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Appendix 14: Nutritional and physical interventions for mania – GRADE profiles
Appendix 15: Interventions for acute depression – network meta-analysis plots and WinBugs code
Appendix 16: Interventions for acute depression – study characteristics
Appendix 17: Interventions for acute depression – risk of bias table
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Appendix 21: Interventions for long-term management – forest plots
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Appendix 32: Health economics – evidence tables
Appendix 33: Health economics – economic evidence profiles
Appendix 34: Excluded studies
Appendix 35: Data extraction table
Appendix 36: Pharmacological interventions for mania - sensitivity analysis
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BME</td>
<td>black and minority ethnic</td>
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<tr>
<td>BNF</td>
<td>British National Formulary</td>
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<tr>
<td>CBT</td>
<td>cognitive behavioural therapy</td>
</tr>
<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>Cochrane Central Register of Controlled Trials</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<tr>
<td>DARE</td>
<td>Cochrane Database of Abstracts of Reviews of Effects</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association</td>
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<td>EED</td>
<td>Economic Evaluation Database</td>
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<td>Embase</td>
<td>Excerpta Medica Database</td>
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<td>GDG</td>
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<td>HMIC</td>
<td>Health Management Information Consortium</td>
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<td>HE</td>
<td>health economics</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>MEDLINE</td>
<td>Medical Literature Analysis and Retrieval System Online</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>RCT</td>
<td>randomised controlled trial</td>
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<td>National Collaborating Centre for Mental Health</td>
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<td>In process bibliographic citations for MEDLINE</td>
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<td>PsycINFO</td>
<td>Psychological Information Database</td>
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<td>RQ</td>
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APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

1 GUIDELINE TITLE

Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care

1.1 Short title

Bipolar disorder (update)

2 THE REMIT

This is an update of Bipolar Disorder (National Institute for Health and Care Excellence [NICE] clinical guideline 38). This update is being undertaken as part of the guideline review cycle.

3 CLINICAL NEED FOR THE GUIDELINE

3.1 Epidemiology

a) Bipolar disorder is an episodic, potentially life-long, disabling disorder. Diagnostic features include periods of mania and depression, or hypomania and depression. Bipolar disorder is characterised by periods of abnormally elevated mood or irritability, which may alternate with periods of depressed mood. These episodes are distressing and often interfere with occupational or educational functioning, social activities and relationships.

b) The lifetime prevalence of bipolar I disorder (depression and mania) is estimated at 1% of the adult population, with a range between 0.4% and 1.6%. Bipolar II disorder (depression and hypomania) affects approximately 0.75% of the adult population with a range between 0.4 and 1.1%. Bipolar II disorder is more common in women, bipolar I disorder appears to be evenly distributed between men and women. The median age of onset is 19 years for both men and women, although the disorder may first appear through to the mid-forties. The peak age at which symptoms first appear is 15–19 years, followed closely by 20–24 years. However, there is often a substantial delay between the onset of the disorder and first contact with treatment services.

c) Bipolar disorder in children and young people can be difficult to diagnose because of the nature of its presentation and complex comorbidities, for example, with attention deficit hyperactivity disorder. As a consequence, epidemiological data are very limited. A nationally representative US survey from 2010 found the combined prevalence of bipolar I and II disorder in 13- to 18-year-olds to be 2.9%. Onset of bipolar disorder after the age of 60 years is
more likely to be associated with identifiable general medical conditions, including stroke or other central nervous system disorders.

d) The aetiology of the disorder is uncertain but genetic and biological factors are important. The impact of environmental factors is also uncertain but there is growing evidence that environmental and lifestyle features can have an impact on severity and course of illness.

3.2 Current practice

a) Bipolar disorder is often comorbid with a range of other mental disorders (for example, substance misuse, personality disorders and attention deficit hyperactivity disorder) and this has significant implications for both the course of the disorder and its treatment.

b) People with bipolar disorder are currently treated in a range of National Health Service (NHS) settings, including primary-care services, general mental health services and specialist secondary-care mental health services. While most people with bipolar disorder are treated or maintained in the community, during severe depressive and manic episodes hospital admission is sometimes needed.

c) There have been recent proposals to extend the diagnostic group of bipolar disorder.

d) Recognition of hypomania, in particular, remains poor in parts of the NHS.

e) Since the publication of NICE clinical guideline 38, some important steps in the treatment pathway and the treatment approaches most likely to lead to benefit have been published.

f) Bipolar disorder is associated with very high levels of need for mental health and physical health services, personal social and occupational impairment and a high risk of suicide.

4 THE GUIDELINE

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.
4.1 Population

4.1.1 Groups that will be covered

a) Children, young people and adults, including older adults, with bipolar I, bipolar II, mixed affective and rapid cycling bipolar disorder.

4.1.2 Groups that will not be covered

a) The guideline will not make recommendations about other mental health conditions (such as substance misuse and alcohol-use disorders) that commonly coexist with bipolar disorder; it will nevertheless, refer to other guidelines where relevant, and highlight any necessary modifications to the treatment of either bipolar disorder or the coexisting condition where the coexisting condition is already the subject of an existing NICE guideline.

b) Non-bipolar affective conditions will not be covered because these are covered in other guidelines.

