21.3%), citalopram (20.1%), sertraline (19.1%) and mitazepine (7.9%). There was little difference in mean endpoint depression scores between the venlafaxine group and the other antidepressant group (venlafaxine 7.89 (sd; 6.5); other antidepressants 8.84 (6.7)). However, 967 people (52% of the number randomised) taking venlafaxine achieved remission (HRSD <= 7) as did 755 (45% of the number randomised) taking other antidepressants.
antidepressants. The response rate (50% reduction in baseline HRSD scores) was 1262 (69%) in the venlafaxine group and 1034 (62%) in the other group. Figures are calculated from number randomised rather than ‘ITT’ population used by study authors.

As the STAR D study contained both switching and augmentation arms, the data from these studies are summarised in the augmentation section below.

Given the paucity of evidence from switching studies, evidence from primary efficacy studies in which antidepressants were directly compared were also considered. Caution is required in extrapolating from these studies to those whose illness has not responded to sequential trials of antidepressant drugs.

Data from switching studies and head to head studies suggest that there may be a very small efficacy advantage for venlafaxine and escitalopram over other antidepressants. This advantage is too small to be clinically meaningful when all people with depression are considered together, but may be large enough to be clinically worthwhile in those who have not benefited from treatment with a first or second antidepressant.

### 10.1.4 Augmenting an antidepressant with another antidepressant

Combining antidepressant drugs with different modes of action is increasingly used in clinical practice. Combinations of serotonergic and noradrenergic drugs may result in a ‘dual action’ combination while combinations of serotonergic drugs with different modes of action may be expected to increase serotonergic neurotransmission more than either drug alone.

While the efficacy of these combinations may be additive (this is not proven for the majority of combinations), so too may the toxicity. Both pharmacokinetic and pharmacodynamic interactions must be considered. Fluoxetine, fluvoxamine and paroxetine may substantially and unpredictably increase TCA serum levels increasing the risk of adverse effects (Taylor, 1995). Combinations of serotonergic antidepressants increase the risk of developing serotonin syndrome, which can be fatal. Features include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus.

#### Studies considered for review

No new studies of augmentation with a second antidepressant were found. Summary study characteristics of the included studies are in Table 95 with full details in Appendix 17 which also includes details of excluded studies. There were data for a range of strategies, including adding mianserin, desipramine (not available in the UK), mirtazapine, moclobemide and atomoxetine to an antidepressant.
Table 95 Summary study characteristics of included studies of antidepressant augmentation in people whose depression had not responded adequately to treatment

<table>
<thead>
<tr>
<th>Augmentation with a second antidepressant</th>
<th>No. trials (Total participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study IDs</td>
<td></td>
</tr>
<tr>
<td>(1) FAVA1994</td>
<td>(1) 104 (unclear)</td>
</tr>
<tr>
<td>(2) FAVA2002</td>
<td>(2) 295 (unclear)</td>
</tr>
<tr>
<td>(3) FERRERI2001 H0P1</td>
<td>(3) 34</td>
</tr>
<tr>
<td>(4) LICHT2002 H0P1</td>
<td>(4) 26</td>
</tr>
<tr>
<td>(5) MAES1999 H1P0</td>
<td>(5) 59</td>
</tr>
<tr>
<td>(6) CARPENTER2002 H0P1</td>
<td>(7) TANGHE1997 H2P0</td>
</tr>
<tr>
<td>N/% female</td>
<td></td>
</tr>
<tr>
<td>(1) 104 (unclear)</td>
<td>(2) 295 (unclear)</td>
</tr>
<tr>
<td>(3) 34</td>
<td>(4) 26</td>
</tr>
<tr>
<td>(5) 59</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td></td>
</tr>
<tr>
<td>(1) Not given</td>
<td>(2) Not given</td>
</tr>
<tr>
<td>(3) Not given</td>
<td>(4) 46</td>
</tr>
<tr>
<td>(5) 43</td>
<td></td>
</tr>
<tr>
<td>Augmenting agent</td>
<td></td>
</tr>
<tr>
<td>(1) Mianserin 60 mg</td>
<td></td>
</tr>
<tr>
<td>(2) Mianserin 30 mg</td>
<td></td>
</tr>
<tr>
<td>(3) Mianserin 30 mg</td>
<td></td>
</tr>
<tr>
<td>(4) Mirtazapine 15 mg (30 mg in 3 patients)</td>
<td></td>
</tr>
<tr>
<td>(5) Moclobemide 200-600mg</td>
<td></td>
</tr>
<tr>
<td>Antidepressant</td>
<td></td>
</tr>
<tr>
<td>(1) Fluoxetine 20 mg</td>
<td></td>
</tr>
<tr>
<td>(2) Sertraline 100 mg</td>
<td></td>
</tr>
<tr>
<td>(3) Fluoxetine 20 mg</td>
<td></td>
</tr>
<tr>
<td>(4) SSRIs, venlafaxine or bupropion</td>
<td></td>
</tr>
<tr>
<td>(5) Amitriptyline up to 280mg</td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
</tr>
<tr>
<td>(1) In/outpatients</td>
<td></td>
</tr>
<tr>
<td>(2) Outpatients</td>
<td></td>
</tr>
<tr>
<td>(3) Inpatients</td>
<td></td>
</tr>
<tr>
<td>(4) Outpatients</td>
<td></td>
</tr>
<tr>
<td>(5) Inpatients</td>
<td></td>
</tr>
<tr>
<td>Length of treatment</td>
<td></td>
</tr>
<tr>
<td>(1) 6 weeks</td>
<td></td>
</tr>
<tr>
<td>(2) 5 weeks</td>
<td></td>
</tr>
<tr>
<td>(3) 5 weeks</td>
<td></td>
</tr>
<tr>
<td>(4) 4 weeks</td>
<td></td>
</tr>
<tr>
<td>(5) 4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Evidence profile and clinical summary

Results showed that combination treatment tended to reduce depression symptoms more than continuing with the existing single antidepressant at ‘standard’ dose. However, the data are not strong, and participants taking combination treatment reported more side effects than those taking a single antidepressant. See Table 96 for the summary evidence profile. The full profile is in Appendix 16.

Since the majority of studies used mianserin as the augmentor, the analyses are weighted towards this drug. There is some evidence that combinations of antidepressants are associated with a higher burden of side effects than a single antidepressant at either standard or high dose, but there is insufficient evidence to comment on the number of patients leaving treatment early.
### Table 96 Summary evidence profile for augmentation with an antidepressant versus antidepressant with/out placebo

<table>
<thead>
<tr>
<th>Augmentation Strategy</th>
<th>SSRI + Mianserin</th>
<th>Fluoxetine + Desipramine vs High-dose Fluoxetine</th>
<th>Antidepressant + Mirtazapine</th>
<th>Amitriptyline + Moclobemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean depression change scores at endpoint*</td>
<td>SMD -0.46 (-1.07 to 0.15)</td>
<td>SMD 0.67 (0.05 to 1.28)</td>
<td>SMD -0.83 (-1.64 to -0.01)</td>
<td>SMD -0.63 (-1.28 to 0.01)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=288</td>
<td>K=2; n=96</td>
<td>K=1; n=26</td>
<td>K=1; n=39</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 07.03</td>
<td>Pharm next-step 07.03</td>
<td>Pharm next-step 07.03</td>
<td>Pharm next-step 07.03</td>
</tr>
<tr>
<td>Non-response</td>
<td>RR 0.71 (0.44 to 1.17) (34.8% vs 43.6%)</td>
<td>RR 0.67 (0.05 to 1.28)</td>
<td>RR 0.45 (0.2 to 1.03) (36.4% vs 80%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=290</td>
<td>K=2; n=96</td>
<td>K=1; n=26</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 07.01</td>
<td></td>
<td>Pharm next-step 07.01</td>
<td></td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.81 (0.62 to 1.04) (56.2% vs 67.9%)</td>
<td>RR 1.32 (0.96 to 1.81) (71.7% vs 54.2%)</td>
<td>RR 0.63 (0.35 to 1.12) (54.5% vs 86.7%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=267</td>
<td>K=2; n=96</td>
<td>K=1; n=26</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 07.02</td>
<td>Pharm next-step 07.02</td>
<td>Pharm next-step 07.02</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 1.44 (0.81 to 2.58) (17.7% vs 12.4%)</td>
<td>RR 1.71 (0.61 to 4.83) (17.4% vs 10.4%)</td>
<td>RR 0.68 (0.07 to 6.61) (9.1% vs 13.3%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=267</td>
<td>K=2; n=96</td>
<td>K=1; n=26</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 07.05</td>
<td>Pharm next-step 07.05</td>
<td>Pharm next-step 07.05</td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 1.52 (0.58 to 4.36) (6.9% vs 4.4%)</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=167</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 07.06</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N/R = not reported

In a mixed population of patients there is some evidence that augmenting one antidepressant with another leads to better outcomes on response, remission and mean endpoint scores compared with a single antidepressant at ‘standard’ dose. There is insufficient evidence to determine whether this is the case when compared with a single antidepressant at high dose.

Since the majority of studies used mianserin as the augmentor, the analyses are weighted towards this drug. Importantly, there are no RCTs of combinations of a TCA and irreversible MAOI or any two from venlafaxine, mirtazapine and reboxetine.
There is some evidence that combinations of antidepressants are associated with a higher burden of side effects than a single antidepressant at either standard or high dose, but there is insufficient evidence to comment on the number of patients leaving treatment early.

10.1.5 Augmentation with an antipsychotic

A total of 5 new studies found in the update search met inclusion criteria for the review of antipsychotic augmentation (BERMAN2007; CORYA2006; MAHMOUD2007; MARCUS2008; MCINTRYRE2007). The previous guideline included only 1 study. See Table 97 for summary study characteristics, with full details in Appendix 17.

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>(1) BERMAN2007 H2P1</th>
<th>(2) CORYA2006 H1P1</th>
<th>(3) MAHMOUD2007 H1P1</th>
<th>(4) MARCUS2008 H1P1</th>
<th>(5) MCINTRYRE2007 H1P0</th>
<th>(6) SHELTON2001 H2P1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/% female</td>
<td>(1) 362/70</td>
<td>(2) 483/73</td>
<td>(3) 274/72</td>
<td>(4) 381/67</td>
<td>(5) 58/64</td>
<td>(6) 28/unclear</td>
</tr>
<tr>
<td>Mean age</td>
<td>(1) 45</td>
<td>(2) 46</td>
<td>(3) 46</td>
<td>(4) 44</td>
<td>(5) 44</td>
<td>(6) 42</td>
</tr>
<tr>
<td>Augmenting agent</td>
<td>(1) Aripiprazole</td>
<td>(2) Olanzapine</td>
<td>(3) Risperidone</td>
<td>(4) Aripiprazole</td>
<td>(5) Quetiapine</td>
<td>(6) Olanzapine</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>(1) SSRI or venlafaxine</td>
<td>(2) Fluoxetine</td>
<td>(3) Range of ADs</td>
<td>(4) SSRI or venlafaxine</td>
<td>(5) SSRI or venlafaxine</td>
<td>(6) Fluoxetine</td>
</tr>
<tr>
<td>Setting</td>
<td>(1) Outpatients</td>
<td>(2) Unclear</td>
<td>(3) Mix including primary care</td>
<td>(4) Unclear</td>
<td>(5) Primary care and outpatients</td>
<td>(6) Outpatients</td>
</tr>
<tr>
<td>Length of treatment</td>
<td>(1) 6 weeks</td>
<td>(2) 12 weeks</td>
<td>(3) 6 weeks</td>
<td>(4) 6 weeks</td>
<td>(5) 8 weeks</td>
<td>(6) 8 weeks</td>
</tr>
</tbody>
</table>

There were data for augmentation with aripiprazole, olanzapine, risperidone and quetiapine. Overall, there was a moderate, but statistically significant effect on depression symptoms favouring antipsychotic augmentation, which was mirrored in small effects on remission and response. Results for individual antipsychotics were
similar, but tended not to be statistically significant because of the small number of studies for each drug. There were no head-to-head trials. Participants taking antipsychotics were more likely to leave treatment early for any reason and specifically because of side effects. There were also more likely to report side effects (see Table 98 for the summary evidence profile, and Appendix 16 for the full profile).

Table 98 Summary evidence profile for augmentation with an antipsychotic versus antidepressant with/out placebo

<table>
<thead>
<tr>
<th>Overall</th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean depression change scores at endpoint*</td>
<td>SMD -0.45 (-0.62 to -0.28)</td>
<td>SMD -0.32 (-0.53 to -0.12)</td>
<td>SMD -0.35 (-0.77 to 0.07)</td>
<td>SMD -0.56 (-0.78 to -0.33)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=6; n=1146</td>
<td>K=1; n=369</td>
<td>K=2; n=401</td>
<td>K=2; n=318</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 08.03</td>
<td>Pharm next-step 08.03</td>
<td>Pharm next-step 08.03</td>
<td>Pharm next-step 08.03</td>
</tr>
<tr>
<td>Non-response</td>
<td>RR 0.88 (0.82 to 0.95) (64.3% vs 73%)</td>
<td>RR 0.94 (0.81 to 1.1) (59% vs 71.8%)</td>
<td>RR 0.81 (0.67 to 1) (65.5% vs 96.9%)</td>
<td>RR 0.86 (0.77 to 0.97) (51.7% vs 72.4%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=9; n=1689</td>
<td>K=2; n=734</td>
<td>K=3; n=436</td>
<td>K=3; n=471</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 08.01</td>
<td>Pharm next-step 08.01</td>
<td>Pharm next-step 08.01</td>
<td>Pharm next-step 08.01</td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.88 (0.84 to 0.92) (74.7% vs 85.2%)</td>
<td>RR 0.88 (0.82 to 0.95) (74.7% vs 84.8%)</td>
<td>RR 0.87 (0.79 to 0.97) (73% vs 83.5%)</td>
<td>RR 0.88 (0.81 to 0.96) (76.6% vs 88%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=8; n=1670</td>
<td>K=2; n=734</td>
<td>K=2; n=406</td>
<td>K=3; n=472</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 08.02</td>
<td>Pharm next-step 08.02</td>
<td>Pharm next-step 08.02</td>
<td>Pharm next-step 08.02</td>
</tr>
<tr>
<td>Leaving treatment early</td>
<td>RR 1.19 (0.93 to 1.51) (19.3% vs 16.3%)</td>
<td>RR 1.3 (0.71 to 2.39) (12.1% vs 9.3%)</td>
<td>RR 1.29 (0.9 to 1.84) (25.2% vs 19.9%)</td>
<td>RR 1.21 (0.64 to 2.29) (17.1% vs 13.3%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Very low</td>
</tr>
<tr>
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<td>K=1; n=354</td>
<td>K=3; n=436</td>
<td>K=2; n=371</td>
</tr>
<tr>
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<td>Pharm next-step 08.04</td>
<td>Pharm next-step 08.04</td>
<td>Pharm next-step 08.04</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 2.43 (1.18 to 5.03) (7.9% vs 3%)</td>
<td>RR 2.01 (0.76 to 5.33) (3.5% vs 1.7%)</td>
<td>RR 5.53 (2.17 to 14.08) (13.5% vs 2.4%)</td>
<td>RR 1.13 (0.27 to 4.74) (7.8% vs 6%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=7; n=1566</td>
<td>K=2; n=735</td>
<td>K=2; n=420</td>
<td>K=2; n=371</td>
</tr>
<tr>
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<td>Pharm next-step 08.05</td>
<td>Pharm next-step 08.05</td>
<td>Pharm next-step 08.05</td>
<td>Pharm next-step 08.05</td>
</tr>
</tbody>
</table>

The previous guideline found little evidence on which to make an evidence-based recommendation regarding antipsychotic augmentation of antidepressants for people whose depression had not responded to treatment with an antidepressant alone. A number of studies have been published since, which, when considered together, show a statistically significant, but clinically modest advantage for antipsychotic augmentation.
of an antidepressant over an antidepressant alone. Patients whose antidepressant is augmented by an antipsychotic are much more likely to leave treatment early because of side effects. This was most marked for olanzapine.

10.1.6 Augmentation with lithium
Lithium is an established mood stabilising drug that is used in the treatment of mania and the prophylaxis of bipolar affective disorder. It is also widely used to augment antidepressant response in depression which has not responded adequately to intial treatment with an antidepressant.

Lithium is primarily excreted renally and can cause hypothyroidism, renal damage and a number of other adverse effects. Baseline biochemical tests and ongoing monitoring are essential (full details can be found in the NICE Bipolar Disorder guideline, 2005).

Lithium is a potentially toxic drug. Plasma levels of 0.5 to 1.0 mmol/L are usually considered to be therapeutic. Above 1.5 mmol/L toxicity invariably develops and death may occur at levels as low as 2.0 mmol/L. Many commonly prescribed drugs can interact with lithium to precipitate lithium toxicity (BNF 45; Taylor et al., 2007).

No new studies were found which met inclusion criteria with 1 study being excluded (no extractable data). The data were reanalysed without dividing the dataset by antidepressant-response history.
### Augmentation with lithium

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>No. trials (Total participants)</th>
<th>N/% female</th>
<th>Mean age (range if mean not given)</th>
<th>Lithium dose</th>
<th>Antidepressant</th>
<th>Setting</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) BAUMMAN1996 H0P1 (2) BLOCH1997 (3) CAPPIELLO1998 (4) JANUEL2002 (5) JENSEN1991 (6) JOFFE1993 H1P0 (7) NIERENBERG2003 H2P0 (8) SHAHAL1996 (9) STEIN1993 (10) ZUSKY1988 H1P0</td>
<td>10 RCTs</td>
<td>(1) 24 (unclear) (2) 31/(unclear) (3) 149/(unclear) (4) 44/(unclear) (6) 51 (unclear) (7) 35 (n=16) (8) 22/(unclear) (9) 34/79 (10) 18 (unclear)</td>
<td>(1) Not given (2) Not given (3) 40 (4) 18-65 (5) 65+ (6) 37 (7) not given (8) 53 (10) 47 (11) not given</td>
<td>(1) Lithium 800mg (2) Lithium 900mg (3) Lithium 900mg (4) Lithium 750mg (5) Lithium 450mg (6) Lithium 450mg (7) Lithium (8) Lithium 630mg (10) Lithium 250 mg (11) Lithium 300-900mg</td>
<td>(1) Citalopram 40-60mg (2) Desipramine 200mg (3) Desipramine 200mg (4) Clomipramine 150mg (5) Nortriptyline 75mg (6) TCA (7) Nortriptyline 100 mg (8) Imipramine (105-175mg) (9) Amitriptyline &gt;= 150 mg (10) Any</td>
<td>(1) Inpatients (2) Outpatients (3) In/outpatients (4) Inpatients (5) Inpatients (6) Outpatients (7) Outpatients (8) Inpatients (9) Unclear (10) Unclear</td>
<td>(1) 1 week (2) 5 weeks (3) 5 weeks (4) 6 weeks (5) 6 weeks (6) 2 weeks</td>
</tr>
</tbody>
</table>
There was some evidence that lithium augmentation was effective in reducing depression symptoms (see for the summary evidence profile – see full profile in Appendix 16).

**Table 99 Summary evidence profile for augmentation with lithium versus antidepressant with/out placebo**

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean depression change scores at endpoint</strong>*</td>
<td>SMD -0.32 (-0.56 to -0.08)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
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</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 09.03</td>
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<tr>
<td><strong>Non-response</strong></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
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</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 09.01</td>
</tr>
<tr>
<td><strong>Non-remission</strong></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=3; n=216</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 09.02</td>
</tr>
<tr>
<td><strong>Leaving treatment early</strong></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=8; n=356</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 09.04</td>
</tr>
<tr>
<td><strong>Leaving treatment early due to side effects</strong></td>
<td>N/R</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td></td>
</tr>
</tbody>
</table>

N/R = not reported

**Clinical summary**

There is some evidence of a clinically significant advantage of adding lithium to an antidepressant over adding placebo, although this effect was not found for mean endpoint scores on all outcome measures. Adding lithium to an antidepressant appears to be less acceptable to patients, with just over 30% leaving treatment early compared with 17.4% on placebo. There is insufficient evidence to determine whether this is due to side effects.
10.1.7 Augmenting an antidepressant with anticonvulsants

Introduction

Anticonvulsants are increasingly being prescribed for people with bipolar disorder; there is growing data related to their efficacy in the treatment of depression and mania and in the prophylaxis of bipolar disorder. These developments have led to the use of anticonvulsants in unipolar disorder. No new data were found of augmentation with carbamazepine or valproate.

Carbamazepine

Carbamazepine has attracted the most interest since it was the first anticonvulsant to be shown to have efficacy in bipolar disorder and because carbamazepine shares some neurochemical properties with tricyclic antidepressants. However, no RCTs met the inclusion criteria set by the GDG. There are some open studies (Dietrich & Emrich, 1998), and one RCT in major depression (Zhang et al, 2008), and some open studies in treatment-resistant depression (Ketter et al., 1995; Cullen et al., 1991) that show some benefit. It is noteworthy that in Cullen’s study a high percentage of the older patients who responded had to discontinue carbamazepine because of adverse effects.

Carbamazepine has a wide range of side effects, contraindications and interactions with other drugs. In the context of depression, it is noteworthy that carbamazepine co-administration reduces TCA levels by up to 50% (Dietrich & Emrich, 1998) and SSRIs may interfere with carbamazepine metabolism leading to intoxication.

There is a lack of controlled data and a high likelihood of adverse effects or clinically important interactions and, therefore, carbamazepine cannot be recommended as a routine next-step treatment for poorly responsive depression.

Valproate

There are no RCTs of valproate in unipolar major depression. Evidence to date suggests that valproate is more effective in preventing hypomania rather than depression in people with bipolar disorder.

One open study enrolled 33 patients with MDD in an eight-week study of valproate as monotherapy (Davis et al., 1996). Approximately 50% of the patients achieved remission. Valproate is associated with a number of side effects including significant weight gain. It can also increase plasma levels of other commonly prescribed drugs such as TCAs, quetiapine and warfarin. Fluoxetine may elevate valproate levels by interfering with its metabolism.

Valproate is also a major human teratogen.

There are a lack of controlled data and a high likelihood of adverse effects or clinically important interactions and, therefore, valproate cannot be recommended in the routine management of depression which has not responded adequately to other treatments.

Lamotrigine
Lamotrigine is an anti-convulsant drug that is used in the treatment of partial and generalized seizures. In clinical trials in epilepsy it was noted that those who received lamotrigine reported improvements in mood, alertness and social interaction.

Studies have shown evidence of efficacy for lamotrigine in bipolar depression, however in a study of 437 MDD patients randomised to lamotrigine, desipramine or placebo, ‘last observation carried forward’, ratings demonstrated no difference between groups (Hurley et al, 2002). In a further RCT, 40 depressed patients (30 unipolar, 10 bipolar) were given lamotrigine (200 mg) or placebo added to paroxetine (40 mg) for 9 weeks. There was no benefit for lamotrigine over placebo in HRSD scores at end point (Normann et al., 2002). There was a high frequency of adverse effects and dropouts in both groups. Barbosa et al. (2003) reported on 23 depressed patients (65% MDD) who had failed at least one trial of an antidepressant, and were randomised to receive either placebo or 25 mg to 100 mg of lamotrigine in addition to fluoxetine 20 mg/day. There was no statistical difference in HRSD or MADRS ratings between the two groups at six weeks. A further small study (N=34) of outpatients whose depression had not responded to at least 2 antidepressants of different classes for at least 6 weeks at the highest tolerated dose, compared augmentation with lamotrigine in doses up to 200mg with augmentation with placebo for 8 weeks (Santos et al, 2008). Participants continued with their existing antidepressant. There was no advantage for lamotrigine augmentation when endpoint depression scores were compared. Finally, in an 8-week randomised open-label study of antidepressant augmentation with either lamotrigine (150 mg) or lithium (serum level 0.6 to 0.8 mmol/L) in 34 inpatients with a diagnosis of major depressive disorder whose depression had not responded to 2 trials of different antidepressants Schindler et al, 2007, reported no significant difference between the treatment groups at endpoint based on HRSD scores, remission or response.

In view of the lack of positive data lamotrigine cannot be recommended for use in unipolar disorder. Although it is generally well tolerated and free of major interactions, it can cause a severe rash that can be life-threatening in a small minority of cases. Its profile in epilepsy and bipolar disorder suggests that further trials of lamotrigine in treatment-resistant depression are worthwhile.

There are no data that indicate that other anticonvulsants – for example, gabapentin or topiramate – can be recommended in depression.

10.1.8 Augmenting an antidepressant with pindolol

Introduction

Serotonergic antidepressants inhibit the reuptake of serotonin into the presynaptic neurone thus increasing serotonergic neurotransmission. The immediate effect of this increase is to stimulate serotonin 1a autoreceptors, which results in a decrease in serotonin release. In time, these autoreceptors become desensitised and serotonin release returns to normal. This, in combination with the inhibition of serotonin reuptake, is thought to lead to the onset of antidepressant effect.

Pindolol is primarily an adrenergic b-blocking drug, which also blocks serotonin 1a autoreceptors. The co-administration of pindolol with a serotonergic antidepressant could be expected to result in an immediate increase in serotonin neurotransmission, thus eliminating the delay in onset of antidepressant response.
As well as being used to speed the onset of antidepressant response, pindolol has also been used to augment the efficacy of antidepressant drugs in acute-phase non-responders and treatment-resistant depression.

**Studies considered for review**

Twenty-four studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (BORDET1998, MAES1999, PEREZ1997, PEREZ1999, TOME1997, ZANARDI1997) and 18 of which did not. No new studies were found in the update search.

Only studies comparing pindolol plus an antidepressant with pindolol plus placebo were included in the analyses. Apart from one study (PEREZ1999), which included clomipramine as well as a range of SSRIs, all studies used a single SSRI as the antidepressant. Efficacy data were available from up to 282 participants and tolerability data from up to 333 participants.

All included studies were published between 1997 and 1999 with participants being randomised to an experimental treatment phase of between 10 days and six weeks (mean = 4.25 weeks).

In two studies participants were described as inpatients (MAES1999, ZANARDI1997), in a further two as outpatients (PEREZ1999, TOME1997), in one as primary care (PEREZ1997) and in the remaining trial participants were from mixed sources (BORDET1998). In no trial were participants exclusively older or had atypical depression. The mean dose of pindolol was 9.23 mg, ranging from 7.5 mg to 15 mg.

No trial was classified acute-phase non-responder, and only one was classified treatment-resistant (PEREZ1999). Here patients were randomised to receive augmentation for ten days with either pindolol (7.5 mg) or placebo after receiving fluoxetine (40 mg), fluvoxamine (200 mg), paroxetine (40 mg) or clomipramine (150 mg) for at least six weeks beforehand. In addition participants had already failed between one and four courses of antidepressants (median two). Most patients were outpatients aged 18 to 65. Results from a separate analysis of this trial are presented below.

Outcomes are classified according to when assessment measures were taken. Up to 14 days after treatment was begun was categorised ‘early assessment point’ and more than 20 days was categorised ‘late assessment point’. Three studies (BORDET1998, TOME1997, ZANARDI1997) gave outcomes at both assessment points.

**Evidence statements: effect of treatment on efficacy - early assessment point**

There is evidence suggesting that there is no clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the 10th day of treatment (N = 2; n = 160; RR = 0.95; 95% CI, 0.82 to 1.11).
There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on:
• increasing the likelihood of achieving remission by the 10th or 14th day of treatment (N = 3; n = 222; Random effects RR = 0.73; 95% CI, 0.44 to 1.20)
• reducing depression symptoms by the 10th or 14th day of treatment (N = 3; n = 237; Random effects SMD = -0.30; 95% CI, -0.88 to 0.28).

Late assessment point
There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the 35th or 42nd day of treatment (N = 3; n = 214; RR = 0.75; 95% CI, 0.54 to 1.03).

There is some evidence suggesting that there is a clinically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on increasing the likelihood of achieving remission by the 21st, 28th or 42nd day of treatment (N = 3; n = 253; RR = 0.73; 95% CI, 0.55 to 0.98).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on reducing depression symptoms by the 21st, 35th or 42nd day of treatment, but the size of this difference is unlikely to be of clinical significance (N = 4; n = 282; SMD = -0.26; 95% CI, -0.49 to -0.02).

Acceptability of treatment
There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on any measure of tolerability.

Effect of treatment on efficacy for people whose depression is treatment resistant

Early assessment point
For people whose depression is treatment resistant there is evidence suggesting that there is no clinically significant difference when assessment is made between days 10 and 14 between pindolol augmentation and antidepressant monotherapy on:
• increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 1; n = 80; RR = 1; 95% CI, 0.85 to 1.18)
• increasing the likelihood of achieving remission (N = 1; n = 80; RR = 1.03; 95% CI, 0.88 to 1.2).

There is insufficient evidence to determine if there is a clinically significant difference between pindolol augmentation and antidepressant monotherapy on reducing depression symptoms in people whose depression is treatment resistant (N = 1; n = 80; WMD = 1.6; 95% CI, -0.96 to 4.16).

Acceptability of treatment for people whose depression is treatment resistant
There are no data on the acceptability of treatment for people whose depression is treatment resistant.

Clinical summary
While there is some evidence of an advantage (at 21 to 42 days) favouring the addition of pindolol to antidepressants over adding placebo on achieving remission, this effect
is not evident for response or mean endpoint scores. There is no evidence of any effect on outcomes in people whose depression is treatment resistant at early assessment point. No data were available for late assessment points.

There is insufficient evidence to comment on the tolerability of adding pindolol to antidepressants.

It should be noted that there is uncertainty regarding optimum dose and duration of treatment.

10.1.9 Augmenting an antidepressant with triiodothyronine (T3)

Introduction

Consistent with the observations that the prevalence of depression is increased in hypothyroidism (Loosen, 1987), and subclinical hypothyroidism is more prevalent in people who are clinically depressed (Maes et al., 1993), triiodothyronine (T3) has been used as an antidepressant augmenting agent both to increase the speed of onset of antidepressant response and to increase the magnitude of response.

Increase the speed of onset of antidepressant response

T3, at a dose of 25 mcg per day, may hasten response to tricyclics and this effect may be more robust in women (Altshuler et al., 2001). The optimal duration of treatment is unknown although there is a suggestion in the literature that T3 may be safely withdrawn once response has been achieved (Altshuler et al., 2001). There are no studies with SSRIs or any of the newer antidepressants.

Increase the magnitude of antidepressant response

Although the RCT that satisfied the inclusion criteria set by the GDG found T3 and lithium to be equally effective and superior to placebo (see below), several ‘negative’ non-RCTs also exist (Steiner et al., 1978; Gitlin et al., 1987; Thase et al., 1989). The response rate has been variable across studies (Aronson et al., 1996). All studies used tricyclic antidepressants. There are no studies with SSRIs or any of the newer antidepressants apart from STAR*D which used an open-label design. T4 has been shown to be inferior to T3 in one study (Joffe & Singer, 1990). Most studies used a dose of 37.5 mcg T3 per day. The optimum duration of treatment is unknown.

Studies considered for review

One study was found in a search of electronic databases (JOFFE1993A), and this met the inclusion criteria set by the GDG. It compares a range of antidepressants augmented with T3 (37.5 mcg) with antidepressants augmented with placebo. Participants are outpatients who have not achieved remission after five weeks’ treatment with either desipramine or imipramine. No new double-blind studies were found in the update search, although the STAR*D trial includes a T3 augmentation arm (described elsewhere in this chapter).

Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring T3 augmentation over antidepressant plus placebo on increasing the
likelihood of achieving a 50% reduction in depression symptoms (N = 1; n = 33; RR = 0.51; 95% CI, 0.27 to 0.94).

There is insufficient evidence to determine if there is a clinically significant difference between T3 augmentation and antidepressant plus placebo on reducing depression symptoms (N = 1; n = 33; WMD = –3.9; 95% CI, –8.86 to 1.06).

Acceptability of treatment
There was no evidence on which to assess the acceptability of treatment.

Clinical summary
There is little evidence on which to make an evidence-based recommendation of augmentation of antidepressants with T3 for the treatment of treatment-resistant depression. The prevalence of cardiovascular disease is increased in people with depression (Glassman & Shapiro, 1998) and T3 should be used with caution in cardiovascular disease. Potential adverse effects include tachycardia, anginal pain and arrhythmias. Tricyclic antidepressants also have cardiac side effects including arrhythmias, tachycardia and postural hypotension. Caution is advised in combining TCAs and T3.

10.1.10 Augmenting an antidepressant with a benzodiazepine
Introduction
Depression and anxiety commonly co-exist and insomnia is a core symptom of depression. Antidepressants usually take two to four weeks to take effect.

Benzodiazepines are effective anxiolytic and hypnotic drugs with an immediate onset of action and therefore could be expected to produce early improvement in some symptoms of depression. They do not have a specific antidepressant effect.

Benzodiazepines are associated with tolerance and dependence and withdrawal symptoms can occur after four to six weeks of continuous use. To avoid these problems, it is recommended that they should not routinely be prescribed for their hypnotic or anxiolytic effects for longer than four weeks (Royal College of Psychiatrists, 1997; BNF 45).

The National Service Framework for Mental Health (Department of Health, 1999b) discourages the use of benzodiazepines and many primary care prescribing incentive schemes include low prescribing rates for benzodiazepines as a marker of good practice. A Cochrane review, however, concludes that early time limited use of benzodiazepines in combination with an antidepressant drug may accelerate treatment response (Furukawa et al., 2002b).

Studies considered for review
The GDG used an existing review (Furukawa et al., 2002b) as the basis for this section. The original review included nine studies of which four met the inclusion criteria set by the GDG (FEET1985, NOLEN1993, SCHARF1986, SMITH1998). New searches of electronic databases found an additional study (SMITH2002) which was included in the present review. Together these studies provided tolerability data from up to 196
participants and efficacy data from up to 186 participants. No new studies were found in the update search.

All included studies were published between 1985 and 2002 and were between three and 12 weeks long (mean = seven weeks). One study was of inpatients (NOLEN1993), three of outpatients (FEET1985, SMITH1998, SMITH2002) and in the remaining study (SCHARF1986) participants were from mixed sources. No study was undertaken in primary care, nor was any of exclusively older participants or those with atypical depression. Other than in FEET1985, where participants had been ‘treated in general practice without success’, study participants were not described as having failed previous courses of antidepressants.

All studies compared an antidepressant plus benzodiazepine with an antidepressant plus placebo. The included trials used the following antidepressant/benzodiazepine combinations:

- Maprotiline or nortriptyline plus flunitrazepam (2 mg) or lormetazepam (2 mg) (NOLEN1993)
- Fluoxetine plus clonazepam (0.5 mg up to 1 mg) (SMITH1998, SMITH2002)
- Imipramine plus diazepam (10 mg) (FEET1985)
- Amitriptyline plus chlordiazepoxide (mean 44 mg) (SCHARF1986)

The mean dose of TCAs was between 122.5 mg and 200 mg, and fluoxetine was given at between 20 mg and 40 mg.

Evidence statements

Effect of treatment on efficacy

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any efficacy measure.

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any tolerability measure.

Clinical summary

There is insufficient evidence to determine whether there is any effect of adding a benzodiazepine to antidepressant treatment in terms of both efficacy and tolerability.

10.1.11 Buspirone augmentation

There are no extractable efficacy data from double-blind RCTS of buspirone augmentation.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between buspirone augmentation and SSRI monotherapy on any tolerability measure.
There is no evidence on which to make an evidence-based recommendation of augmentation of antidepressants with buspirone for the treatment of treatment-resistant depression.

10.1.12 Augmenting an antidepressant with atomoxetine

Introduction

One study was found in the update search of augmentation with atomoxetine.

<table>
<thead>
<tr>
<th>Table 100 Summary study characteristics for augmentation with atomoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
</tr>
<tr>
<td>Study IDs</td>
</tr>
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<td>N/% female</td>
</tr>
<tr>
<td>Mean age (range if mean not given)</td>
</tr>
<tr>
<td>Study drug</td>
</tr>
<tr>
<td>Antidepressant</td>
</tr>
<tr>
<td>Setting</td>
</tr>
<tr>
<td>Length of treatment</td>
</tr>
</tbody>
</table>

This showed no significant effect on depression symptoms, and increased the number of people leaving treatment early for any reason because of side effects compared with those taking an antidepressant alone. See Table 101 for the summary evidence profile.