4.2 Healthcare setting

a) The guideline will cover the care and shared care provided in primary and secondary health care services, and that provided by healthcare professionals and others working in healthcare settings.

b) The guideline will also be relevant to the work of, but will not provide specific recommendations to, non-NHS services, including social services, voluntary and educational sectors. The guideline will consider the interface between healthcare services and these services.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

a) Instruments and procedures for the recognition and assessment of bipolar disorder.

b) Psychological and psychosocial interventions for the acute and

c) long-term management of mania, hypomania or bipolar depression (including psychotherapies, exercise, self-help and supported self-help, psychoeducation, self-management, early warning signs, family therapy, peer support, befriending and support groups).
d) Information and communication technologies for monitoring and managing mania, hypomania or bipolar depression (for example, online monitoring or text messaging).

e) Service-level interventions specifically for bipolar disorder (for example, mood clinics, lithium clinics and collaborative care) that are not covered in 'Psychosis and schizophrenia in adults' or in 'Psychosis and schizophrenia in children and young people' NICE clinical guidelines in development (publication dates to be confirmed).

f) Nutritional supplements (for example, fish oil, folic acid, zinc, coenzyme Q10) for mania, hypomania or bipolar depression.

g) Pharmacological interventions for the treatment of depression, mania and hypomania in bipolar disorder.

h) Pharmacological interventions for the long-term management of bipolar disorder.

i) Combined pharmacological, psychological and psychosocial interventions.

j) Physical treatments (including transcranial magnetic stimulation and vagus nerve stimulation) as these apply to bipolar disorder.

k) Modifications needed to manage bipolar disorder in people of different ages (for example, children and young people, older adults), gender, race (for example, African-Caribbean or South Asian groups).

l) Monitoring of side effects and physical health.

m) Pharmacological and non-pharmacological interventions for managing weight gain and promoting health for people with bipolar disorder.

4.3.2 Clinical issues that will not be covered

a) Service-level interventions for people with psychosis or schizophrenia that also apply to people with bipolar disorder (except those noted in section 4.3.1) because these will be addressed in the NICE clinical guidelines ‘Psychosis and schizophrenia in adults’ and ‘Psychosis and schizophrenia in children and young people’ which are currently in development.

b) Pharmacological interventions for the management of side effects of treatment for bipolar disorder, except weight gain.
4.4 Main outcomes

a) Symptoms, frequency, and time to event for:
   - mania
   - hypomania
   - depression
   - mixed episodes

b) Side effects of interventions

c) Physical health

d) Quality of life

e) Functional disability (including work, educational, family, and social domains)

f) Carer outcomes

g) Service use

h) Dropout (including all-cause and dropout because of side effects)

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in ‘The guidelines manual’ (see ‘Further information’).

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in October 2012.
5 RELATED NICE GUIDANCE

5.1 Published guidance

5.1.1 NICE guidance to be updated

- This guideline will update and replace the following NICE guidance: Bipolar disorder. NICE clinical guideline 38 (2006).

5.1.2 Other related NICE guidance

- Schizophrenia. NICE clinical guideline 82 (2009).
- Psychosis with coexisting substance misuse. NICE clinical guideline 120 (2011).
- Service user experience in adult mental health. NICE clinical guideline 136 (2011).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Psychosis and schizophrenia in children and young people. NICE clinical guideline. Publication expected January 2013.
- Psychosis and schizophrenia in adults. NICE clinical guideline. Publication expected March 2014.

6 FURTHER INFORMATION

Information on the guideline development process is provided in the following documents, available from the NICE website:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual’.

Information on the progress of the guideline will also be available from the NICE website.
APPENDIX 2: DECLARATIONS OF INTERESTS BY GUIDELINE DEVELOPMENT GROUP MEMBERS

With a range of practical experience relevant to bipolar disorder in the GDG, members were appointed because of their understanding and expertise in healthcare for people with bipolar disorder and support for their families/carers, including: scientific issues; health research; the delivery and receipt of healthcare, along with the work of the healthcare industry; and the role of professional organisations and organisations for people with bipolar disorder and their families/carers.

To minimise and manage any potential conflicts of interest, and to avoid any public concern that commercial or other financial interests have affected the work of the GDG and influenced guidance, members of the GDG must declare as a matter of public record any interests held by themselves or their families which fall under specified categories (see below). These categories include any relationships they have with the healthcare industries, professional organisations and organisations for people with bipolar disorder and their families/carers.

Individuals invited to join the GDG were asked to declare their interests before being appointed. To allow the management of any potential conflicts of interest that might arise during the development of the guideline, GDG members were also asked to declare their interests at each GDG meeting throughout the guideline development process. The interests of all the members of the GDG are listed below, including interests declared prior to appointment and during the guideline development process.

Categories of interest to be written in third person

Paid employment

**Personal pecuniary interest:** financial payments or other benefits from either the manufacturer or the owner of the product or service under consideration in this guideline, or the industry or sector from which the product or service comes. This includes holding a directorship or other paid position; carrying out consultancy or fee paid work; having shareholdings or other beneficial interests; receiving expenses and hospitality over and above what would be reasonably expected to attend meetings and conferences.

**Personal family interest:** financial payments or other benefits from the healthcare industry that were received by a member of your family.