<table>
<thead>
<tr>
<th>Table 101 Summary evidence profile for atomoxetine augmentation</th>
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<tbody>
<tr>
<td>Atemoxetine</td>
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<tr>
<td>Mean depression change scores at endpoint*</td>
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</tr>
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</tr>
<tr>
<td>Forest plot</td>
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<tr>
<td>Non-response</td>
</tr>
<tr>
<td>Quality</td>
</tr>
<tr>
<td>Number of studies; participants</td>
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<td>Forest plot</td>
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<td>Non-remission</td>
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<td>Quality</td>
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<td>Number of studies; participants</td>
</tr>
<tr>
<td>Forest plot</td>
</tr>
<tr>
<td>Leaving treatment early</td>
</tr>
<tr>
<td>Quality</td>
</tr>
<tr>
<td>Number of studies; participants</td>
</tr>
<tr>
<td>Forest plot</td>
</tr>
</tbody>
</table>
Leaving treatment early due to side effects

<table>
<thead>
<tr>
<th>RR 1.8 (0.55 to 5.88)</th>
<th>(9.7% vs 5.4%)</th>
</tr>
</thead>
</table>

Quality

Low

Number of studies; participants

K=1; n=146

Forest plot

10.1.13 Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

STAR*D is a four-level study designed to assess treatments in patients who had not responded to previous treatment. At each level patients who had not responded to treatment at the previous level were randomised to different treatment options. At the first level, all patients received citalopram. Those not responding (QIDS-SR > 5) moved to level 2 where they were randomised to switch to another antidepressant (bupropion, sertraline or venlafaxine ER) or to receive an augmentation treatment (bupropion, buspirone or CBT). Those not responding to treatment in level 2 moved to level 3 where they were randomised again to switch to mirtazepine or nortriptyline or to receive an augmentation agent (lithium or T3 for those on bupropion, sertraline, or venlafaxine ER). In addition, those who had not responded to CBT at level 2 were randomised to buproprion or venlafaxine ER to ensure that all those in level 3 had failed 2 courses of antidepressants. Those not responding moved to level 3. Those not responding to level 3 treatment moved to level 4 and were re-randomised to tranylcypromine or mirtazepine plus venlafaxine ER.

The study was designed to be as analogous as possible to real clinical practice. In order to achieve this, patients were allowed to opt out of being randomised to drug switching, augmentation treatments and, in level 2, to CBT. They were not allowed to opt out of randomisation to a particular agent within the drug switching or drug augmentation arms. Also all treatments were given open label. Patients also had to pay for CBT treatment (Ellen Frank editorial 2007). The patient preference aspect of the trial meant that there were 12 permutations of randomisation preferences at level 2 which greatly adds to the complexity of the trial. For example, only data from patients accepting randomisation to an augmenting or switching option including CBT can be used in comparisons with CBT (either as a switching option or as an augmenting treatment).

It is difficult to draw conclusions about suitable sequencing options since there are so many permutations of treatments possible within the trial. Patients who reach level four (i.e., have failed 3 drug trials or 3 drugs plus a course of CBT) will have taken a variety of routes through the study. He or she may have taken citalopram continuously (augmented with 2 separate agents), or may have tried 3 different single antidepressants, or switched from single to combination drugs and back again. The percentage remission achieved by each treatment strategy is shown in Table 102.

Table 102 Percentage remission by treatment strategy in STAR*D

<table>
<thead>
<tr>
<th>STAR*D - level 1</th>
<th>% remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>28%</td>
</tr>
<tr>
<td>STAR*D - level 2</td>
<td>% remission</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>25%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>18%</td>
</tr>
<tr>
<td>Buproprion</td>
<td>21%</td>
</tr>
</tbody>
</table>
Cognitive therapy 25%
Citalopram + buproprion 30%
Citalopram + buspirone 30%
Citalopram + cognitive therapy 23%

**STAR*D - level 3**
- Mirtazapine 12%
- Nortriptyline 20%
- Lithium augmentation 16%
- T3 augmentation 21%

**STAR*D - level 4**
- Tranylcypromine 7%
- Venlafaxine + mirtazapine 14%

### Table 103 Raw remission rates following switch to another antidepressant (data from RCTs)

<table>
<thead>
<tr>
<th>Previous drug</th>
<th>Class</th>
<th>Drug (mean dose (SD))</th>
<th>% remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR*D - level 2</td>
<td>Citalopram</td>
<td>SSRI Sertraline (135 (57.4) mg)</td>
<td>18%</td>
</tr>
<tr>
<td>POIRIER1999*</td>
<td>SSRIs SSRIs</td>
<td>Fluoxetine (60 mg)</td>
<td>18%</td>
</tr>
<tr>
<td>FERRER2001*</td>
<td></td>
<td>TCA-Related Mianserin (60 mg)</td>
<td>18%</td>
</tr>
<tr>
<td>STAR*D - level 3</td>
<td>Range of ADs</td>
<td>TCA Nortriptyline (96.8 mg (41.1))</td>
<td>20%</td>
</tr>
<tr>
<td>STAR*D - level 2</td>
<td>Citalopram</td>
<td>SNRI Venlafaxine XR (193.6 (106.2) mg)</td>
<td>25%</td>
</tr>
<tr>
<td>POIRIER1999</td>
<td>SNRIs SNRIs</td>
<td>Venlafaxine (269 mg (46.7))</td>
<td>36%</td>
</tr>
<tr>
<td>BALDOMERO2005</td>
<td>SNRIs SNRIs</td>
<td>Venlafaxine XR (164 mg (64))</td>
<td>52%***</td>
</tr>
<tr>
<td>STAR*D - level 2</td>
<td>Citalopram</td>
<td>Other Buproprion**</td>
<td>21%</td>
</tr>
</tbody>
</table>

* comparators in this trial were continuing with fluoxetine and mianserin augmentation
** not licensed for depression in the UK
*** calculated from number randomised rather than 'ITT' population used by study authors

### Comment

Data from RCTs support switching from one antidepressant to another as being clinically worthwhile; within class switches being associated with remission rates of approximately 20%. Open switching studies report higher remission rates when SSRI non-responders are switched to venlafaxine. This advantage holds in blinded studies, but the magnitude of the benefit is considerably more modest.

#### 10.1.14 Clinical summary for next-step treatments

The evidence for effective strategies in people whose depression has not responded adequately to treatment is not strong. A common first-line strategy, increasing the dose, is not supported by convincing evidence of effectiveness, although this strategy may well be effective in some people, particularly if they have been able to tolerate the drug at the initial dose.

The evidence for switching to another antidepressant is stronger, but data for switching between classes of antidepressant is not. Overall though, switching is likely to be a worthwhile strategy, and data from primary efficacy head to head studies suggest than venlafaxine and escitalopram may offer marginal benefits over other antidepressants in this regard. Augmenting with lithium, a second antidepressant or
an antipsychotic is also worthwhile but the effect size clinically, is modest, and the side effect burden increased. The main message from STAR D is that some patients will achieve remission with each successive treatment strategy although the proportion doing so falls each time. The lack of good objective data to clearly demonstrate the superior efficacy of one strategy over another probably reflects the fact that the overall difference in effect size between strategies is likely to be small. As was seen in STAR D, some patients have clear preferences for one treatment over another, based at least partly on perceived acceptability of the treatment.

10.1.15 From evidence to recommendations

Since the evidence for sequencing pharmacological strategies for people whose depression has not responded adequately to initial treatment is weak, the recommendations in the previous guideline are largely unchanged, although they have been updated to reflect new NICE styles. Choice of new medication should be guided by similar principles to those guiding choice of initial medication, for example, a drug’s potential for side-effects. Since it is possible that poor response to initial treatment may be because the treatment was not properly initiated or adhered to, these factors should be reviewed first.

10.1.16 Clinical practice recommendations

10.1.16.1 When initiating or revising a pharmacological treatment for a person with depression whose symptoms have not adequately responded to initial pharmacological interventions practitioners should:

- increase the frequency of appointments using outcome monitoring with a validated outcome measure
- be aware that the use of a single agent rather than combination medication or augmentation causes a lower side-effect burden
- consider re-introducing previous treatments that have been inadequately delivered or adhered to including increasing dose or switching to an alternative antidepressant.

The evidence for an advantage of switching to another antidepressant over continuing treatment with the existing antidepressant is not strong. In addition, there is no clear evidence about which antidepressant to switch to. Choice should therefore be guided by side effects and possible interactions during the period of the switch.

10.1.16.2 When switching to another antidepressant, practitioners should be aware that the evidence for the relative advantage of switching either within a class or between classes is weak. Reasonable choices for a second antidepressant include:

- initially a different SSRI or better tolerated newer generation antidepressant
  - subsequently switching to an antidepressant of a different pharmacological class that may be less well tolerated, for example, venlafaxine, a TCA or an MAOI.
10.16.3 When switching to another antidepressant, which can normally be achieved within a week when switching from drugs with a short half-life, prescribers should consider the potential for interactions in determining the choice of new drug and the nature and duration of the transition. Exercise caution when switching:

- from fluoxetine or paroxetine to a TCA, as these drugs inhibit the metabolism of TCAs. A lower starting dose of the TCA will be required, particularly with fluoxetine because of its long half-life
- to a new serotonergic antidepressant or MAOI, because of the risk of serotonin syndrome. Features of serotonin syndrome include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus.
- from a non-reversible MAOI, a 2-week washout period is required. Other antidepressants should not routinely be prescribed during this 2 week period.

Following several courses of treatment, it may be appropriate to refer someone with depression to a specialist (for example, someone with a special interest in treating depression or a specialist service). Before deciding the next course of action, there should be a thorough assessment of factors affecting treatment choice, including suicide risk and associated comorbidities. It may be appropriate to re-introduce previous treatments, if these were not adequately delivered or adhered to.

10.16.4 For a person whose depression has failed to respond to various strategies for augmentation and combination treatments, referral to a clinician with a specialist interest in treating depression or a specialist service should be considered.

10.16.5 The assessment of a person with depression referred to specialist mental health services should include a full assessment of:

- their symptom profile and suicide risk and, where appropriate, previous treatment history
- associated psychosocial stressors, personality factors and significant relationship difficulties, particularly where the depression is chronic or recurrent
- associated comorbidities including alcohol and substance misuse, and personality disorders.

58 Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.
10.1.16.6 In specialist mental health services, after a thorough review of previous treatments for depression has been undertaken, consideration should be given to re-introducing previous treatments that have been inadequately delivered or adhered to.\(^{59}\)

10.1.16.7 Medication in secondary-care mental health services should be initiated under the supervision of a consultant psychiatrist.

Given the higher side effect burden of taking 2 drugs rather than one, combining medication would not normally be an initial next-step option. However, there is some evidence of efficacy. Most of the data published since the previous guideline are for augmentation of an antidepressant with an antipsychotic, and this shows some benefit. However, antipsychotics do not have UK marketing authorisation for use in depression. There is still limited evidence for combinations of antidepressants. The recommendations are largely unchanged. That for augmentation with a benzodiazepine has been amended since this strategy is recommended elsewhere in the guideline for the short-term management of agitation.

10.1.16.8 When using combinations of medications, the healthcare professional should:

- ensure they select medications that are known to be safe when used together
- be aware of the increased side effect burden this causes
- discuss the rationale for any combination with the person with depression, inform them if off-label medication is prescribed, and monitor carefully for adverse effects.
- when using unusual combinations prescribers should familiarise themselves with the primary evidence, and consider obtaining a second opinion

10.1.16.9 Where a person with depression is informed about and prepared to tolerate the increased side effect burdens consider augmenting an existing antidepressant with:

- lithium
- an antipsychotic – there is some evidence for aripiprazole\(^ {60}\), olanzapine, quetiapine and risperidone
- another antidepressant – there is some evidence for mianserin, and mirtazapine in augmenting SSRIs.

10.1.16.10 When prescribing lithium, ensure that renal and thyroid function are monitored before and during treatment, and consider using ECG monitoring in high-risk people with depression. Serum lithium levels must be monitored.

\(^{59}\) Where recommendations are shaded in grey the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.

\(^{60}\) None of these drugs have UK marketing authorisation for the treatment of depression.
10.1.16.11 When prescribing antipsychotics monitor weight, lipid and glucose levels, and side effects relevant to the chosen drug (for example, extrapyramidal side effects and prolactin-related side effects with risperidone).

10.1.16.12 When augmenting an antidepressant with another drug or using a combination of antidepressants, practitioners should document the rationale for the chosen combination and consider seeking a second opinion where evidence for the efficacy of a chosen strategy is limited or where the risk-benefit ratio is unclear.

10.1.16.13 The following strategies are not recommended for routine use as there is insufficient evidence for their use:
- augmentation of an antidepressant with a benzodiazepine for more than 2 weeks
- augmentation of an antidepressant with buspirone, carbamazepine, lamotrigine, pindolol, valproate or thyroid hormones
- dosulepin, which should not be initiated because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.

10.2 Non-pharmacological physical treatments

10.2.1 Repetitive transcranial magnetic stimulation (rTMS)
Repetitive transcranial magnetic stimulation (rTMS) involves focal stimulation of the superficial layers of the cerebral cortex using a rapidly changing magnetic field applied using an external coil. It does not require anaesthesia and can be performed on an outpatient basis. Treatment with rTMS usually involves daily sessions lasting about 30 minutes for 2-4 weeks and possibly longer. Its use in the treatment of depression has recently been the subject of a NICE Interventional Procedures Overview (IP 346) and Interventional Procedure Guidance (242, Nov 2007).

The main evidence points highlighted in the review and guidance were:
- Uncertainty about the procedure’s clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date.
- No major safety concerns associated with rTMS.

Included in the review was consideration of a meta-analysis of 33 short-term RCTs in depression (Herrmann & Ebmeier, 2006) which found a large significant effect size of 0.71 against sham treatment but the studies were small, heterogeneous in methodology and effect size and it was not possible to identify any significant predictors of outcome. A more recent meta-analysis for patients with treatment resistant depression which included 24 studies (1092 patients) meeting their inclusion criteria (Lam et al 2008) found that active rTMS was significantly superior to sham conditions in producing...
clinical response, with a risk difference of 17%. However the pooled response and remission rates were only 25% and 17%, and 9% and 6% for active rTMS and sham conditions respectively. They concluded that further studies are required before adopting rTMS as a first-line treatment for treatment resistant depression.

From evidence to recommendations

The guideline uses the recommendations from the current NICE Interventional Procedure Guidance on TMS.

10.2.1.1 Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure’s clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors. [NICE Interventional Procedure Guidance 242]

10.2.1.2 Future research should aim to address patient selection criteria, the optimal use of this procedure in relation to other treatments, and the duration of any treatment effect. Clinicians should collaborate to ensure that studies are sufficiently large to be adequately powered. The Institute may review the procedure upon publication of further evidence. [NICE Interventional Procedure Guidance 242]

10.2.2 Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) therapy is a type of treatment where a small electrical pulse is administered through an implanted neurostimulator to a bipolar lead attached to the left vagus nerve. A battery-powered pulse-generating device is implanted under the skin of the upper left chest. A wire is tunnelled under the skin and connected to the left vagus nerve in the neck. The stimulation parameters (pulse width and frequency, current intensity, and on/off cycles) are programmed into the pulse generator via a programming wand. Patients or carers can give additional stimulation or temporarily inhibit stimulation. The battery lasts 8–10 years and can be replaced under local anaesthesia. A typical treatment regimen might comprise intermittent stimulation for 30 seconds every 5 minutes throughout the day and night. This procedure has been studied in patients with treatment-resistant epilepsy and it is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients who are refractory to anti-epileptic medication. NICE guidance on VNS for refractory epilepsy in children concluded that current evidence appears adequate to support the use of this procedure ‘provided that the normal arrangements are in place for consent, audit and clinical governance’ (NICE 2004, Interventional Proceure Guidance 50). In addition antidepressant effects of VNS in epilepsy patients have been described, independent of reduction of seizure frequency (eg Harden et al. 2000).

Clinical summary
VNS has been studied in one RCT in patients with highly recurrent or chronic major depression who had failed to respond to between 2 and 7 adequate treatment trials. Active VNS was no more effective than sham treatment (15% vs 10% response after 10 weeks) but it was argued that this was a failed, rather than a negative, trial due to insufficient stimulus titration (Rush et al., 2005). In a continuation of the same study, after twelve months VNS treatment, more patients had responded compared with a group of comparable treatment-as-usual patients recruited using the same selection criteria (27% vs 13%) (George et al., 2005). A recently reported European study open treatment study in recurrent/chronic major depression (Schlaepfer et al 2008) reported higher response rates over 1 year (53%, with 44% showing sustained response). In open treatment there appears to be a high maintenance of response over 2 years (60-75%) (Sackeim et al., 2007) compared with only 38% of 12 month responders maintaining response at 24 months in a comparable treatment-as-usual patient population (Dunner et al., 2006). A limitation of VNS is that in open studies it did not appear to be useful in patients who have failed to respond to 7 or more treatments.

10.2.3 Clinical practice recommendations

10.2.3.1 Vagus nerve stimulation should only be undertaken as part of research studies carried out in specialist centres with expertise in the techniques.

10.3 The pharmacological management of relapse prevention

10.3.1 Introduction

Major depressive disorder is among the most important causes of death and disability worldwide in both developing and developed countries (Murray & Lopez, 1997). Because of the long-term nature of depressive disorder, with many patients at substantial risk of later recurrence, there is a considerable need to establish how long such patients should stay on antidepressants. Existing clinical guidelines recommend that treatment should be continued for four to six months after the acute episode (Anderson et al., 2000; American Psychiatric Association, 2000b; Bauer et al., 2002a). There is a considerable variation in practice, suggesting that many patients do not receive optimum treatment. Recently Geddes et al. (2003a) reviewed all published and unpublished trials available for review by August 2000 in which continued antidepressant drug therapy was compared with placebo in patients who had responded to acute treatment with antidepressants. It was found that antidepressants reduced the risk of relapse in depressive disorder and continued treatment with antidepressants appeared to benefit many patients with recurrent depressive disorder. The treatment benefit for an individual patient depended on their absolute risk of relapse with greater absolute benefits in those at higher risk. It was estimated that for patients who were still at appreciable risk of recurrence after four to six months of treatment with antidepressants, another year of continuation treatment would approximately halve their risk. The authors found no evidence to support the contention that the risk of relapse after withdrawal from active treatment in the placebo group was due to a direct pharmacological effect (e.g. ‘withdrawal’ or
‘rebound’) since there was not an excess of cases within a month of drug discontinuation.