**Non-personal pecuniary interest:** financial payments or other benefits received by the GDG member’s organisation or department, but where the GDG member has not personally received payment, including fellowships and other support provided by the healthcare industry. This includes a grant or fellowship or other payment to sponsor a post, or contribute to the running costs of the department; commissioning of research or other work; contracts with, or grants from, NICE.
**Personal non-pecuniary interest:** these include, but are not limited to, clear opinions or public statements you have made about individuals with bipolar disorder, holding office in a professional organisation or advocacy group with a direct interest in bipolar disorder, other reputational risks relevant to bipolar disorder.

### GDG – declarations of interest

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</tr>
<tr>
<td>Andrea Cipriani</td>
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<tr>
<td>Anthony James</td>
</tr>
<tr>
<td>Carnice John</td>
</tr>
<tr>
<td>Steven Jones</td>
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<tr>
<td>Tim McDougall</td>
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<td>Thomas Meyer</td>
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Action taken on bipolar disorder at this present time.

Principal investigator of the only publicly funded German randomised controlled trial (RCT) so far evaluating the efficacy of cognitive behavioural therapy (CBT) for bipolar disorders [funding: Deutsche Forschungsgemeinschaft]
### Declarations of interests by Guideline Development Group members

(DFG ME 1681/6-1 to 6.3)]. The publication is in press: Meyer TD, Hautzinger M. (2012). Cognitive behavior therapy and supportive therapy for bipolar disorder. Relapse rates for treatment period and 2 year follow-up? *Psychological Medicine*

Co-investigator in a new study: ‘A feasability study of a randomised controlled trial of a family focused treatment (FFT – a UK version) in the management of early onset bipolar disorder’

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**Carol Paton**

**Employment**
Chief Pharmacist, Oxleas NHS Foundation Trust

**Personal pecuniary interest**
Attended a one-off advisory board for Sunovion to discuss data related to the use of lurasidone for schizophrenia. Did not participate in any discussions relating to the place of lurasidone in treatment with respect to the NICE bipolar guideline

**Personal family interest**
None

**Non-personal pecuniary interest**
None

**Personal non-pecuniary interest**
None

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**Matthias Schwannauer**

**Employment**
Professor of Clinical Psychology, University of Edinburgh

**Personal pecuniary interest**
None

**Personal family interest**
None

**Non-personal pecuniary interest**
None

**Personal non-pecuniary interest**
None

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**Donna Swinden**

**Employment**
Modern Matron, Acute Adult Inpatients, Tees, Esk and Wear Valleys NHS Foundation Trust

**Personal pecuniary interest**
None

**Personal family interest**
None

**Non-personal pecuniary interest**
None

**Personal non-pecuniary interest**
Completed an MSc dissertation in 2009 entitled ‘Engaging bipolar patients with cognitive behavioural therapy’ and has presented work at several conferences

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**Robert Westhead**

**Employment**
Representing service user and carer views

**Personal pecuniary interest**
None

**Personal family interest**
None

**Non-personal pecuniary interest**
None

**Personal non-pecuniary interest**
None

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**Faye Wilson**

**Employment**
Approved Mental Health Social Worker / Chair, British Association Of Social Workers Mental Health Group

**Personal pecuniary interest**
None

**Personal family interest**
None

**Non-personal pecuniary interest**
Chair of Bases Mental Health Forum who are involved in campaigning on the closure of inpatient beds and...
### Declarations of interests by Guideline Development Group members

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### National Collaborating Centre for Mental Health (NCCMH)

#### Tim Kendall

**Employment**
- Director, NCCMH
- Medical Director, Sheffield Health and Social Care Trust
- Consultant Adult Psychiatrist

**Personal pecuniary interest**
- Grant holder for £1.44 million per year (approximately) from NICE for guidelines work. Work with NICE International
- Undertake some research into mental health, and the mental health workforce for Department of Health, Royal College of Psychiatrists and the academy of medical royal colleges

**Personal family interest**
- None

**Non-personal pecuniary interest**
- Co-applicant for a £1.7-2 million National Institute for Health Research Health Technology Assessment (HTA) grant for a multicentre, randomised controlled trial of a diabetes intervention to induce weight loss (DESMOND) for people who are overweight and have a severe mental illness, including people with schizophrenia and bipolar disorder.

**Personal non-pecuniary interest**
- None

**Action Taken**
- None

#### Ruth Braidwood

**Employment**
- Research Assistant, NCCMH

**Personal pecuniary interest**
- None

**Personal family interest**
- None

**Non-personal pecuniary interest**
- None

**Personal non-pecuniary interest**
- None

**Action Taken**
- None

#### Katherine Leggett

**Employment**
- Senior Project Manager

**Personal pecuniary interest**
- None

**Personal family interest**
- None

**Non-personal pecuniary interest**
- None

**Personal non-pecuniary interest**
- None

**Action Taken**
- None

#### Elena Marcus

**Employment**
- Research Assistant, NCCMH

**Personal pecuniary interest**
- None

**Personal family interest**
- None

**Non-personal pecuniary interest**
- None

**Personal non-pecuniary interest**
- None

**Action Taken**
- None

#### Ifigeneia Mavranezouli

**Employment**
- Senior Health Economist, NCCMH

**Personal pecuniary interest**
- None

**Personal family interest**
- None

**Non-personal pecuniary interest**
- None

**Personal non-pecuniary interest**
- None

**Action Taken**
- None
Declarations of interests by Guideline Development Group members

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<tr>
<td><strong>Evan Mayo-Wilson</strong></td>
<td>Senior Systematic Reviewer, NCCMH</td>
<td>None</td>
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<td><strong>Sarah Stockton</strong></td>
<td>Senior Information Scientist, NCCMH</td>
<td>None</td>
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<tr>
<td><strong>Clare Taylor</strong></td>
<td>Senior Editor, NCCMH</td>
<td>None</td>
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<tr>
<td><strong>Craig Whittington</strong></td>
<td>Associate Director (Clinical Effectiveness), NCCMH</td>
<td>None</td>
<td>None</td>
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APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

John Geddes
Head of Department Professor of Epidemiological Psychiatry
University of Oxford
Associate Medical Director (Research & Development), Honorary Consultant Psychiatrist, Oxford Health NHS Foundation Trust

Kate Hughes
Occupational Therapist / Advanced Vocational Specialist

Peter Pratt
Chief Pharmacist, Sheffield Health and Social Care NHS Foundation Trust
APPENDIX 4: STAKEHOLDERS WHO RESPONDED TO EARLY REQUESTS FOR EVIDENCE

AstraZeneca UK Ltd
Bristol-Myers Squibb Pharmaceuticals Ltd
Cheshire & Wirral Partnership NHS Trust
GlaxoSmithKline
Lancashire Care NHS Foundation Trust
Lundbeck UK
Mindfulness Centre of Excellence
APPENDIX 5: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

Stakeholders

British Association for Behavioural and Cognitive Psychotherapies
Bipolar UK
British Association for Psychopharmacology
Cheshire & Wirral Partnership NHS Trust
College of Mental Health Pharmacy
College of Occupational Therapists
Department of Health
Global Organization for EPA and DHA Omega-3s (GOED)
Greater Manchester West Mental Health NHS Foundation Trust
International Society for Psychological and Social Approaches to Psychosis (UK branch)
Lancashire Care NHS Foundation Trust
Lonsdale Medical Centre
Lundbeck UK Otsuka Pharmaceuticals UK
Mersey Care NHS Trust
NHS Choices (Digital Assessment Service)
NHS England
Rethink Mental Illness
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Psychiatrists
South London and Maudsley NHS Foundation Trust’s CAMHS department.

Experts

Warren Mansell
Nicol Ferrier
Sheri Johnson
Researchers contacted to request information about unpublished or soon-to-be published studies

APPENDIX 6: RESEARCHERS CONTACTED TO REQUEST INFORMATION ABOUT UNPUBLISHED OR SOON-TO-BE PUBLISHED STUDIES

Abbott Laboratories
Mohammad Alsuwaidan
Lori L Altshuler
Jay Amsterdam
Amit Anand
AstraZeneca
Won-Myong Bahk
Jillian R Ball
Caryl Barnes
Mark S Bauer
Beacon Pharmaceuticals
Ashkan Heshmatzade Behzadi
Robert H Belmaker
Joris Berwaerts
Zubin Bhagwagar
Bial
Alberto Bochetta
Mohammad RF Bordbar
Charles Bowden
Brian P Brennan
Bristol-Myers Squibb
Eileen Brown
Ashley Bush
Joseph Calabrese
Cameo Healthcare
James Chamberlain
Chanelle Medical
Kadiamada NR Chengappa
John F Clarkin
Philippe Conus
Rafael Thomaz da Costa
Mark Crowther
Colleen Cummings
Deborah Dauphinais
Lori Davis
Karina de Barros Pellengrini
Melissa P Delbello
Kirk D Denicoff
Ellen B Dennehy
Desitin
Selma Doğan
Robert T Dunn
David L Dunner
Marielle Eerdekens
Eisai
Fatma Eker
Élan
Eli Lilly
Rif S El-Mallakh
Jane L Elmslie
Anne E Evins
Robert L Findling
Forest Laboratories
Sophia Frangou
Ellen Frank
Mark A Frye
Jens Gaab
Igor I Galynker
Keming Gao
Gedeon Richter
Alan J Gelenberg
Barbara Geller
Fateneh Ghadirian
Nassir S Ghaemi
Claire Gindre
Glaxo Smith-Kline
Ira D Glick
Global Pharmaceuticals
Joseph F Goldberg
Bernardo Carramão Gomes
David J Goodrich
Barbara L Gracious
Waldemar Greil
Fred Grossman
Magali Haas
Erwin Hartong
Researchers contacted to request information about unpublished or soon-to-be published studies