10.3.2 Studies considered for review
The GDG used the review by Geddes et al. (2003a) as the basis for this section for the review in the previous guideline. This included 37 studies of which 20 met the inclusion criteria set by the GDG. An additional five studies were identified in searches for the previous guideline, one of which was excluded. Another study was identified through searching journal tables of contents and a further study was identified from searches undertaken for the review of lithium augmentation elsewhere in this guideline. Both of these were included. Therefore, 26 studies formed the basis of this review in the previous (ALEXOPOULOUS2000, BAUER2000, COOK1986, DOOGAN1992, FEIGER1999, FRANK1990, GEORGOTASI1989, GILABERTE2001, HOCHSTRASSE2001, KELLER1998, KISHIMOTO1994, KLYSNER2002, KUPFER1992, MONTGOMERY1988, MONTGOMERY1992, MONTGOMERY1993, PRIEN1984, REIMHERR1998, ROBERT1995, ROBINSON1991, SACKHEIM2001, SCHMIDT2000, TERRA1998, THASE2001, VERSIANI1999, WILSON2003) and 18 were excluded. A further 7 studies were identified in update searches and added to the review (KORNSTEIN2006 (escitalopram vs placebo); MCGRATH2006 (fluoxetine vs placebo); PREVENT study A (venlafaxine ER vs placebo); PREVENT study B (venlafaxine ER vs placebo); RAPAPORT2004 (escitalopram vs placebo); VAN DEN BROEK2006 (imipramine vs placebo); GORWOOD2007 (escitalopram vs placebo)).

Studies included a pre-maintenance phase during which participants continued to receive medication after they had achieved remission. This was followed by a maintenance phase in which participants who had achieved remission were randomised either to pharmacological treatment or to placebo. Studies were included provided participants were classified as remitted only if they no longer met diagnosis for major depression or had achieved an HRSD or MADRS score below the cut-off for mild depression. Similarly, studies were included only if participants had been assessed as having relapsed using some kind of formal criteria such as exceeding a specific HRSD or MADRS score or meeting formal diagnostic criteria for depression rather than clinical judgement alone.

A single outcome, number of study participants experiencing relapse, was extracted. Since the length of both the pre-maintenance and the maintenance phase varied between studies, sub-analyses were undertaken splitting the data set as follows:
• by length of continuation treatment (i.e. length of time continued with medication after remission but before randomisation) – less than or more than six months
• by length of maintenance treatment – less than or more than 12 months.

The longest maintenance phase was two years. Further sub-analyses were undertaken combining these factors - for example, studies with pre-maintenance treatment of less than six months and maintenance treatment of less than 12 months.

Fifteen studies used an SSRI as the maintenance treatment, 8 studies used a TCA, and 7 studies used other antidepressants. Three studies (BAUER2000, PRIEN1984,
SACKHEIM2001) compared lithium (with and without an antidepressant) with an antidepressant or placebo61. One study compared SSRIs augmented with other agents with the SSRI alone. Twenty-seven studies used the same treatment in both acute and maintenance phases, and 4 did not.

All included studies were published between 1984 and 2008. In 21 studies participants were described as outpatients, one was from primary care and in the others it was either not clear from where participants were sourced or they were from mixed sources. There were no studies of inpatients. Five studies were classified elderly, and none was of atypical depression.

Of the 24 trials of antidepressant medication, 13 (BAUER2000, COOK1986, FRANK1990, GILABERTE2001, HOCHSTRASSER2001, KISHIMOTO1994, KUPFER1992, MONTGOMERY1988, MONTGOMERY1993, PERAHIA2006, ROBINSON1991, TERRA1998, VERSIANI1999) included only participants who had had at least one previous depressive episode. Five studies (ALEXOPOULOS2000, FEIGER1999, KLYSNER2002, THASE2001, WILSON2003) were of participants with a mix of first episode and previous episode depression. For the purpose of a sub-analysis by number of episodes, two of these (KLYSNER2002, WILSON2003) were classified first episode since more than 70% of participants were in their first episode. In the remaining seven studies (DOOGAN1992, GEORGOTAS1989, KELLER1998, MONTGOMERY1992, ROBERT1995, SCHMIDT2000, SACKHEIM2001) it was not possible to assess the proportion of participants with first or subsequent episode depression. Additional sub-analyses were undertaken by number of previous episodes.

### 10.3.3 Evidence statements

#### Effect of treatment on relapse

In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo, there is strong evidence suggesting that there is a clinically significant difference favouring continuing antidepressant treatment over discontinuing antidepressant treatment on reducing the likelihood of relapse (N = 32; n = 4982; RR = 0.46; 95% CI, 0.4 to 0.52; RD = -0.25 (-0.29 to -0.22)).

There was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

With regard to lithium augmentation:

There is some evidence suggesting that there is a clinically significant difference on reducing the likelihood of relapse favouring continuing lithium augmentation of an antidepressant over:

- discontinuing lithium (i.e. continuing on antidepressant monotherapy) (N = 3; n = 160; RR = 0.58; 95% CI, 0.37 to 0.92).
- discontinuing lithium and antidepressant treatment (i.e. taking a placebo) (N = 2; n = 129; RR = 0.42; 95% CI, 0.28 to 0.64).

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61 One four-arm trial (PRIEN1984) has both antidepressant and lithium treatment groups.
In patients who have achieved remission whilst taking an antidepressant plus lithium, there is some evidence suggesting that there is a clinically significant difference favouring discontinuing lithium treatment (i.e. continuing with the antidepressant alone) over discontinuing antidepressant treatment (i.e. continuing lithium alone) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N = 1; n = 77; RR = 1.75; 95% CI, 1.03 to 2.96).

In patients who have achieved remission whilst taking an antidepressant plus lithium there is insufficient evidence to determine if there is a clinically significant difference between discontinuing antidepressant treatment (i.e. continuing with lithium alone) and discontinuing antidepressant and lithium treatment (i.e. taking a placebo) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N = 1; n = 71; RR = 0.88; 95% CI, 0.60 to 1.28).

10.3.4 Clinical summary

The majority of study participants had experienced multiple depressive episodes. There is strong evidence that responders to medication, who have had multiple relapses, should stay on medication to avoid relapse, irrespective of the length of treatment pre-response (between six weeks and 12 months). This effect holds true beyond 12 months. From the available data, it is not possible to determine effects beyond two years. These effects were evident with both TCAs and SSRIs. Whether this effect is evident in those recovering from a first episode or with placebo is unknown. Since most studies randomised participants either to continue with medication or to a placebo, there is little data comparing lengths of maintenance treatment with active medication.

10.3.5 From evidence into recommendations

The previous guideline recommended initially continuing treatment for at least 6 months after remission, and up to two years for patients who are high risk of relapse. There is no new evidence which suggests that these recommendations should be changed. For patients who have achieved remission whilst taking lithium in addition to an antidepressant it appears to be worthwhile continuing treatment. If one or other drug is stopped the evidence suggests that lithium should be stopped in preference to the antidepressant. The recommendations have been updated to match the updated NICE style.

10.3.6 Clinical practice recommendations

10.3.6.1 Practitioners should be aware of the need to support and encourage people taking antidepressants to continue medication for at least 6 months after remission of an episode. In addition, they should discuss with the person: [KP]

- that this greatly reduces the risk of relapse
- that antidepressants are not associated with physical dependence
Review with the patient the need for continued antidepressant treatment after 6 months, taking into account the number of previous episodes, the presence of residual symptoms, and concurrent physical health problems and psychosocial difficulties.

10.3.6.2 For people with depression who are at significant risk of relapse or have a history of recurrent depression practitioners should discuss the choice of treatments to reduce the risk of recurrence. The choice of treatment should be influenced by:

- Preference of the person with depression
- Previous treatment history including the consequences of a relapse, residual symptoms, the response to previous treatment and problems with side effects of discontinuation of treatment

Treatment choices include continuing current medication, augmentation with additional medication or the provision of psychological treatment (CBT).

10.3.6.3 People with depression should be advised to continue antidepressants for at least 2 years if they are at risk of relapse, maintaining the level of medication at which acute treatment was effective unless there is good reason to reduce the dose (such as unacceptable adverse effects) if:

- they have had two or more depressive episodes in the recent past, during which they experienced significant functional impairment
- they have other risk factors for relapse such as residual symptoms, multiple previous episodes, history of severe or prolonged episodes or of poor response
- the consequences of relapse are likely to be severe (for example, suicide attempts, loss of functioning, severe life disruption, and inability to work).

10.3.6.4 When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate in conjunction with the person with depression taking into account age, comorbid conditions and other risk factors.

10.3.6.5 Person with depression on long-term maintenance treatment should be regularly re-evaluated, with frequency of contact determined by the following:

- comorbid conditions
- risk factors for relapse
- severity and frequency of episodes of depression

10.3.6.6 For people with depression who have had multiple episodes of depression, and who have had a good response to treatment with an antidepressant and an augmentating agent, they should remain on this combination after remission if the side effects are tolerable and acceptable to the person with depression. If one medication is stopped it should
usually be the augmenting agent. Lithium should not be used as a sole agent to prevent recurrence.

10.3.6.7 Research recommendations: sequencing antidepressant treatment after inadequate initial response

What is the best medication strategy for people with depression who have failed to have sufficient response to a first SSRI antidepressant after 6-8 weeks of adequate treatment?

This question should be addressed using a randomised controlled trial design and compare the effects of continuing on the same drug treatment (with dose increase if appropriate) and switching to another SSRI or to an antidepressant of another class. Built into the design should be an assessment of the effect of increased frequency of follow-up and monitoring alone on improvement. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design and mediators and moderators of response should be investigated.

Why this is important

Inadequate response to a first antidepressant is a frequent problem but the best way of sequencing treatments is not clear from the available evidence. There is good evidence that the likelihood of eventual response decreases with the duration of depression and number of failed treatment attempts so that maximising the response at an early stage may be an important factor in final outcome. The results of this study will be generalisable to a large number of people with depression and will inform the choice of treatment.

10.4 Electroconvulsive therapy (ECT)

10.4.1 Introduction

Electroconvulsive therapy (ECT) has been used as a treatment for depression since the 1930s. In its modern form ECT is perceived by many healthcare professionals to be a safe and effective treatment for severe depression that has not responded to other standard treatments (Geddes et al, 2003b). But many others, including many patient groups, consider it to be an outdated and potentially damaging treatment (Rose et al, 2003). During ECT, an electric current is passed briefly through the brain, via electrodes applied to the scalp, to induce generalised seizure activity. The individual receiving treatment is placed under general anaesthetic and muscle relaxants are given to prevent body spasms. The ECT electrodes can be placed on both sides of the head (bilateral placement) or on one side of the head (unilateral placement). Unilateral placement is usually to the non-dominant side of the brain, with the aim of reducing cognitive side effects. The standard bilateral placement is bitemporal/temporofrontal but some studies have used bifrontal placement which may reduce cognitive side-effects compared with the standard placement. The number of sessions undertaken during a course of ECT usually ranges from six to twelve, although a substantial
minority of patients responds to fewer than six sessions. ECT is usually given twice a week in the UK; less commonly it is given once a fortnight or once a month as continuation or maintenance therapy to prevent the relapse of symptoms. It can be given on either an inpatient or day patient basis.

ECT causes short-term disorientation immediately after treatment and may cause short- or long-term memory impairment for past events (retrograde amnesia) and current events (anterograde amnesia). These effects appear to be dose related, to depend on electrode placement, possibly the type of electrical stimulus and patient characteristics (Ingram et al 2008). However the persistence, severity and, precise characterisation of such impairments are still a subject of debate. There is preliminary evidence that prolonged short-term disorientation immediately after treatment predicts retrograde amnesia after the end of a course of treatment (Sobin et al 1995) but not 2 months after the course. Cognitive impairments have been highlighted as a particular concern by many patients, especially retrograde amnesia for autobiographical events (Rose et al, 2003). There is no simple relationship between subjective cognitive impairment and cognitive test measures which has contributed to polarising views about the relative risks and benefits of ECT.

At present there is a lack of consensus as to the best method of assessing cognitive function during a course of ECT. The benefit of using only a global measure such as the Mini-Mental State Examination (MMSE) in its original or modified form (3MSE) is uncertain given the inconsistent effects of ECT on these measures in trials. Given the evidence that the ability to learn new material (anterograde memory) recovers after the end of ECT treatment a main concern is in the early detection and minimizing of persistent retrograde memory loss, particularly for important autobiographical memories. Detecting cognitive impairments only at the end of treatment has little practical use as it is too late to alter this. A battery consisting of a formal mood rating scale (MADRS), the 3MSE, an autobiographical memory task, a word learning task, and tests of digit span forward and backward has been suggested (Porter et al 2008) but it takes and hour to administer.

In line with NICE policy regarding the relationship of Technology Appraisals to clinical practice guidelines, this guideline updates the NICE Technology Appraisal on ECT (TA59) for depression in adults only (the Technology Appraisal covered the use of ECT in the treatment of mania and schizophrenia as well as depression in children and adolescents (NICE, 2003)).

Key points to emerge from the reviews underpinning the NICE Technology Appraisal on ECT (NICE, 2003), which concluded that ECT is an effective treatment, include:

- Real ECT had greater short-term benefit than sham ECT
- ECT had greater benefit than the use of certain antidepressants
- Bilateral ECT was reported to be more effective than unilateral ECT
- The combination of ECT with pharmacotherapy was not shown to have greater short-term benefit than -ECT alone
- Cognitive impairment does occur but may only be short-term
• Compared with placebo, continuation pharmacotherapy with tricyclic antidepressants and/or lithium reduced the rate of relapses in people who had responded to ECT
• Preliminary studies indicate that ECT is more effective than repetitive transcranial magnetic stimulation.

10.4.2 Updated review

For the updated review double-blind randomised controlled trials were sought which compared ECT either with sham ECT or another active treatment in the treatment of people in an acute depressive episode or in relapse prevention following successful treatment (either with ECT or another treatment). The electronic databases searched for published trials are given in Table 104. Details of the search strings used are in appendix 8.

Table 104: Databases searched and inclusion/exclusion criteria for clinical effectiveness of ECT

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>January 2002 to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008; January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of depression according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>ECT</td>
</tr>
</tbody>
</table>

In total, 21 new trials were found from searches of electronic databases. These included 10 trials comparing ECT with TMS, which the GDG decided not to review since NICE has produced guidance on TMS (NICE, 2007), 4 trials of continuation treatment following successful treatment with ECT (2 of which included continuation ECT), which are considered in the section on relapse prevention, and 7 comparing bilateral with unilateral ECT which are considered in the section on next-step treatments. Several studies included populations with a relatively high proportion of participants with bipolar disorder (up to 30%). These were included since ECT is not known to cause switching to mania (and, indeed, is used as a treatment for mania).

Summary study characteristics of the included studies are in Table 105 with full details in Appendix 17 which also includes details of excluded studies.
Table 105 Summary study characteristics of studies of ECT or of treatment following successful ECT published since the systematic reviews underpinning the NICE Technology Appraisal were undertaken

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>Relapse prevention studies following remission with ECT</th>
<th>Next-step treatment studies (bilateral ECT vs unilateral ECT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 8 RCTs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study IDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) GRUNHAUS2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) KELLNER2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) NAVARRO2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) VAN DEN BROEK2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) ESCHWEILER2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) HEIKMAN2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) McCALL2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) RANJKESH2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) SACKEIM2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) SEINAERT2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(67) STOPPE2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(78) TEW2002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/ % female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) 39/56</td>
<td></td>
<td></td>
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<tr>
<td>(2) 201/68</td>
<td></td>
<td></td>
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<tr>
<td>(3) 38/55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) 27/74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) 92/58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) 24/54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) 77/64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) 45/60</td>
<td></td>
<td></td>
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<tr>
<td>(5) 90/57</td>
<td></td>
<td></td>
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<tr>
<td>(6) 81/60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) 39/56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7) 24/NA</td>
<td></td>
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<tr>
<td>Mean age</td>
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<tr>
<td>(1) 60</td>
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<tr>
<td>(2) 57</td>
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<tr>
<td>(3) 70</td>
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<tr>
<td>(4) 51</td>
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<tr>
<td>(1) 54</td>
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<tr>
<td>(2) 57</td>
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<tr>
<td>(3) 57</td>
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<tr>
<td>(4) 35</td>
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<tr>
<td>(5) 50</td>
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<tr>
<td>(6) 55</td>
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<tr>
<td>(67) 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(78) 67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) MDD, 17% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) MDD, 39% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) MDD, 100% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) MDD, 33% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) MDD and failed &gt;= 2 antidepressants courses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) MDD, 21% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) MDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) MDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) MDD (30% with bipolar disorder)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) MDD (20% with bipolar disorder, 27% with psychotic features)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(67) MDD, 33% psychotic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(78) MDD, some psychotic features (% NA), insufficient response to 5-8 unilateral ECT (150% above ST)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatments (% above seizure threshold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Fluoxetine 20 mg, 40 mg + melatonin 5mg or 10 mg vs fluoxetine 20 mg – 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) ECT vs nortriptyline + lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) nortriptyline vs nortriptyline + ECT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) imipramine vs placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) bilateral 50% vs unilateral 150%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) bilateral 0% vs unilateral 400% vs unilateral 150%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) bilateral 50% vs unilateral 700%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) bilateral 50% vs bilateral 0% vs unilateral 400%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) bilateral 150% (separate groups for ultrabrief and brief ECT) vs unilateral ECT (500% (separate groups for ultrabrief and brief ECT))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(67) bilateral ‘high’ dose vs unilateral ‘high’ dose’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(78) bilateral 150% vs unilateral 450%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not examined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Bifrontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Bifrontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Bitemporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) Bifrontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) Bifrontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) Bifrontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7) Bitemporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8) Bitemporal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10.4.3 ECT as a next-step treatment

The reviews of ECT compared with sham ECT and with pharmacological interventions were not updated since no new studies were found. However, that comparing bilateral ECT with unilateral ECT, including a sub-analysis by dose, was updated. In addition a narrative review of cognitive impairment related to electrode placement and dose was undertaken.

Bilateral ECT versus unilateral ECT

The review by Geddes et al (2003) was used as the basis of this review. The effect sizes calculated in this review reported in the published paper were input into CMA and combined with effect sizes from the 86 new studies found. The overall standardised mean difference calculated by Geddes et al (2003) was -0.322 (random effects) (-0.458 to -0.186) (22 studies, 1137 participants). With the addition of the 6 new studies the effect size was reduced slightly to -0.23 (random effects) (-0.37, -0.09) (31 studies, 1,693 participants; P =39%), thus confirming an overall small to medium effect favouring bilateral ECT. See Figure 5.
Bilateral ECT versus unilateral ECT – the effect of dose dose and electrode placement on efficacy

A sub-analysis by dose was also undertaken on efficacy related to electrode placement. This topic was also included in the review by Geddes et al (2003) which included studies comparing different doses of unilateral ECT and different doses of bilateral ECT, as well as 45 which specifically compared bilateral ECT with unilateral ECT at doses related to seizure threshold. These 54 studies were included in our sub-analysis (SACKHEIM1993; SACKHEIM2000; LETEMENDIA1993; MALITZ1986; SACKHEIM1987).

Dose was classified based on percentage above seizure threshold (one new study described doses as ‘high’ (STOPPE2006)). Doses described as ‘just above seizure threshold’ were classified 0%. The doses given in the studies available for the sub-analysis are in Table 106.

Table 106 Doses (% above seizure threshold) of bilateral ECT and unilateral ECT given in the available studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Comparison</th>
<th>Doses for each study</th>
<th>Statistics for each study</th>
<th>Hedges' g and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 5 Bilateral ECT vs unilateral ECT: updated forest plot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Low-dose was defined as doses up to 150% above seizure threshold and high-dose unilateral ECT was defined as doses over 150%. There was no evidence to suggest a difference between low-dose bilateral ECT and low-dose unilateral ECT. There was some evidence on one outcome measure (non-remission) that high-dose unilateral ECT may be more effective than low-dose bilateral ECT, but this was not supported by other outcome measures. See Table 107.

Table 107 Summary evidence profile for acute-phase ECT: bilateral ECT vs unilateral ECT

<table>
<thead>
<tr>
<th></th>
<th>Low-dose bilateral ECT vs low-dose unilateral ECT</th>
<th>Low-dose bilateral ECT vs high-dose unilateral ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean depression scores at endpoint (clinician-rated)</strong></td>
<td>SMD -0.46 (-1.69 to 0.76)</td>
<td>SMD 0.01 (-0.27 to 0.29)</td>
</tr>
<tr>
<td>Quality</td>
<td>Very low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=91</td>
<td>K=4; n=204</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 12.05</td>
<td>Pharm next-step 12.08</td>
</tr>
<tr>
<td><strong>Non-response</strong></td>
<td>RR 0.65 (0.35 to 1.21) (52% vs 69.7%)</td>
<td>RR 0.98 (0.74 to 1.29) (35.2% vs 36.1%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Very low</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=4; n=217</td>
<td>K=7; n=362</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 12.04</td>
<td>Pharm next-step 12.06</td>
</tr>
<tr>
<td><strong>Non-remission</strong></td>
<td>RR 0.93 (0.77 to 1.14) (64.2% vs 68.7%)</td>
<td>RR 1.24 (0.97 to 1.6) (52.5% vs 42.9%)</td>
</tr>
<tr>
<td>Quality</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=2; n=134</td>
<td>K=5; n=237</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm next-step 12.05</td>
<td>Pharm next-step 12.07</td>
</tr>
</tbody>
</table>

A visual inspection of the forest plots indicated that there appears to be neither no consistent effect for electrode placement (bifrontal or bitemporal) nor any relationship between electrode placement and dose, although there are insufficient studies to allow these factors to be explored systematically.
Cognitive side effects related to electrode placement and dose

Geddes et al (2003) reported that patients who received bilateral ECT seemed to take longer to recover orientation than those treated with unilateral ECT (based on 6 trials which reported this), and that they showed greater impairment in retrograde memory (based on 4 trials which reported this) and anterograde memory (7 trials reported this). Geddes et al (2003) also report that they found only two trials reporting long-term data, which were both small and underpowered, and which found no long-term differences between bilateral and unilateral ECT on cognitive functioning.

In the studies considered we have taken bifronto-temporal placement as bitemporal. Combining the new studies with relevant studies from Geddes et al (2003) there was comparison between different doses of bitemporal ECT and unilateral ECT in 6 studies, bifrontal ECT and unilateral ECT in 4 studies and bifrontal ECT and bitemporal ECT in one study (See Table 108). Sackeim 2008 had approximately 30% bipolar patients and Siegaerd 2008 20% bipolar patient; both were included in this review of cognitive effects.

Table 108 Studies comparing bilateral and unilateral ECT: reported differences in cognitive functioning and efficacy
AMI: autobiographical memory impairment; BF: bifrontal; BT: bitemporal; UL: right

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Dose above threshold</th>
<th>MMSE/3MS</th>
<th>Other cognition</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eschweiler 2007</td>
<td>BF v UL</td>
<td>50% v 150%</td>
<td>No change with treatment (BF=UL)</td>
<td>Reorientation time BF=UL. Non-verbal anterograde amnesia (BF&lt;UL) and decreased verbal fluency with treatment (BF=UL)</td>
<td>Equal – (low response rate)</td>
</tr>
<tr>
<td>Heikman 2002</td>
<td>BF v high dose UL v lower dose UL</td>
<td>0% v 400% v 150%</td>
<td>No change with treatment (BF=UL)</td>
<td>-</td>
<td>High dose UL faster onset, tendency to greater response</td>
</tr>
<tr>
<td>McCall 2002</td>
<td>BT v UL</td>
<td>50% v 700%</td>
<td>-</td>
<td>AMI, anterograde amnesia with of treatment but improved at 4 weeks; still below baseline for AMI (BT=UL)</td>
<td>Equal</td>
</tr>
<tr>
<td>Ranjeksh 2005</td>
<td>BT v BF v UL</td>
<td>0% v 50% v 400%</td>
<td>Decreased with treatment (BF&lt;BT=UL)</td>
<td>-</td>
<td>Equal</td>
</tr>
<tr>
<td>Sackeim 2000/</td>
<td>BT v 3 doses UL v</td>
<td>150% v 50% v 150%</td>
<td>Decreased with treatment (BT&gt;UL-dose related)</td>
<td>Anterograde &amp; retrograde amnesia, AMI, persisting to 2 months (BT&gt;UL- mostly dose related)</td>
<td>BT=high dose UL, both&gt;lower dose UL</td>
</tr>
<tr>
<td>Lisanby 2000</td>
<td>2BT v UL v UL v 2UL</td>
<td>150% v 150% v 450%</td>
<td>Decrease with treatment standard v ub (BT=UL)</td>
<td>Reorientation time, anterograde &amp; retrograde amnesia, AMI less in ub groups (AMI difference persisting to 6 months). AMI less in UL groups. 2ULa group had no significant cognitive effects</td>
<td>2BTub&lt; other groups</td>
</tr>
<tr>
<td>Sackeim 2008</td>
<td>2BFub v 2ULub v</td>
<td>50% v 500%</td>
<td>Increased with treatment (BF=UL)</td>
<td>-</td>
<td>UL faster onset, equal response</td>
</tr>
<tr>
<td>Stoppe 2006</td>
<td>Both fixed high dose</td>
<td>Decrease with treatment in BT v UL</td>
<td>Trend to more delirium with BT v UL. No significant change in anterograde &amp; retrograde amnesia, AMI 1 month after treatment, some improvent with UL not BL. Overall BT=UL</td>
<td>Equal</td>
<td></td>
</tr>
<tr>
<td>Tew 2002</td>
<td>1BT v UL</td>
<td>150% v 450%</td>
<td>Decrease with treatment in BT v UL</td>
<td>-</td>
<td>Equal</td>
</tr>
</tbody>
</table>
unilateral; MMSE: mini-mental state examination; 3MSE: modified mini-mental state examination; ub: ultra brief pulse; =: equal; <: less than; >: more than

- Bilateral mode not explicitly stated but taken as bitemporal
- Ultra brief pulse (0.3msec)

The new studies had differences in bilateral electrode placement (bifrontal compared with the standard bitemporal placement) and in stimulus pulse width (ultra brief pulse compared with standard brief pulse). There was variation in the lower/’standard’ dose of bitemporal ECT with 150% above seizure threshold often used in key US studies compared with lower UK recommendations from the Royal College of Psychiatrists (50% to 100% above seizure threshold) (Royal College of Psychiatrists, 2005). As explored quantitatively above, high dose (≥400% above seizure threshold) unilateral ECT generally appeared as effective as low/standard dose (0-150% above seizure threshold) bilateral ECT whether bitemporal or bifrontal. One study including low dose unilateral ECT arms found them to be less effective than standard dose bilateral and high dose unilateral ECT.

The range of cognitive side-effects assessments varied between studies and were not consistent with regard to global scores (MMSE/3MS) but more consistent memory effects (including autobiographical memory impairment) were seen.

Previous studies have suggested that bifrontal ECT may cause fewer cognitive effects than bitemporal ECT but with similar efficacy (Letemendia 1993, Lawson 1990, Bailine 2000) so the two types of bilateral ECT were considered separately.

In the five studies in which bitemporal low/standard dose ECT was compared with unilateral high dose ECT, 2 found no difference in cognitive effects, 2 found that bitemporal ECT caused a greater global decrease and one found that bitemporal ECT had cause greater impairment of autobiographical memory but not other measures of retrograde and anterograde memory. In one study with high dose bitemporal ECT a global decrease in cognitive function compared with high dose unilateral ECT was seen. The studies in which bitemporal ECT worsened cognitive function compared with unilateral ECT used high standard doses (150% above seizure threshold).

In the 3 studies where bifrontal low/standard dose ECT was compared with high dose unilateral ECT, 2 studies found no difference in global cognitive effects and one found less impairment. A study where both doses were low found no difference in most cognitive effects except less nonverbal anterograde amnesia with bifrontal ECT. In 2 studies there was faster onset of improvement with high dose unilateral ECT.

Ultra-brief pulse (0.3msec) high dose ECT caused no cognitive impairment in 2 studies and cognitive impairment was significantly less than standard brief pulse (1.5msec) treatment in one study.

A soon to be reported large study comparing bitemporal (50% above seizure threshold), bifrontal (50% above seizure threshold) and right unilateral (400% above seizure threshold) with a 1msec pulse width, similar to treatment practice in the UK, has found few differences in cognitive effects and efficacy between placements (Charles Kellner, personal communication).
NICE Technology Appraisal on ECT (TA59) concluded that cognitive impairment is greater in individuals who have had electrodes applied bilaterally than in those who have had them placed unilaterally, and that unilateral placement to the dominant hemisphere causes more impairment than placement to the non-dominant hemisphere. They also found that raising the stimulus threshold above the individual’s seizure threshold increased the efficacy of unilateral ECT at the expense of increased cognitive impairment. Overall the conclusion was that reduction in the risk of cognitive impairment is mirrored by a reduction in efficacy.

The new studies provide insufficient evidence to determine whether efficacy and cognitive side-effects can be dissociated by manipulating electrode placement and stimulus dose or parameters. Results with high dose ultra-brief unilateral ECT need to be replicated.

**Effect of ethnicity**

The data from the acute phase of the KELLNER2007 trial included in the analyses above were also analysed by race, looking at data for black and white participants separately (Williams et al., 2008). Of 515 participants, 483 were white and 32 black. Of these, 63.4% of white participants and 71.9% of black participants achieved remission. The difference was not statistically significant, although may indicate a trend towards ECT being more effective in black participants. It should be noted that the study was undertaken in the US where the ethnic populations are different to those in England and Wales so the results of this study are unlikely to be generalisable.

**10.4.4 Relapse prevention following successful treatment with ECT in relapse prevention**

Four studies were found of continuation treatment after successful treatment with ECT, two of which included maintenance ECT. In these studies, there was little difference after 6 months between adding ECT to an antidepressant and maintaining the antidepressant alone, or between ECT alone compared with a combination of nortriptyline and lithium. However, at 12 months, fewer participants experienced relapse if they had received ECT plus nortriptyline compared with those continuing treatment with nortriptyline alone. Similar data were not available for the other study. See Table 109 Summary evidence profile for relapse prevention with ECT.

<table>
<thead>
<tr>
<th></th>
<th>ECT + nortriptyline vs nortriptyline</th>
<th>ECT vs nortriptyline + lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse – 1st follow-up</td>
<td>6 months RR 0.5 (0.05 to 4.98) (6.3% vs 12.5%)</td>
<td>6 months RR 1.16 (0.77 to 1.74) (33.7% vs 29.1%)</td>
</tr>
<tr>
<td>Quality</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies; participants</td>
<td>K=1; n=32</td>
<td>K=1; n=201</td>
</tr>
</tbody>
</table>
In studies of pharmacological maintenance strategies, only nortriptyline plus lithium was effective (compared with placebo), although there was a trend towards nortriptyline plus lithium compared with nortriptyline alone being more effective. The data are weak since there is only one study comparing each strategy, with relatively low numbers. However, the data suggest that combination treatment with nortriptyline and lithium may be effective in reducing the likelihood of relapse following successful treatment with ECT.

### Table 110 Summary evidence profile for studies of pharmacological strategies for relapse prevention following successful ECT

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine + placebo vs fluoxetine + melatonin</th>
<th>Nortriptyline + lithium vs placebo</th>
<th>Nortriptyline vs placebo</th>
<th>Nortriptyline + lithium vs nortriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse – 1st follow-up</strong></td>
<td>12 weeks RR 1.17 (0.4 to 3.39) (27.8% vs 23.8%)</td>
<td>6 months RR 0.44 (0.25 to 0.8) (32.1% vs 72.4%)</td>
<td>6 months RR 0.77 (0.51 to 1.15) (56.6% vs 72.4%)</td>
<td>6 months RR 0.6 (0.32 to 1.14) (32.1% vs 53.6%)</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Number of studies; participants</strong></td>
<td>K=1; n=39</td>
<td>K=1; n=57</td>
<td>K=1; n=56</td>
<td>K=1; n=56</td>
</tr>
<tr>
<td><strong>Forest plot</strong></td>
<td>Pharm relapse-prevention 10.01</td>
<td>Pharm relapse-prevention 10.01</td>
<td>Pharm relapse-prevention 10.01</td>
<td>Pharm relapse-prevention 10.01</td>
</tr>
</tbody>
</table>

### Continuation/maintenance ECT and cognitive function

A particular concern in the NICE Technology Appraisal on ECT (TA59) about continuation or maintenance ECT was the lack of evidence about potential long-term cognitive effects. Since then there have been further data published although the numbers of patients studied have been small. Russell et al (2003) reported a retrospective evaluation of 43 patients who had received maintenance ECT for at least a year. They had an improved clinical status and slight improvement in their MMSE scores compared with before starting ECT. Adverse effects included falls, delirium and cardiac dysthymias, each in about 10% of patients but none causing significant morbidity. Rami-Gonzalez et al (2003) undertook a cross sectional study of 11 patients on maintenance ECT compared to a matched group not receiving ECT. The patients receiving ECT had impaired encoding of new information and frontal lobe test results compared with the control group but no difference in delayed recall. Vothknecht et al (2003) undertook a prospective study (mean 61 weeks) of 11 patients receiving maintenance ECT compared with 13 patients receiving only antidepressants. There was no difference between groups on a test battery including attention and concentration.
anterograde memory and frontal lobe function. An equal number in each group had subjective memory complaints. Rami et al (2004) reported results on a prospective assessment of 26 patients of whom 20 carried on with maintenance ECT over 1 year in comparison with 10 controls. There were no differences found between groups nor significant changes over 1 year in attention and concentration, anterograde memory and frontal lobe function. There have also been a few case reports showing no effects on cognitive function with maintenance ECT (Wijkstra 2005, Zisselman 2007).

10.4.5 **Health Economic Evidence and considerations**

The systematic literature search identified only 1 economic evaluation on ECT. The economic evidence reviewed in this guideline was the evaluation conducted by Greenhalg et al. 2005 as part of the HTA on ECT. The economic evaluation was undertaken to determine the cost-effectiveness of ECT for depressive illness as well as schizophrenia, catatonia and mania. The authors found no literature concerned with the cost-effectiveness of ECT to review and therefore set about to build an economic model based on the how ECT is used in the UK for people with MDD who require hospitalisation. They conferred with experts on the development of the model. The analysis compared inpatient administered ECT with other pharmacological treatments (TCAs, SSRIs, SNRIs, Lithium Augmentation). These therapies were combined to form eight scenarios in which ECT featured as a 1st, 2nd and 3rd line therapy. The modeling however failed to demonstrate that any of the scenarios had a clear benefit over any of the others. The authors stated that this was due to high levels of uncertainty around the effectiveness data and the utility estimates. This study was one of the first attempts at evaluating the cost effectiveness of ECT and although many of the model inputs were based on published literature many assumptions underlie the results due to the lack of available data. The authors pointed out that one of the main drawbacks in terms of cost-effectiveness of prescribing ECT was the associated high resource use. They also mention a higher rate of relapse with ECT than pharmacological therapies. This statement points to one of the limitations of this evaluation, also highlighted by McDonald and colleagues in their critique of this evaluation. Studies with very dissimilar populations were combined to compute model inputs such as relapse and response rates, medication trials with patient populations that were less depressed or not treatment resistant depressives were combined with populations who were treatment resistant or referred specifically for ECT. Underlying patient characteristics do play a vital role in determining the outcomes of studies and using data in this way makes the accuracy of the effectiveness estimates used in the model questionable. However, the authors did acknowledge the lack of data and conducted many sensitivity analyses, which showed little effect on the results. Both the authors of the HTA and Mcdonald et al. pointed to the clear need for RCTs that directly compare the efficacy of treating severely depressed patients with ECT versus pharmacological treatments.