Paria Hebrani
Jonathan Himmelhoch
Intas Pharmaceuticals
Janssen
Johnson & Johnson
Steven Jones
Mario F Juruena
Vivian Kafantaris
Paul E Keck
David E Kemp
Lars V Kessing
Terrence Ketter
Amy Kilbourne
Nikolaus Kleindienst
Robert A Kowatch
Frank A Kozel
Jayashri Kulkarni
David J Kupfer
Stuart F Kushner
Guillermo Lahera
Dominic H Lam
Sue D Lauder
Bernard Leder
Rasmus W Licht
Daniel Z Lieberman
Fiona Lobban
Ru-Band Lu
Dave A Luckenbaugh
Lundbeck
Wayne Macfadden
Ronald Marcus
John Matthews
Susan McElroy
Susan L McIntyre
Elrige Mellerup
Merck & Co
Mercury Pharma
Thomas Meyer
David J Miklowitz
Ivan Miller
Ricardo Alberto Moreno
David J Muzina
Mylan Pharmaceuticals
Charles B Nemeroff
Andrew A Nierenberg
NIMH
Norgine
Novartis Pharmaceuticals
Maria A Oquendo
Otsuka
Randall Owen
Atul C Pande
Sagar V Parikh
Gordon Parker
Sanjeev Pathak
Mani Pavuluri
Deborah A Perlick
Pfizer
Piramal Healthcare
Per Plenge
Robert M Post
Samir K Praharaj
Judit Proudfoot
Arnim Quante
Jorge Quiroz
Luiz A Rohde
Rosemont
Asia J Ruchlewska
Gary S Sachs
Martha Sajatovic
Samarth
Sanofi-Aventis
Aylaba Saricicek
Ayal Schaffer
Joy M Schmitz
Jan Scott
Emmanuel Severus
Shire
Justine Shults
Trevor Silverstone
Gregory E Simon
Joyce Small
Daniel Smith
Jair C Soares
David Solomon
Thomas Stamm
Sumitomo
Sun Pharmaceutical Industries Ltd
Suresh Sundram
Sunovion Pharmaceuticals
Trisha Suppes
Alan Swann
Researchers contacted to request information about unpublished or soon-to-be published studies

Holly Swartz
Taj Pharmaceuticals
Tania Perich
Teva Pharmaceuticals
Micheal E Thase
Martha Thompson
Nicholas Todd
Mauricio Tohen
Torrent Pharmaceuticals
UCB Pharma
Marc LM van der Loos
Trijntje YG van der Voort
Sheri Van Dijk
Eduard Vieta
Karen D Wagner
Watson Pharma Inc
Richard H Weisler
Roger D Weiss
J Mark G Williams
Wockhardt
Christian Wolf
Joseph C Wu
Fu De Yang
Lakshmi N Yatham
Sujung J Yoon
Allan Young
L Trevor Young
Robert C Young
Carlos A Zarate
Ari Zaretsky
Christian Zeni
Zhang-Jin Zhang
APPENDIX 7: REVIEW PROTOCOLS AND QUESTIONS

Reviews relating to the experience of carers and the physical health of people with serious mental illness were undertaken in conjunction with a NICE guideline being developed at the same time, *Psychosis and Schizophrenia in Adults* (2014), which includes the full methods and results of those reviews, including the review protocols.

1. Case identification and assessment

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ1.1: For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM(^1) or ICD(^2) criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?</td>
</tr>
<tr>
<td></td>
<td>RQ1.2: For children (less than 13 years) and young people (13 to 18 years) at risk of or suspected of having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?</td>
</tr>
<tr>
<td></td>
<td>RQ1.3: For people with possible bipolar disorder, what are the key components of, and the most effective structure for, diagnostic assessment?</td>
</tr>
<tr>
<td>Objectives</td>
<td>For RQ1.1 and RQ1.2: To identify brief screening instruments to assess need for further assessment of people with suspected bipolar disorder and to assess their diagnostic accuracy.</td>
</tr>
<tr>
<td></td>
<td>For RQ1.3: To identify the key components of a comprehensive assessment.</td>
</tr>
</tbody>
</table>

Criteria for considering studies for the review

- Intervention
  - For case identification (RQ1.1 and RQ1.2): Brief screening questionnaires (< 15 items) identified by the GDG.

- Comparator
  - Gold standard: DSM or ICD diagnosis of bipolar disorder.

- Types of participants
  - Children and young people (aged 18 years and younger) and adults with suspected bipolar disorder.

- Outcomes
  - Sensitivity (percentage of true cases identified).
  - Specificity (percentage of non-cases excluded).

---

1 Diagnostic and Statistical Manual of Mental Disorders.
2 International Classification of Diseases.
## Review protocols and questions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Studies had to include participants with and without bipolar disorder completing a case-identification instrument and a diagnostic interview.</td>
</tr>
<tr>
<td><strong>Search strategy</strong></td>
<td><strong>Databases searched:</strong> Excerpta Medica Database (Embase), MEDLINE, PreMEDLINE, Psychological Information Database (PsycINFO).</td>
</tr>
<tr>
<td></td>
<td><strong>Date limits:</strong> Database inception to 20 January 2014.</td>
</tr>
<tr>
<td><strong>Study design filter/limit used</strong></td>
<td>None; no language restriction</td>
</tr>
<tr>
<td><strong>Question specific search strategy</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Amendments to search strategy/study design filter</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Searching other resources</strong></td>
<td></td>
</tr>
<tr>
<td><strong>The review strategy</strong></td>
<td>To conduct pooled test accuracy meta-analyses on the sensitivity and specificity of case identification instruments where possible.</td>
</tr>
</tbody>
</table>

*Note.*
2. Pharmacological and medical interventions for acute episodes

2.1. Pharmacological and nutritional interventions for mania, hypomania, and mixed episodes for adults with bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ2.1: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
</tbody>
</table>

Objectives
To estimate the efficacy of interventions to treat mania, hypomania and mixed episodes.

Criteria for considering studies for the review
- Intervention: All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
- Comparator: Placebo. Other interventions.
- Types of participants: Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
- Outcomes: 1) Response (50% reduction in symptoms). 2) Discontinuation (due to side effects, other).
- Time: The main analysis will include outcomes at the end of the acute treatment phase.
- Study design: Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies will be excluded.
- Dosage: Fixed or flexible doses within the therapeutic range (British National Formulary [BNF] recommended).
- Study setting: Primary, secondary, tertiary, health and social care.