For the effectiveness update, reviews of ECT with pharmacological interventions were not updated since no new studies were found. As a result, the cost effective analysis was not updated. However, the review comparing bilateral ECT with unilateral ECT, including a sub-analysis by dose, was updated. The HTA explored these differences by varying the efficacy, outcomes and cost in the sensitivity analysis to incorporate the different approaches used in providing ECT with no effect on results. There should be no
resource use differences between bilateral versus unilateral treatment. The clinical evidence review shows little difference in effect between bilateral and unilateral ECT with a slight advantage for bilateral ECT. These results are in keeping with previous effectiveness evidence.

The authors also mentioned uncertainty around the utility estimates used from the study by Bennet et al. 2000. In this study the depression specific McSad health state classification system was utilised; NICE recommends using a generic tool (NICE2004). The health state descriptions used referred to untreated depression. The population of the study was made up of patients who had experienced at least one episode of major, unipolar depression in the previous 2 years but who were currently in remission. This is not typical of the patients who are usually prescribed ECT. This study therefore, may underestimate quality of life gains from the treatment and also potentially overestimate benefit if one takes cognitive impairment following ECT into account. However, utility data for mental health related conditions are very sparse and at the time this study was 1 of a very small number of studies available for patients with depression. The utility values were also subject to sensitivity analysis, with no effect on the results. To date no studies have been found reporting utility values that have been elicited in a group of patients with a chronic course/severe depression requiring/having received ECT.

ECT is resource intensive however patients who require ECT usually have a chronic form of the illness or undergo several treatment options before being referred on for ECT. This group of people usually makes up a small proportion of the entire depressive population in a health system and the costs they incur to health systems can be quite significant. The clinical evidence points to ECT having a higher success rate for certain groups of people with severe depression, and providing this high cost intervention may prove to be cost effective as it may reduce subsequent resource use and potentially improve quality of life if prescribed as recommended.

10.4.6 From evidence to recommendations

The review of ECT for the updated guideline found relatively little additional data to update the reviews undertaken for the original NICE Technology Appraisal. There were no new data comparing ECT with sham ECT, antidepressants, or combination treatment. The new data comparing bilateral ECT with unilateral ECT did not change the conclusion that bilateral ECT is more effective than unilateral for people with depression, although the effect size is small. A sub-analysis by dose found some evidence that high-dose unilateral ECT (doses over 150% above seizure threshold) is more effective than low-dose bilateral ECT, but only on one outcome measure, although there are relatively few data. Similarly, there were insufficient data on which to base a comparison of electrode placements, or to explore whether there is a relationship between electrode placement and dose with regard to efficacy.

With regard to cognitive impairment, it is still not clear whether cognitive side-effects can be reduced by manipulating dose and electrode placement. Therefore, the recommendations from the Technology Appraisal have been redrafted to match the style of other recommendations in the NICE guideline. More detailed advice is given on measuring cognitive side-effects.

The data on maintenance ECT is no clearer than those available previously, and this is still not recommended. However, where maintenance ECT is used, advice on measuring cognitive side-effects and collecting data for national audit has been added. Relapse prevention using pharmacological strategies has also been examined, and the
data suggest that lithium augmentation of antidepressants is effective. A recommendation about this has therefore been added.

10.4.6.1 ECT should be considered for severe depression which is life-threatening and when a rapid response is required, or when other treatments have failed. ECT should not be routinely used for people with moderate depression but may be considered for those whose depression has not responded to multiple treatments. For those who have not responded well to a previous course of ECT, consider a repeat trial of ECT only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate.

10.4.6.2 When considering ECT as a treatment choice, ensure the person with depression is fully informed of the risks associated with ECT, and with the risks and benefits specific to them. The assessment should be documented and consider the following:

- the risks associated with a general anaesthetic
- current medical comorbidities
- potential adverse events, notably cognitive impairment
- the risks associated with not receiving ECT.

The risks associated with ECT may be enhanced in older people and therefore clinicians should exercise particular caution when considering ECT treatment in this group.

10.4.6.3 A decision to use ECT should be made jointly with the person as far as possible, taking into account the following factors:

- valid informed consent should be obtained where the person has the capacity to grant or refuse consent, without pressure or coercion, which may occur as a result of the circumstances and clinical setting,
- the person should be reminded of their right to withdraw consent at any point
- there should be strict adherence to recognised guidelines about consent and the involvement of patient advocates and/or carers to facilitate informed discussion is strongly encouraged
- if informed consent is not possible, ECT should only be given where it does not conflict with a valid advance directive and the individual’s advocate and/or carer should be consulted.

10.4.6.4 The choice of electrode placement and stimulus dose related to seizure threshold should balance efficacy against the risk of cognitive impairment. It should be noted that:

- bilateral ECT is more effective than unilateral ECT but may cause more cognitive impairment
• with unilateral ECT, higher stimulus dose is associated with greater efficacy, but also increased cognitive impairment compared with lower stimulus dose.

10.4.6.5 Clinical status should be assessed after each ECT treatment using a formal valid outcome measure, and treatment should be stopped when an adequate response has been achieved, or sooner if side effects outweigh the potential benefits.

10.4.6.6 Cognitive function should be assessed before the first treatment and monitored at least every 2-4 treatments, and at the end of a course of treatment. Assessment should include:

- orientation and time to reorientation after each treatment
- measures of new learning, retrograde amnesia and subjective memory impairment carried at least 24 hours after a treatment

If there is evidence of significant cognitive impairment at any stage, in discussion with the patient, consideration should be given to changing from bilateral to unilateral electrode placement, reducing the dose, or stopping treatment depending on the balance of risks and benefits.

10.4.6.7 When a person with depression has responded to a course of ECT, medication should be continued or initiated to prevent relapse. Lithium augmentation of antidepressants should be considered.

10.4.6.8 Maintenance ECT for relapse prevention should not be routinely used in the treatment of depression because the longer-term benefits and risks of ECT have not been clearly established. If maintenance ECT is undertaken:

- cognitive assessment, consisting, of at a minimum, measures of new learning, retrograde amnesia and subjective memory impairment, should be conducted at initiation of treatment and during follow up together with assessment of clinical status using standardised outcome measures
- the data on the outcome of the treatment and the cognitive assessment should be submitted to a national audit of the use of maintenance ECT.
11 The management of minor (subthreshold) depression

11.1 Introduction

The previous guideline made recommendations only for major depressive disorder. However, the scope for the update included the management of milder depression disorders, including minor (subthreshold) depression and persistent minor depression (dysthymia). This chapter brings together the evidence for pharmacological and psychological interventions for this group.

Depression that is ‘subthreshold’, i.e., does not meet the full criteria for a depressive/major depressive episode is increasingly recognised as causing considerable morbidity and human and economic costs. It is more common in those with a history of major depression and is a risk factor for future major depression (Rowe & Rapaport, 2006).

There is no accepted classification for this in the current diagnostic systems with the closest being minor depression, a research diagnosis in DSM-IV. At least two but less than 5 symptoms are required of which one must be depressed mood or diminished interest. It is important to realise that overlaps with ICD-10 depressive episode with 4 symptoms. Given the practical difficulty and inherent uncertainty in deciding thresholds for significant symptom severity and disability, there is no natural discontinuity between minor depression and mild major depression in routine clinical practice.

Both DSM-IV and ICD-10 have the category of dysthymia which consists of depressive symptoms which are sub-threshold for major depression but which persist (by definition for more than 2 years). There appears to be no empirical evidence that dysthymia is distinct from minor depression apart from duration of symptoms, and the term persistent minor depression is preferred in this guideline. The term dysthymia is still used in this chapter when describing the evidence from studies using this term.

ICD10 has a category of mixed anxiety and depression, which is less clearly defined than minor depression, and is largely a diagnosis of exclusion in those with anxiety and depressive symptoms sub-threshold for specific disorders. It is a heterogeneous category with a lack of diagnostic stability over time and for this reason it has not been included in this guideline.

This chapter is in 2 sections: the first considers pharmacological strategies and the second psychological interventions (including studies comparing pharmacological treatments with psychological interventions).
11.2 Pharmacological strategies for minor (subthreshold) depression and persistent minor depression (dysthymia)

11.2.1 Introduction

Although milder depressive disorders are common there has been much less research carried out into their treatment and their definitions have been more varied. Best recognised in classification systems has been dysthymia (minor depression that has persisted for at least 2 years); an acknowledgment that chronic disorders tend to persist and therefore may warrant treatment even if relatively mild. The assumption has been that acute minor depression has a high natural remission rate and therefore does not benefit from active treatment. This is supported by post-hoc analyses of two studies (Stewart et al., 1983; Paykel et al., 1988) which found that patients with depression below the threshold for major depression generally responded well and showed no advantage for a tricyclic over placebo whereas there was for those with major depression. Similarly 2 RCTs in primary care of enhanced treatment resulting in improved medication adherence showed benefits for the intervention over treatment as usual in those with major depression but not those with minor (subthreshold) depression, where again improvement was the rule (Katon et al., 1996; Peveler et al., 1999).

A problem in the evidence base is that many studies including people with persistent minor depression often have a mixed population including those with major depression. There is also the difficulty that because dysthymia requires 2 years of symptoms there is little evidence on outcomes in patients with intermediate durations of illness (eg from about 3 months to 2 years) on which to determine after how long minor depression becomes sufficiently persistent to warrant specific treatment; it is unlikely that this occurs only after 2 years. In UK clinical practice the term dysthymia has not been embraced; probably because of confusion about what includes, the duration requirement, difficulty in ruling out a prior major depression (which would technically make it partially remitted major depression), and lack of guidelines on its treatment.

11.2.2 Search for studies for review

The electronic databases searched for published trials are given in Table 111. Details of the search strings used are in appendix 8.

Table 111: Databases searched and inclusion/exclusion criteria for clinical effectiveness of pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008, January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of dysthymia, minor depression or subthreshold according to DSM, ICD or similar criteria</td>
</tr>
<tr>
<td>Treatments</td>
<td>Any pharmacological treatment</td>
</tr>
</tbody>
</table>
In total, 53 trials were sourced from searches of electronic databases, with 20 being included and 33 excluded. A number of trials included populations with a mixture of diagnoses, including dysthymia, minor depression and major depressive disorder. Trials in which more than 50% of participants had a diagnosis of major depressive disorder were excluded from this review (but included in other reviews where appropriate). The majority of trials were of acute-phase treatments, with one being of relapse prevention. Summary study characteristics of the included studies are below, with full details in Appendix 17 which also includes details of excluded studies.

Data were available to compare antidepressants and one antipsychotic with placebo, and to compare a range of antidepressants, and antidepressants with antipsychotics.

### 11.2.3 Acute-phase treatments for persistent minor depression (dysthymia)

**Placebo-controlled studies**

A total of 9 placebo-controlled trials met inclusion criteria. See Table 112 for the summary study characteristics, with full details in Appendix 17.
Table 112 Summary study characteristics of placebo-controlled RCTs of pharmacological treatments for dysthymia

<table>
<thead>
<tr>
<th>SSRIs</th>
<th>TCAs</th>
<th>MAOIs</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
<td>6 RCTs (1226)</td>
<td>4 RCTs (654)</td>
<td>1 RCT (212)</td>
</tr>
<tr>
<td>Study IDs</td>
<td>(1) BARRETT1999</td>
<td>(2) HELLESTEIN1993</td>
<td>(3) RAVINDRAN1999</td>
</tr>
<tr>
<td>(1) BAKISH1993</td>
<td>(2) BOYER1999</td>
<td>(3) THASE1996</td>
<td>(4) VERSIANI1997</td>
</tr>
<tr>
<td>N/% female</td>
<td>(1) 252*/50</td>
<td>(2) 35/46</td>
<td>(3) 97/58</td>
</tr>
<tr>
<td>(1) 50/50</td>
<td>(2) 121*/75</td>
<td>(3) 276*/65</td>
<td>(4) 207*/71</td>
</tr>
<tr>
<td>Mean age (range if not given)</td>
<td>(1) 61</td>
<td>(2) 36</td>
<td>(3) 21-54</td>
</tr>
<tr>
<td>(1) 38</td>
<td>(2) 48</td>
<td>(3) 42</td>
<td>(4) 41</td>
</tr>
<tr>
<td>Drug</td>
<td>(1) Paroxetine</td>
<td>(2) Fluoxetine</td>
<td>(3) Sertraline</td>
</tr>
<tr>
<td>(1) Imipramine</td>
<td>(2) Amineptine</td>
<td>(3) Imipramine</td>
<td>(4) Imipramine</td>
</tr>
<tr>
<td>Setting</td>
<td>(1) Primary care</td>
<td>(2) Community/referral</td>
<td>(3) Community</td>
</tr>
<tr>
<td>(1) Outpatients</td>
<td>(2) Outpatients</td>
<td>(3) Outpatients</td>
<td>(4) Outpatients</td>
</tr>
<tr>
<td>(1) Length of treatment</td>
<td>(1) 11 weeks</td>
<td>(2) 8 weeks</td>
<td>(3) 12 weeks</td>
</tr>
<tr>
<td>(1) 7 weeks</td>
<td>(2) 12 weeks</td>
<td>(3) 12 weeks</td>
<td>(4) 8 weeks</td>
</tr>
</tbody>
</table>

* N with dysthymia in relevant antidepressant and placebo groups

All treatments were effective compared with placebo (quality of evidence: low, moderate and high). Compared with placebo, fewer participants left treatment early for any reason if they took an SSRI or an MAOI, but more participants left treatment early if they took a TCA or an antipsychotic. More left treatment early specifically because of side effects if they had taken a psychotropic drug than if they had taken placebo, whilst the number reporting side effects (not reported for MAOIs) was also greater in the active treatment groups. See Table 113 and Table 114 for the summary evidence profiles and Appendix 16 for the full profiles.

Table 113 Summary evidence profile for treatments versus placebo for dysthymia (efficacy data)

<table>
<thead>
<tr>
<th>SSRIs</th>
<th>TCAs</th>
<th>MAOI</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Depression in adults (update): full guideline DRAFT (February 2009)
<table>
<thead>
<tr>
<th>Non-response</th>
<th>RR 0.72 (0.63 to 0.82)</th>
<th>RR 0.52 (0.37 to 0.73)</th>
<th>RR 0.5 (0.36 to 0.71)</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=5; n=727</td>
<td>K=1; n=144</td>
<td>K=1; n=146</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.01</td>
<td>Pharm subthreshold 01.01</td>
<td>Pharm subthreshold 01.01</td>
<td></td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.78 (0.68 to 0.89)</td>
<td>RR 0.81 (0.63 to 1.03)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=3; n=608</td>
<td>K=1; n=420</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.02</td>
<td>Pharm subthreshold 01.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean endpoint/mean change</td>
<td>SMD -0.56 (-0.83 to -0.29)/ SMD -0.31 (-0.51 to -0.11)</td>
<td>SMD -0.62 (-0.9 to -0.35)/ SMD -0.61 (-0.9 to -0.31)</td>
<td>NR/ SMD -0.97 (-1.32 to -0.62)</td>
<td>SMD -0.66 (-0.94 to -0.38)/SMD -0.67 (-0.95 to -0.39)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High/high</td>
<td>Moderate/moderate</td>
<td>NR/Moderate</td>
<td>Moderate/moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=219/K=2; n=285</td>
<td>K=1; n=212/k=3; n=623</td>
<td>K=1; n=139</td>
<td>K=1; n=206/K=1; n=206</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.03/01.04</td>
<td>Pharm subthreshold 01.03/01.04</td>
<td>Pharm subthreshold NR/01.04</td>
<td>Pharm subthreshold 01.03/01.04</td>
</tr>
</tbody>
</table>

NR= not reported

Table 114 Summary evidence profile for treatments versus placebo for dysthymia (acceptability/tolerability data)

<table>
<thead>
<tr>
<th></th>
<th>SSRIs</th>
<th>TCAs</th>
<th>MAOI</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 0.84 (0.57 to 1.24)</td>
<td>RR 1.1 (0.84 to 1.44)</td>
<td>RR 0.83 (0.42 to 1.67)</td>
<td>RR 0.66 (0.36 to 1.22)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=6; k=1030</td>
<td>K=4; n=734</td>
<td>K=1; n=212</td>
<td>K=1; n=212</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 02.01</td>
<td>Pharm subthreshold 02.01</td>
<td>Pharm subthreshold 02.01</td>
<td>Pharm subthreshold 02.01</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 1.77 (0.71 to 4.41)</td>
<td>RR 5.44 (2.66 to 11.11)</td>
<td>RR 3.37 (0.72 to 15.85)</td>
<td>RR 3.12 (0.33 to 29.47)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=497</td>
<td>K=4; n=735</td>
<td>K=1; n=112</td>
<td>K=1; n=112</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 02.02</td>
<td>Pharm subthreshold 02.02</td>
<td>Pharm subthreshold 02.02</td>
<td>Pharm subthreshold 02.02</td>
</tr>
<tr>
<td>Number reporting side effects</td>
<td>RR 1.09 (0.95 to 1.25)</td>
<td>RR 1.4 (1.08 to 1.81)</td>
<td>NR</td>
<td>RR 1.23 (0.94 to 1.62)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>Moderate</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>N=3; k=673</td>
<td>K=1; n=218</td>
<td>K=1; n=112</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold</td>
<td>Pharm subthreshold</td>
<td>Pharm subthreshold</td>
<td></td>
</tr>
</tbody>
</table>
Head-to-head studies

There were 10 studies making head-to-head comparisons of active treatments, including antidepressants and antipsychotics. Three studies had fewer than 100% of participants with dysthymia (although all had at least 50% with dysthymia). These studies were analysed separately. See Table 115 for the summary study characteristics.