Search strategy
**Databases searched:**
- RCT: Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Medical Literature Analysis and Retrieval System Online (MEDLINE), in process bibliographic citations for MEDLINE (PreMEDLINE), PsycINFO.
- Systematic review (SR): Cochrane Database of Systematic Reviews (CDSR), CINAHL, Cochrane Database of Abstracts of Reviews of Effects (DARE), Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**
- RCT: 2005 to 20 January 2014;

**Study design filter/limit used**
- RCT; SR.

**Language restrictions:** none.

**Question specific search strategy**
No
### Review protocols and questions

<table>
<thead>
<tr>
<th>Amendments to search strategy/study design filter</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Searching other resources</strong></td>
<td>The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.</td>
</tr>
<tr>
<td><strong>The review strategy</strong></td>
<td>The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method. If reviews are found, the GDG will assess their quality, completeness and applicability to the NHS. If the GDG identify a systematic review appropriate to the review question, they will search for RCTs conducted or published since the review was conducted, and will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. If no reviews are found, the GDG plans to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing response and discontinuation at the end of the acute treatment. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (for example, people with comorbid substance abuse). For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage black and minority ethnic [BME]); diagnosis (percentage bipolar I disorder); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.</td>
</tr>
</tbody>
</table>

**Note.**
## 2.2. Pharmacological and nutritional interventions for episodes of acute bipolar depression in adults

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ2.2: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for acute episodes of acute bipolar depression? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
<tr>
<td>Objectives</td>
<td>To estimate the efficacy of interventions to treat acute episodes of bipolar depression.</td>
</tr>
<tr>
<td>Criteria for considering studies for the review</td>
<td></td>
</tr>
<tr>
<td>• Intervention</td>
<td>All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.</td>
</tr>
<tr>
<td>• Comparator</td>
<td>Placebo Other interventions</td>
</tr>
<tr>
<td>• Types of participants</td>
<td>Adults (18+) with bipolar disorder who are experiencing an acute episodes of bipolar depression. Special consideration will be given to the groups above.</td>
</tr>
<tr>
<td>• Outcomes</td>
<td>1) Response (50% reduction in symptoms). 2) Discontinuation (due to side effects, other).</td>
</tr>
<tr>
<td>• Time</td>
<td>The main analysis will include outcomes at the end of the acute treatment phase.</td>
</tr>
<tr>
<td>• Study design</td>
<td>Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.</td>
</tr>
<tr>
<td>• Dosage</td>
<td>Fixed or flexible doses within the therapeutic range (BNF recommended).</td>
</tr>
<tr>
<td>• Minimum sample size</td>
<td>To be included in a network meta-analysis, drugs must have been evaluated in at least 20 participants.</td>
</tr>
<tr>
<td>• Study setting</td>
<td>Primary, secondary, tertiary, health and social care.</td>
</tr>
<tr>
<td>Study design filter/limit used</td>
<td>RCT; SR. Language restrictions: none.</td>
</tr>
<tr>
<td>Question specific search strategy</td>
<td>No</td>
</tr>
<tr>
<td>Amendments to search strategy/study design filter</td>
<td>None</td>
</tr>
</tbody>
</table>
**Review protocols and questions**

<table>
<thead>
<tr>
<th><strong>Searching other resources</strong></th>
<th>The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The review strategy</strong></td>
<td>The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method.</td>
</tr>
<tr>
<td></td>
<td>If reviews are found, the GDG will assess their quality, completeness and applicability to the NHS. If they identify a systematic review appropriate to the review question, they will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.</td>
</tr>
<tr>
<td></td>
<td>If no reviews are found, the GDG plans to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing response, symptoms of depression and discontinuation at the end of the acute treatment. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (for example, people with comorbid substance abuse). For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I disorder); and risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.</td>
</tr>
</tbody>
</table>

**Note.**
### 2.3. Non-pharmacological interventions for adults with bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question(s)</strong></td>
<td>RQ2.3: For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for mania, hypomania, and mixed episodes?</td>
</tr>
<tr>
<td></td>
<td>RQ2.4: For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for depressive episodes?</td>
</tr>
<tr>
<td></td>
<td>What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To estimate the efficacy of physical interventions for adults with bipolar disorder.</td>
</tr>
<tr>
<td><strong>Criteria for considering studies for the review</strong></td>
<td></td>
</tr>
<tr>
<td>- Intervention</td>
<td>Non-pharmacological medical interventions</td>
</tr>
<tr>
<td>- Comparator</td>
<td>A credible no-intervention control (for example, sham intervention).</td>
</tr>
<tr>
<td>- Types of participants</td>
<td>Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.</td>
</tr>
<tr>
<td>- Outcomes</td>
<td>1) Change in symptoms (of mania or depression)</td>
</tr>
<tr>
<td></td>
<td>2) Response (50% reduction or greater)</td>
</tr>
<tr>
<td></td>
<td>3) Discontinuation</td>
</tr>
<tr>
<td>- Time</td>
<td>The main analysis will include outcomes at the end of the acute treatment phase.</td>
</tr>
<tr>
<td>- Study design</td>
<td>Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.</td>
</tr>
<tr>
<td>- Study setting</td>
<td>Primary, secondary, tertiary, health and social care.</td>
</tr>
<tr>
<td>- Comparator</td>
<td>A credible no-intervention control (for example, sham intervention).</td>
</tr>
<tr>
<td>- Types of participants</td>
<td>Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.</td>
</tr>
<tr>
<td>- Outcomes</td>
<td>4) Change in symptoms (of mania or depression).</td>
</tr>
<tr>
<td></td>
<td>5) Response (50% reduction or greater).</td>
</tr>
<tr>
<td></td>
<td>6) Discontinuation</td>
</tr>
<tr>
<td>- Time</td>
<td>The main analysis will include outcomes at the end of the acute treatment phase.</td>
</tr>
<tr>
<td>- Study design</td>
<td>Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.</td>
</tr>
</tbody>
</table>
Review protocols and questions

<table>
<thead>
<tr>
<th><strong>Study setting</strong></th>
<th>Primary, secondary, tertiary, health and social care.</th>
</tr>
</thead>
</table>
| **Search strategy** | **Databases searched:**  
RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
**Date limits:**  
RCT: 2005 to 20 January 2014;  
| **Study design filter/limit used** | RCT; SR.  
Language restrictions: none. |
| **Question specific search strategy** | No |
| **Amendments to search strategy/study design filter** | None |
| **Searching other resources** | The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies. |
| **The review strategy** | The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted. |

*Note.*
3. **Long-term management of bipolar disorder**

3.1. **Service-level intervention for bipolar disorder**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ3.1: For adults with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
<tr>
<td>Objectives</td>
<td>To estimate the efficacy of services in treating bipolar disorder.</td>
</tr>
</tbody>
</table>

**Criteria for considering studies for the review**

- **Intervention**
  - Lithium clinics
  - Mood clinics
  - Collaborative care
- **Comparator**
  - Treatment-as-usual
  - Other services
- **Types of participants**
  - Adults (18+) with suspected bipolar disorder. Special consideration will be given to the groups above.
- **Outcomes**
  - 1) Relapse (all, mania/mixed, depression)
  - 2) Hospitalisation (rate, duration)
  - 3) Quality of life
  - 4) Mortality
- **Time**
  - At least 1 year after initiating treatment.
- **Study design**
  - Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.

### Search strategy

- **Databases searched:**
  - RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.
  - SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO
- **Date limits:**
  - RCT: 2005 to 20 January 2014;

- **Study design filter/limit used**
  - RCT; SR.
  - Language restrictions: none.
- **Question specific search strategy**
  - No
- **Amendments to search strategy/study design filter**
  - None
- **Searching other resources**
  - The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
- **The review strategy**
  - We will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender
Review protocols and questions

<table>
<thead>
<tr>
<th>(percentage female); race (percentage BME); diagnosis (percentage bipolar I); number of previous episodes; risk of bias.</th>
</tr>
</thead>
</table>

Note.
### 3.2. Communication technologies for monitoring the symptoms of bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ3.3: What are the relative benefits and harms of information and communication technologies (for example, text messaging) for monitoring symptoms? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
</tbody>
</table>

**Objectives**

To estimate the efficacy of communication technologies for monitoring symptoms.

**Criteria for considering studies for the review**

- **Intervention**: Internet and computer programmes, automated telephone systems, and text messaging.
- **Comparator**: Waitlist, no-intervention and other interventions.
- **Types of participants**: People with bipolar disorder. Special consideration will be given to the groups above.
- **Outcomes**: 1) Relapse (all, mania/mixed, depression). 2) Hospitalisation (rate, duration). 3) Mortality (all-cause, suicide attempts, suicides completed).
- **Time**: Outcomes will be grouped by time point.
- **Study design**: Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
- **Study setting**: Primary, secondary, tertiary, health and social care.

**Search strategy**

**Databases searched:**

RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.

SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**


**Study design filter/limit used**: RCT; SR.

**Language restrictions**: none.

**Amendments to search strategy/study design filter**: None

**Searching other resources**: The NCCMH review will team write to all stakeholders and authors of all included studies to request unpublished studies.

**The review strategy**: The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis.
3.3. Pharmacological and nutritional interventions for long-term management of adults with bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ3.4: For adults with bipolar disorder, what are the relative benefits and harms of starting a new pharmacological or nutritional intervention outside of an acute episode?</td>
</tr>
<tr>
<td></td>
<td>RQ3.5: For adults with bipolar disorder, what are the relative benefits and harms of continuing an acute treatment for 1 year or more?</td>
</tr>
<tr>
<td></td>
<td>What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?</td>
</tr>
</tbody>
</table>

**Objectives**
To estimate the efficacy of interventions for the long-term management of bipolar disorder.

**Criteria for considering studies for the review**

- **Intervention**
  All licensed oral medications (and their combinations) delivered for 1 year or more.

- **Comparator**
  Pill placebo
  Other pharmacological interventions

- **Types of participants**
  Adults (18+) with bipolar disorder.
  Special consideration will be given to the groups above.

- **Outcomes**
  1) Relapse (all, mania/mixed, depression) (for the purposes of the guideline, relapse was defined as a new episode meeting criteria for MDD or mania)
  2) Discontinuation (due to side effects, other)
  3) Hospitalisation (rate)
  4) Quality of life
  5) Mortality (all-cause, suicides completed)
  6) Weight

- **Time**
  Included studies must have included controlled measures of outcomes at 12 months or later.

- **Study design**
  Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.