Table 115 Summary study characteristics of studies comparing active treatments for dysthymia

<table>
<thead>
<tr>
<th>No. trials (Total participants)</th>
<th>Antidepressants vs antidepressants</th>
<th>Antidepressants vs antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 RCTs (383)</td>
<td></td>
<td>5 RCTs (1237)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study IDs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) BAKISH1993</td>
<td></td>
<td>(1) AMORE2001*</td>
</tr>
<tr>
<td>(2) DEJONGHE1991*</td>
<td></td>
<td>(2) BOYER1999</td>
</tr>
<tr>
<td>(3) SALZMANN1995</td>
<td></td>
<td>(3) GEISLER1992</td>
</tr>
<tr>
<td>(4) VALEJO1987</td>
<td></td>
<td>(4) RAVIZZA1999</td>
</tr>
<tr>
<td>(5) VERSIAN11997</td>
<td></td>
<td>(5) SMERALDI1996 *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N/% female</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 50/48</td>
<td></td>
<td>(1) 313/68</td>
</tr>
<tr>
<td>(2) 48/60</td>
<td></td>
<td>(2) 323/75</td>
</tr>
<tr>
<td>(3) 67/81</td>
<td></td>
<td>(3) 67/78</td>
</tr>
<tr>
<td>(4) 73/71</td>
<td></td>
<td>(4) 253/64</td>
</tr>
<tr>
<td>(5) 211/71</td>
<td></td>
<td>(5) 281/65</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Mean age (range if not given)</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>(1) 38</td>
<td></td>
<td>(1) 47</td>
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<tr>
<td>(2) 40</td>
<td></td>
<td>(2) 48</td>
</tr>
<tr>
<td>(3) 55</td>
<td></td>
<td>(3) 48</td>
</tr>
<tr>
<td>(4) 42</td>
<td></td>
<td>(4) 47</td>
</tr>
<tr>
<td>(5) 41</td>
<td></td>
<td>(5) 55</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Imipramine vs ritanserin</td>
<td></td>
<td>(1) Amisulpride vs sertraline</td>
</tr>
<tr>
<td>(2) Fluvoxamine vs maprotiline</td>
<td></td>
<td>(2) Amisulpride vs aminepine</td>
</tr>
<tr>
<td>(3) Imipramine vs minaprine</td>
<td></td>
<td>(3) Flupenthixol vs ritanserin</td>
</tr>
<tr>
<td>(4) Sertraline vs imipramine</td>
<td></td>
<td>(4) Amisulpride vs amisulpride</td>
</tr>
<tr>
<td>(5) Imipramine vs moclobemide</td>
<td></td>
<td>(5) Amisulpride vs fluoxetine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Outpatients</td>
<td></td>
<td>(1) Outpatients</td>
</tr>
<tr>
<td>(2) Outpatients</td>
<td></td>
<td>(2) Outpatients</td>
</tr>
<tr>
<td>(3) Outpatients</td>
<td></td>
<td>(3) Primary care</td>
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<tr>
<td>(4) Outpatients</td>
<td></td>
<td>(4) Outpatients</td>
</tr>
<tr>
<td>(5) Outpatients</td>
<td></td>
<td>(5) Outpatients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 7 weeks</td>
<td></td>
<td>(1) 12 weeks</td>
</tr>
<tr>
<td>(2) 6 weeks</td>
<td></td>
<td>(2) 12 weeks</td>
</tr>
<tr>
<td>(3) 6 weeks</td>
<td></td>
<td>(3) 6 weeks</td>
</tr>
<tr>
<td>(4) 7 weeks</td>
<td></td>
<td>(4) 6 months</td>
</tr>
<tr>
<td>(5) 8 weeks</td>
<td></td>
<td>(5) 12 weeks</td>
</tr>
</tbody>
</table>

* studies have fewer than 100% of participants with dysthymia (AMORE2001 11% double depression; DEJONGHE1991 46% major depression; SMERALDI1996 6% major depressive disorder in partial remission)

For those with dysthymia there was no difference in efficacy either between different antidepressants (quality of evidence: low) or between antidepressants and antipsychotics (quality of evidence: moderate or high). However, in studies with participants with other diagnoses (see Table 115) an antipsychotic was more effective.
than an SSRI (amisulpride compared with sertraline), although this was not the case when an antipsychotic was compared with a TCA where there was no difference (quality of evidence: low or moderate). See Table 116 and Table 117 for the summary evidence profiles of efficacy data.

In studies where all participants had dysthymia, SSRIs were more acceptable to participants than other antidepressants, with fewer leaving treatment early for any reason (quality of evidence: moderate), and fewer leaving early specifically because of side effects (quality of evidence: moderate). Amisulpride appeared more acceptable and tolerable than amitriptyline, but the effect sizes were small and not statistically significant (quality of evidence: moderate or low). In studies where not all participants had dysthymia, there was inconclusive evidence on the acceptability of an SSRI compared with another antidepressant (quality of evidence: low), some evidence that an SSRI was more acceptable than an antipsychotic (quality of evidence: moderate), but other evidence was inconclusive and graded low in quality. See Table 116, Table 117, Table 118 and Table 119 for summary evidence profiles, and Appendix 16 for the full profile.

Table 116 Summary evidence profile for active treatment comparisons for dysthymia (efficacy)

<table>
<thead>
<tr>
<th></th>
<th>SSRI vs other AD</th>
<th>TCA vs other antidepressant</th>
<th>TCA vs antipsychotic</th>
<th>Antipsychotic vs other drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>NR</td>
<td>RR 1.07 (0.79 to 1.46) (45.1% vs 41.7%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison)</td>
<td>K=2; n=205 (imipramine vs minaprine or moclobemide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 0.87 (0.7 to 1.07) (53% vs 61%)</td>
<td>RR 1.12 (0.81 to 1.55) (54.4% vs 48.6%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison)</td>
<td>K=1; n=270 (sertraline vs imipramine)</td>
<td>K=1; n=138 (imipramine vs moclobemide)</td>
<td>Pharm subthreshold 03.02</td>
<td>Pharm subthreshold 03.02</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.02</td>
<td>Pharm subthreshold 03.02</td>
<td>Pharm subthreshold 03.02</td>
<td></td>
</tr>
<tr>
<td>Mean endpoint</td>
<td>SMD -0.01 (-0.62 to 0.59)</td>
<td>SMD 0.11 (-0.44 to 0.66)</td>
<td>SMD 0.04 (-0.23 to 0.31)</td>
<td>SMD -0.26 (-0.74 to 0.22)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants (comparison)</td>
<td>K=1*; n=42 (fluvoxamine vs maprotiline)</td>
<td>K=1; n=51 (imipramine vs minaprine)</td>
<td>K=1; n=208 (amitriptyline vs amisulpride)</td>
<td>K=1; n=67 (flupenthixol vs ritanserin)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.03</td>
<td>Pharm subthreshold 03.03</td>
<td>Pharm subthreshold 03.03</td>
<td>Pharm subthreshold 03.03</td>
</tr>
<tr>
<td>Mean change</td>
<td>SMD 0.05 (-0.19 to 0.29)</td>
<td>SMD 0.12 (-0.23 to 0.46)</td>
<td>SMD 0.06 (-0.22 to 0.33)</td>
<td>NR</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison)</td>
<td>Forest plot</td>
<td>K=1; n=170 (sertraline vs imipramine)</td>
<td>K=1; n=130 (imipramine vs moclobemide)</td>
<td>K=1; n=208 (amitriptyline vs amisulpride)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Pharm subthreshold 03.04</td>
<td>Pharm subthreshold 03.04</td>
<td>Pharm subthreshold 03.04</td>
<td>Pharm subthreshold 03.04</td>
</tr>
</tbody>
</table>

NR = not reported

**Table 117** Summary evidence profile for active treatment comparisons for studies where have fewer than 100% (but at least 50%) participants have dysthymia (efficacy)

<table>
<thead>
<tr>
<th></th>
<th>SSRI vs other AD</th>
<th>SSRI vs antipsychotic</th>
<th>TCA vs other antidepressant</th>
<th>TCA vs antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response RR 1 (0.72 to 1.39)</td>
<td>RR 1.39 (1.06 to 1.83)</td>
<td>NR</td>
<td>RR 0.97 (0.7 to 1.33)</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison) K=1; n=48 (fluvoxamine vs maprotiline)</td>
<td>K=2; n=594 (SSRI vs amisulpride)</td>
<td>K=1; n=286 (amitriptyline vs amisulpride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot Pharm subthreshold 03.01</td>
<td>Pharm subthreshold 03.01</td>
<td>Pharm subthreshold 03.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-remission RR 1.29 (0.92 to 1.81)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison) K=1; n=313 (SSRI vs amisulpride)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot Pharm subthreshold 03.02</td>
<td>Pharm subthreshold 03.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean endpoint SMD -0.01 (-0.62 to 0.59)</td>
<td>SMD 0.16 (0 to 0.32)</td>
<td>SMD 0.73 (0.01 to 1.45)</td>
<td>SMD -0.01 (-0.27 to 0.25)</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence Low</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants (comparison) K=1; n=42 (fluvoxamine vs maprotiline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot Pharm subthreshold 03.03</td>
<td>Pharm subthreshold 03.03</td>
<td>Pharm subthreshold 03.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaving treatment early for any reason RR 0.47 (0.3 to 0.75)</td>
<td>RR 1.21 (0.61 to 2.42)</td>
<td>RR 1.34 (0.71 to 2.51)</td>
<td>RR 1.29 (0.23 to 7.24)</td>
<td></td>
</tr>
<tr>
<td>Quality of evidence Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants K=1; n=270 (sertraline vs imipramine)</td>
<td>K=1; n=211 (imipramine vs moclobemide)</td>
<td>K=1; n=215 (amitriptyline vs amisulpride)</td>
<td>K=1; n=67 (flupenthixol vs ritanserin)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 119 Summary evidence profile for active treatment comparisons for studies where have fewer than 100% (but at least 50%) participants have dysthymia (acceptability/tolerability)

<table>
<thead>
<tr>
<th></th>
<th>SSRI vs other AD</th>
<th>SSRI vs antipsychotic</th>
<th>TCA vs other antidepressant</th>
<th>TCA vs antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 0.67 (0.22 to 2.07) (16.7% vs 25%)</td>
<td>RR 1.36 (0.98 to 1.89) (22.7% vs 16.7%)</td>
<td>RR 1.22 (0.35 to 4.17) (13.5% vs 11.1%)</td>
<td>RR 1.07 (0.81 to 1.42) (47.1% vs 44%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=48 (fluvoxamine vs maproline)</td>
<td>K=2; n=594 (sertraline vs amisulpride)</td>
<td>K=1; n=73 (imipramine vs phenelzine)</td>
<td>K=1; n=253 (amitriptyline vs amisulpride)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 04.01</td>
<td>Pharm subthreshold 04.01</td>
<td>Pharm subthreshold 04.02</td>
<td>Pharm subthreshold 04.02</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 0.97 (0.55 to 1.7) (7.5% vs 7.7%)</td>
<td>RR 0.91 (0.47 to 1.78) (12.6% vs 13.9%)</td>
<td>RR 0.91 (0.47 to 1.78) (12.6% vs 13.9%)</td>
<td>RR 0.91 (0.47 to 1.78) (12.6% vs 13.9%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=956 (sertraline/fluoxetine vs amisulpride)</td>
<td>K=1; n=253 (amitriptyline vs amisulpride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 04.04</td>
<td>Pharm subthreshold 04.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 11.2.4 Acute-phase treatments for minor depression

**Leaving treatment early due to side effects**

<table>
<thead>
<tr>
<th></th>
<th>RR 0.32 (0.15 to 0.69) (6% vs 18.4%)</th>
<th>RR 1.54 (0.72 to 3.3) (10.9% vs 7.1%)</th>
<th>RR 1.87 (0.48 to 7.3) (5.4% vs 2.9%)</th>
<th>RR 0.92 (0.14 to 6.14) (44.4% vs 46%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=270 (setraline vs imipramine)</td>
<td>K=2; n=278 (imipramine vs minaprine/moclobemide)</td>
<td>K=1; n=115 (amitriptyline vs amisulpride)</td>
<td>K=1; n=39 (flupenthixol vs ritanserin)</td>
</tr>
</tbody>
</table>

**Leaving treatment early due to any reason**

<table>
<thead>
<tr>
<th></th>
<th>RR 1.39 (0.85 to 2.26) (58.8% vs 42.4%)</th>
<th>RR 1.13 (0.9 to 1.42) (62.2% vs 34.8%)</th>
<th>RR 0.98 (0.58 to 1.65) (44.4% vs 45.5%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>---</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=67 (imipramine vs minaprine)</td>
<td>K=1; n=115 (amitriptyline vs amisulpride)</td>
<td>K=1; n=69 (flupenthixol vs ritanserin)</td>
<td>---</td>
</tr>
</tbody>
</table>

**Number reporting side effects**

- SSRI vs other AD: NR
- SSRRI vs antipsychotic: RR 1.39 (0.85 to 2.26) (58.8% vs 42.4%)
- TCA vs other antidepressant: RR 1.13 (0.9 to 1.42) (62.2% vs 34.8%)
- TCA vs antipsychotic: RR 0.98 (0.58 to 1.65) (44.4% vs 45.5%)

**Quality of evidence**

- Moderate
- Moderate
- Low
- Low
Four studies included participants with a diagnosis of minor depression, with 2 including mixed populations. See Table 120 for a summary of the study characteristics, with full details in Appendix 17.

**Table 120 Summary study characteristics for treatments for minor depression**

<table>
<thead>
<tr>
<th>Study IDs</th>
<th>No. trials (Total participants)</th>
<th>N/% female</th>
<th>Mean age (range if not given)</th>
<th>Drug</th>
<th>Setting</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1) BARRETT1999*</td>
<td>(1) 656/50</td>
<td>(1) 61</td>
<td>(1)  Paroxetine</td>
<td>(1) Primary care</td>
<td>(1) 11 weeks</td>
</tr>
<tr>
<td></td>
<td>(2) JUDD2004</td>
<td>(2) 162/59</td>
<td>(2) 44</td>
<td>(2)  Fluoxetine</td>
<td>(2) Unclear</td>
<td>(2) 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) ROCCA2005**</td>
<td>(1) 138/28</td>
<td>(1) 72</td>
<td>(1)  Citiclopramide vs sertraline</td>
<td>(1) Outpatients</td>
<td>(1) 1 year</td>
</tr>
<tr>
<td></td>
<td>(2) SZEgedDI1997***</td>
<td>(2) 543/72</td>
<td>(2) NR</td>
<td>(2) Paroxetine vs maprotiline</td>
<td>(2) Outpatients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* mixed population, but data supplied by study authors for each diagnosis separately ** 49% minor depression; *** 45% minor depression; NR = not reported

In people with minor depression, antidepressants (paroxetine) appeared to be no better than placebo (quality of evidence: moderate or high), although in head-to-head trials paroxetine was more effective than maprotiline, and citalopram was more effective than sertraline.

**Table 121 Summary evidence profile for treatments for minor depression (efficacy data)**

<table>
<thead>
<tr>
<th></th>
<th>SSRI vs placebo</th>
<th>Antidepressant vs antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>RR 0.99 (0.77 to 1.28) (51.9% vs 52.3%)</td>
<td>RR 0.73 (0.48 to 1.09) (23.8% vs 32.8%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=215 (paroxetine)</td>
<td>K=1; n=245 (paroxetine vs maprotiline)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.01</td>
<td>Pharm subthreshold 03.01</td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 1.06 (0.84 to 1.34) (58.5% vs 55%)</td>
<td>RR 1.24 (0.9 to 1.71) (58.3% vs 47%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; k=215 (paroxetine)</td>
<td>K=1; n=138 (sertraline vs citalopram)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.02</td>
<td>Pharm subthreshold 03.02</td>
</tr>
<tr>
<td>Mean endpoint</td>
<td>SMD -0.19 (-0.41 to 0.03)</td>
<td>NR</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=252 (paroxetine or fluoxetine)</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 01.03</td>
<td></td>
</tr>
</tbody>
</table>

NR= not reported
Table 122 Summary evidence profile for treatments for minor depression (acceptability/tolerability data)

<table>
<thead>
<tr>
<th></th>
<th>SSRIs vs placebo</th>
<th>Antidepressant vs antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 1.2 (0.87 to 1.65) (31.6% vs 26.3%)</td>
<td>RR 1.02 (0.59 to 1.75) (27.8% vs 27.3%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=377 (paroxetine or fluoxetine)</td>
<td>K=1; n=138 (sertraline vs citalopram)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.01</td>
<td>Pharm subthreshold 04.01</td>
</tr>
<tr>
<td>Leaving treatment early due to side effects</td>
<td>RR 1.55 (0.51 to 4.68) (9.1% vs 5.3%)</td>
<td>RR 0.73 (0.31 to 1.75) (11.1% vs 15.2%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=377 (paroxetine or fluoxetine)</td>
<td>K=1; n=138 (sertraline vs citalopram)</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.01</td>
<td>Pharm subthreshold 04.04</td>
</tr>
<tr>
<td>Number reporting side effects</td>
<td>RR 0.76 (0.49 to 1.18) (23.6% vs 31.2%)</td>
<td>NR</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=215 (paroxetine)</td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 03.01</td>
<td></td>
</tr>
</tbody>
</table>

NR= not reported

11.2.5 Review of relapse prevention for persistent minor depression (dysthymia)

A single trial was found which considered treatment to prevent relapse in patients who had achieved remission from dysthymia. Patients were randomised following remission or partial remission to open-label acute-phase treatment and 16 weeks' continuation treatment. The acute and continuation phases included patients with major depressive disorder.

<table>
<thead>
<tr>
<th>Relapse prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. trials (Total participants)</td>
</tr>
<tr>
<td>Study IDs</td>
</tr>
<tr>
<td>N/% female</td>
</tr>
<tr>
<td>Mean age (range if not given)</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Setting</td>
</tr>
<tr>
<td>Length of treatment</td>
</tr>
</tbody>
</table>

Far more participants taking placebo suffered relapse compared with those taking desipramine, although because there is only a single small study, the effect size is not statistically significant. See Table 123 for the summary evidence profile and Appendix 16 for the full profile.
Table 123 Summary evidence profile for RCTs of relapse prevention following remission from dysthymia

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician-rated effect</td>
<td>RR 0.07 (0 to 1.16)</td>
</tr>
<tr>
<td></td>
<td>(0% vs 46.2%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=27</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm subthreshold 05.01</td>
</tr>
</tbody>
</table>

### 11.2.6 Clinical summary of pharmacological interventions

There was some evidence the drugs are effective in treating people with persistent minor depression (dysthymia), this included a range of antidepressants and antipsychotics. SSRIs and MAOIs were more acceptable to participants compared with TCAs or antipsychotics. There was no clear advantage for one drug over another, although in studies with participants with other diagnoses an antipsychotic was more effective than an SSRI (amisulpride compared with sertraline), but not a TCA.

In people with minor depression, antidepressants (paroxetine) appeared to be no better than placebo (quality of evidence: moderate or high), although in head-to-head trials paroxetine was more effective than maprotiline, and citalopram was more effective than sertraline.

Antidepressants are not clearly better than placebo in people with recent onset minor depression, but are effective in people with persistent minor depression (dysthymia). People with recent onset minor depression should be offered the same treatment options as those with mild major depression. Antidepressant treatment may be beneficial in those whose symptoms persist. SSRIs are tolerated better than TCAs.

### 11.3 Psychological and other strategies for the treatment of minor depression and persistent minor depression (dysthymia)

#### 11.3.1 Introduction

There have been few psychological treatment studies in people with well defined minor depression and the range of therapies and definitions of subthreshold depression have varied (Cuijpers et al 2007).

This section covers psychological treatments, psychological treatments combined with antidepressants, and exercise.

#### 11.3.2 Search for studies for review
The electronic databases searched for published trials are given in Table 124. Details of the search strings used are in appendix 8.

### Table 124: Databases searched and inclusion/exclusion criteria for clinical effectiveness of non-pharmacological treatments

<table>
<thead>
<tr>
<th>Electronic databases</th>
<th>MEDLINE, EMBASE, PsycINFO, CINAHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date searched</td>
<td>Database inception to January 2008</td>
</tr>
<tr>
<td>Update searches</td>
<td>July 2008; January 2009</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT</td>
</tr>
<tr>
<td>Population</td>
<td>People with a diagnosis of dysthymia, minor depression or subthreshold according to DSM, ICD or similar criteria (&gt;=50 of study population, remainder to have other depression diagnoses) or raised symptom levels as measured by validated rating scale</td>
</tr>
<tr>
<td>Treatments</td>
<td>Any psychological, psychosocial or other non-pharmacological intervention</td>
</tr>
</tbody>
</table>

In total, 12 trials met inclusion criteria and 24 were excluded. A number of trials included populations with a mixture of diagnoses, including dysthymia, minor depression and major depressive disorder. Trials in which more than 50% of participants had a diagnosis of major depressive disorder were excluded from this review (but included in other reviews where appropriate). Summary study characteristics of the included studies are below, with full details in Appendix 17 which also includes details of excluded studies.
Table 125 Summary of study characteristics of RCTs of psychological and other non-pharmacological treatments

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Treatment/second treatment group</th>
<th>Comparison</th>
<th>Diagnosis</th>
<th>Setting</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) ALLARTIVAN2003</td>
<td>(1) Coping With Depression course (group CBT)</td>
<td>(1) Assessment and advice</td>
<td>(1) BDI &gt;= 10 (5% with dysthymia)</td>
<td>(1) Community</td>
<td>(1) 12 weeks</td>
</tr>
<tr>
<td>(2) BARRETT1999*</td>
<td>(2) Problem solving</td>
<td></td>
<td>(2) 52% dysthymia; 48% minor depression</td>
<td>(2) Primary care</td>
<td>(2) 10 weeks</td>
</tr>
<tr>
<td>(3) MAINA2005*</td>
<td>(3) Brief dynamic therapy/brief supportive therapy</td>
<td></td>
<td>(3) 50% dysthymia; 50% depressive disorder NOS; 20% adjustment disorder with depressed mood</td>
<td>(3) Outpatients</td>
<td>(3) 10 weeks</td>
</tr>
<tr>
<td>(4) RAVINDRAN1999*</td>
<td>(4) CBT</td>
<td></td>
<td>(4) 10% dysthymia; 30% minor depression</td>
<td>(4) Community</td>
<td>(4) 6 months</td>
</tr>
<tr>
<td>(5) SPEK2007*</td>
<td>(5) CBT + placebo; CCBT/group CBT - both groups based on Coping With Depression course</td>
<td></td>
<td>(5) 50% dysthymia; 30% minor depression</td>
<td>(5) Community</td>
<td>(5) 6 months</td>
</tr>
<tr>
<td>(6) RAVINDRAN1999*</td>
<td>(6) CBT + placebo; CBT + sertraline</td>
<td></td>
<td>(6) 50% dysthymia; 30% minor depression</td>
<td>(6) Community</td>
<td>(6) 6 months</td>
</tr>
<tr>
<td>(1) BARRETT1999*</td>
<td>(1) Problem solving</td>
<td>(1) Paroxetine 20mg</td>
<td>(1) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(1) Acute care</td>
<td>(1) 3 weeks</td>
</tr>
<tr>
<td>(2) BROWNE2002*</td>
<td>(2) IPT/ IPT + sertraline</td>
<td>(2) Sertraline 200mg</td>
<td>(2) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(2) Community</td>
<td>(2) 10 weeks</td>
</tr>
<tr>
<td>(3) DUNNER1996</td>
<td>(3) CBT</td>
<td>(3) Fluoxetine 20mg</td>
<td>(3) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(3) Outpatients</td>
<td>(3) 10 weeks</td>
</tr>
<tr>
<td>(4) HELLERSTEIN2001**</td>
<td>(4) Group CBT +fluoxetine 37mg</td>
<td>(4) Fluoxetine 39mg</td>
<td>(4) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(4) Tertiary care</td>
<td>(4) 6 months</td>
</tr>
<tr>
<td>(5) MARKOWITZ2006*</td>
<td>(5) IPT/IPT+sertraline/supportive therapy</td>
<td>(5) Sertraline 112 mg</td>
<td>(5) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(5) Community/primary care</td>
<td>(5) 6 months</td>
</tr>
<tr>
<td>(6) RAVINDRAN1999*</td>
<td>(6) CBT + placebo/CBT + sertraline</td>
<td>(6) Sertraline 178mg</td>
<td>(6) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(6) Community</td>
<td>(6) 6 months</td>
</tr>
<tr>
<td>(1) PASSMORE2006</td>
<td>(1) Aerobic exercise + resistance training</td>
<td>(1) Aerobic exercise</td>
<td>(1) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(1) Acute care</td>
<td>(1) 3 weeks</td>
</tr>
<tr>
<td>(2) SINGH1997</td>
<td>(2) Exercise</td>
<td>(2) Psychoeducation</td>
<td>(2) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(2) Community</td>
<td>(2) 10 weeks</td>
</tr>
<tr>
<td>(3) THYME2007</td>
<td>(3) Short-term psychodynamic psychotherapy</td>
<td>(3) Short-term psychodynamic art therapy</td>
<td>(3) Dysthymia (2) 41% depression; 53% minor depression</td>
<td>(3) Outpatients</td>
<td>(3) 10 weeks</td>
</tr>
</tbody>
</table>
11.3.3 Psychological interventions versus no-treatment control

There was no evidence that psychological interventions for people whose depression symptoms do not meet threshold for major depressive disorder (mostly with a diagnosis of dysthymia) are effective compared with no-treatment control (including waitlist, pill placebo, and ‘assessment and advice’). See Table 126.

**Table 126 Summary evidence profile for psychological interventions versus control**

<table>
<thead>
<tr>
<th>Psychological intervention vs control</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-response</strong></td>
<td>RR 0.92 (0.79 to 1.08) (52.5% vs 57.1%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=3; n=489</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 01.01</td>
</tr>
<tr>
<td><strong>Non-remission</strong></td>
<td>RR 0.95 (0.78 to 1.16) (56% vs 58.8%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=2; n=439</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 01.01</td>
</tr>
<tr>
<td><strong>Mean endpoint (clinician-rated)</strong></td>
<td>SMD -0.4 (-0.84 to 0.04)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=335</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 01.02</td>
</tr>
<tr>
<td><strong>Mean endpoint (self-rated)</strong></td>
<td>SMD -0.34 (-0.52 to -0.16)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=3; n=503</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 01.02</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 1.03 (0.85 to 1.25) (31.4% vs 30.1%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
</tr>
</tbody>
</table>
11.3.4 Psychological interventions versus antidepressants

On some outcomes there was evidence that psychological interventions for people whose depression symptoms do not meet threshold for major depressive disorder are as effective as antidepressants (non-response and non-remission), whilst on mean depressions scores at endpoint, antidepressants seem more effective, although the effect size is small. The evidence for combination therapy was inconclusive compared with antidepressants, but compared with psychological therapy there was some evidence that combination treatment was more effective. See Table 127.

The evidence from the study of combination treatment compared with antidepressants alone was inconclusive.

Table 127 Summary evidence profile for psychological interventions (with and without antidepressants) versus antidepressants or psychological treatment alone

<table>
<thead>
<tr>
<th></th>
<th>Psychological intervention vs antidepressants</th>
<th>Follow-up</th>
<th>Psychological intervention + antidepressants vs antidepressants</th>
<th>Follow-up</th>
<th>Psychological intervention + antidepressants vs psychological intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>RR 1.06 (0.92 to 1.22) (57.7% vs 54.4%)</td>
<td>RR 0.96 (0.52 to 1.79) (60.9% vs 65.2%)</td>
<td>RR 0.48 (0.25 to 0.91) (32% vs 66.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=5; n=578</td>
<td>K=2; n=92</td>
<td>K=1; n=49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 02.01</td>
<td>Psych sub-thresh 02.01</td>
<td>Psych sub-thresh 03.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-remission</td>
<td>RR 1.11 (0.96 to 1.28) (61% vs 55.15%)</td>
<td>RR 0.82 (0.47 to 1.43) (47.6% vs 58.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=4; n=532</td>
<td>K=1; n=45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest plot</td>
<td>Psych sub-thresh 02.01</td>
<td>Psych sub-thresh 03.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean endpoint (clinician-rated)</td>
<td>SMD 0.30 (0.17 to 0.44)</td>
<td>6-month: SMD 0.19 (-0.02 to 0.4) 18-month: SMD 0.26 (0.05 to 0.48)</td>
<td>SMD 0.09 (-0.1 to 0.27) 18-month: SMD 0.06 (-0.14 to 0.27)</td>
<td>SMD -0.17 (-0.37 to 0.03) 18-month: SMD -0.2 (-0.41 to 0.01)</td>
<td>6-month: SMD 0.18 (-0.38 to 0.03) 18-month: SMD 0.2 (-0.41 to 0.01)</td>
<td>6-month: SMD 0.18 (-0.38 to 0.03) 18-month: SMD 0.2 (-0.41 to 0.01)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>High</td>
<td>6-month: moderate 18-month: moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=6; n=353</td>
<td>K=2; n=453</td>
<td>K=1; n=392</td>
<td>K=1; n=368</td>
<td>K=1; n=390</td>
<td>K=1; n=363</td>
</tr>
</tbody>
</table>
### Exercise

There was evidence that exercise was more effective in reducing depression symptoms than psychoeducation, although there was only one relatively small study. There was no evidence for any advantage of adding resistance training to aerobic exercise. See Table 128.

**Table 128 Summary evidence profile for exercise**

<table>
<thead>
<tr>
<th></th>
<th>Exercise versus psychoeducation</th>
<th>Follow-up</th>
<th>Aerobic exercise + resistance training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-response</td>
<td>RR 0.56 (0.29 to 1.07)</td>
<td></td>
<td>RR 5.45 (0.29 to 101.55)</td>
</tr>
<tr>
<td></td>
<td>(41.2% vs 73.3%)</td>
<td></td>
<td>(20% vs 0%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=32</td>
<td></td>
<td>K=1; n=21</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 05.01</td>
<td></td>
<td>Pharm sub-thresh 06.01</td>
</tr>
<tr>
<td>Non-remission</td>
<td>After 10 weeks' continuation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR 0.53 (0.25 to 1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(35.3% vs 66.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Quality of evidence

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=32</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 05.01</td>
</tr>
<tr>
<td>Mean endpoint (clinician-rated)</td>
<td>SMD -2.7 (-3.69 to -1.71)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=32</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 05.01</td>
</tr>
<tr>
<td>Mean endpoint (self-rated)</td>
<td>SMD -1.75 (-2.59 to -0.92)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=32</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 05.01</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>Not pooled (0% vs 0%)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=32</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 05.01</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>Not pooled (0% vs 0%)</td>
</tr>
</tbody>
</table>

#### 11.3.6 Short-term psychodynamic psychotherapy vs short-term psychodynamic art therapy

There was no evidence for the superiority of short-term psychodynamic psychotherapy over short-term psychodynamic art therapy. See Table 128.

### Table 129 Summary evidence profile for short-term psychodynamic psychotherapy vs short-term psychodynamic art therapy

<table>
<thead>
<tr>
<th>Mean endpoint (self-rated)</th>
<th>Short-term psychodynamic psychotherapy vs short-term psychodynamic art therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMD -0.11 (-0.74 to 0.52)</td>
<td>3-month: SMD -0.26 (-0.9 to 0.37)</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=39</td>
<td>K=1; n=39</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 07.01</td>
<td>Pharm sub-thresh 07.01</td>
</tr>
<tr>
<td>Leaving treatment early for any reason</td>
<td>RR 0.32 (0.04 to 2.82) (4.5% vs 14.3%)</td>
<td></td>
</tr>
</tbody>
</table>
### Quality of evidence

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies/participants</td>
<td>K=1; n=41</td>
</tr>
<tr>
<td>Forest plot</td>
<td>Pharm sub-thresh 07.02</td>
</tr>
</tbody>
</table>

#### 11.3.7 Clinical summary of psychological and other non-pharmacological interventions

The evidence for psychological and other non-pharmacological interventions in the treatment of minor depression and persistent minor depression is limited and covers a range of different types of treatment making it difficult to assess individual treatments.

There is scant evidence from randomised controlled trials of the effectiveness of psychological and other non-pharmacological interventions in the treatment of people with recent onset depression symptoms which do not meet threshold for major depressive disorder.

In populations mostly with persistent minor depression (dysthymia) there is inconclusive evidence about the relative efficacy of antidepressants and psychological interventions.

Combined antidepressants and psychological interventions are more effective than psychological interventions alone, but not more effective than antidepressants alone. The evidence for combination treatment in people who have partially responded to initial treatment was inconclusive. There was some evidence for the benefit of exercise. However, the datasets for these interventions are relatively small, and further studies would help to clarify whether these interventions are helpful.

#### 11.3.7.1 From evidence to recommendations

The datasets for both pharmacological and psychological treatments are relatively small, particularly compared with that in major depressive disorder. However, there appears to be some benefit for antidepressants in people with persistent minor depression (dysthymia) but not in people with a diagnosis of recent onset minor depression. With regard to psychological and other non-pharmacological interventions, the evidence is weaker because there are fewer studies. There was no convincing evidence of benefit on which a recommendation could be based.

#### 11.4 Clinical practice recommendations

#### 11.4.1.1 Antidepressants are not recommended for the routine treatment of recent-onset minor depression and mild depression because the risk-benefit ratio is poor, but should be considered for people with:
• minor and mild depression which persists after other interventions
• initial presentation of persistent minor depression
• a past history of moderate or severe depression

11.4.1.2 Research recommendation: the efficacy of cognitive behavioural therapy (CBT) compared with antidepressants for persistent minor depression

What is the efficacy of CBT compared with antidepressants for persistent minor depression?

This question should be answered using a randomised controlled design which reports short and medium-term outcomes (including cost effectiveness outcomes) of at least 6 months’ duration. A careful definition of persistence needs to be used which needs to include duration of symptoms and consideration of failure of low-intensity interventions and does not necessarily imply a full diagnosis of dysthymia. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design and mediators and moderators of response should be investigated.

Why this is important
Persistent minor (sub-threshold) depression is increasingly recognised as effecting a considerable number of people and causing significant suffering but the best way to treat it is not known. There are studies of the efficacy of antidepressants for dysthymia (persistent minor depression that has lasted at least 2 years) but a lack of evidence for CBT. Minor depression of recent onset tends to improve but how long one should wait before offering medication or psychological treatment is not known. This research suggestion is aimed at informing the treatment options available for this group of people with minor depression that persists in spite of low-intensity interventions.
12 Appendices

[For Appendices 1-19c see separate documents]
13 References

References to studies reviewed in clinical evidence reviews are in the appendices. Where more than 1 paper has been published from a study, the guideline adopts the convention of the Cochrane Collaboration so that the study is referred to by the author and date of the original study regardless of whether data have been extracted from subsequent papers. The additional papers are listed under the first paper in the appendices.


ABPI (2003). Edronax (reboxetine) SPC. Compendium of Data Sheets and Summaries of Product Characteristics. www.emc.vhn.net/professional/


Family Practice Notebook.com – http://www.fpnotebook.com/PSY74.htm (14/06/02) [Version II].


Hardy, G.E., Cahill, J.C., Shapiro, D.A. *et al.* (2001). Client interpersonal and cognitive styles as predictors of response to time-limited cognitive therapy for depression. *Journal of Consulting and*


HRSD website – http://www.rag.org.au/drbill/depressstest.htm (01/07/02)


IAPT Workforce Capacity Tool: guidance for use, March 2008 NHS: workforce
http://www.iapt.nhs.uk/2008/01/workforce-capacity-tool/


Depression in adults (update): full guideline DRAFT (February 2009)


Malt, U.F., Robak, O.H., Madsbu, H-P. et al. (1999). The Norwegian naturalistic treatment study of...


Marshall, M., Crowther, R., Almaraz-Serrano, A.M. et al. (2001). 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, 5*.


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Rogers, C.R. (1957). The necessary and sufficient conditions of therapeutic personality change. *Journal*


Thase, M.E. (2002). Studying new antidepressants: If there were a light at the end of the tunnel, could we see it? Journal of Clinical Psychiatry, 63 (Suppl. 2), 24–27.


The WISE approach (Whole System Informing Self-Management Engagement) developed by the NPCRDC self-management programme research team
[http://www.bmj.com/cgi/content/extract/335/7627/968](http://www.bmj.com/cgi/content/extract/335/7627/968)


14 Abbreviations

[To be inserted prior to publication]
15 Glossary

[To be inserted prior to publication]