- **Include unpublished data?**
  Unpublished research may be included.

- **Restriction by date?**
  No limit.

- **Dosage**
  Fixed or flexible doses within the therapeutic range (BNF recommended).

- **Minimum sample size**
  Ten participants per group.

- **Study setting**
  Primary, secondary, tertiary, health and social care.
### Search strategy

**Databases searched:**
- RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.
- SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**

**Study design filter/limit used**
- RCT; SR.
- Language restrictions: none.

**Question specific search strategy**
- No

**Amendments to search strategy/study design filter**
- None

**Searching other resources**
The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.

### The review strategy

The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method.

If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations.

If no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing relapse and discontinuation. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (for example, people with comorbid substance abuse). For each study, we will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.

---

*Note.*
### 4. Psychological and psychosocial interventions for adults with bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Review question(s)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mania</strong></td>
<td>RQ4.1: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for mania, hypomania, and mixed episodes?</td>
</tr>
<tr>
<td></td>
<td>RQ4.2: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for mania, hypomania, and mixed episodes?</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>RQ4.3: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for depression?</td>
</tr>
<tr>
<td></td>
<td>RQ4.4: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for depression?</td>
</tr>
<tr>
<td><strong>Long-term management</strong></td>
<td>RQ4.5: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management?</td>
</tr>
<tr>
<td></td>
<td>RQ4.6: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for long-term management?</td>
</tr>
</tbody>
</table>
| **Sub-question(s)** | Does the effectiveness of treatment vary:  
1. For RQ6.4 to RQ6.11: For people taking a mood stabiliser (for example, lithium or valproate) and people not taking a mood stabiliser;  
2. For RQ6.12 to RQ6.15: For people whose most-recent episode was depressive and people whose most-recent episode was manic;  
3. For people with bipolar I and bipolar II;  
4. For adults (18 to 64) and older adults (65+). |
| **Objectives** | To estimate the efficacy of interventions to treat depression. |
| **Criteria for considering studies for the review** | 
- **Intervention**: RQ4.1 to RQ4.6: All psychological and psychosocial interventions (for example, cognitive behaviour therapy), all combined psychological with (licensed) pharmacological interventions.  
- **Comparator**: Wait-list, placebo, and other interventions.  
- **Types of participants**: Adults (18+) with bipolar disorder. Special consideration will be given to the groups above. |
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>FOR PEOPLE IN AN ACUTE EPISODE</th>
</tr>
</thead>
</table>
|                                                                         | 1) Change in symptoms of depression  
|                                                                         | 2) Change in symptoms of mania  
|                                                                         | 3) Response (50% reduction or greater)  
|                                                                         | 4) Discontinuation  
|                                                                         | 5) Quality of life  
|                                                                         | 6) Psychosocial functioning.                                                                 |
|                                                                         | FOR PEOPLE WHO ARE EUTHYMIC AT BASELINE                                                      |
|                                                                         | 1) Relapse  
|                                                                         | 2) Discontinuation  
|                                                                         | 3) Hospitalisation  
|                                                                         | 4) Quality of life  
|                                                                         | 5) Psychosocial functioning.                                                                 |
| Time                                                                    | The main analysis will include outcomes at the end of treatment. For interventions the GDG considers recommending based on post-treatment results, additional analyses will be conducted for further follow-up data. |
| Study design                                                            | Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth. |
| Study setting                                                           | Primary, secondary, tertiary, health and social care.                                         |

**Search strategy**

| Databases searched: | RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
|                     | SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
| **Date limits:**    | RCT: 2005 to 20 January 2014;  

**Study design filter/limit used**

| RCT; SR.  
| Language restrictions: none. |

**Question specific search strategy**

| No |

**Amendments to search strategy/study design filter**

| None |

**Searching other resources**

| The NCCMH review team will write to stakeholders and authors of all included studies to request unpublished studies. |

**The review strategy**

| The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted. |

**Note.**
5. Interventions for children and young people with bipolar disorder

5.1. Pharmacological and nutritional interventions for mania, hypomania and mixed episodes of bipolar disorder in children and young people

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ5.1: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).</td>
</tr>
<tr>
<td>Objectives</td>
<td>To estimate the efficacy of interventions to treat manic, hypomanic and mixed episodes.</td>
</tr>
<tr>
<td>Criteria for considering studies for the review</td>
<td></td>
</tr>
<tr>
<td>• Intervention</td>
<td>All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).</td>
</tr>
<tr>
<td>• Comparator</td>
<td>Waitlist, no intervention, placebo and other interventions.</td>
</tr>
<tr>
<td>• Types of participants</td>
<td>Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.</td>
</tr>
<tr>
<td>• Outcomes</td>
<td>1) Change in symptoms of mania. 2) Response (50% reduction or greater). 3) Discontinuation (because of side effects, other).</td>
</tr>
<tr>
<td>• Time</td>
<td>The main analysis will include outcomes at the end of the acute treatment phase.</td>
</tr>
<tr>
<td>• Study design</td>
<td>Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.</td>
</tr>
<tr>
<td>• Dosage</td>
<td>Fixed or flexible doses within the therapeutic range (BNF recommended).</td>
</tr>
<tr>
<td>• Study setting</td>
<td>Primary, secondary, tertiary health and social care.</td>
</tr>
<tr>
<td>Search strategy</td>
<td>Databases searched: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO. SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.</td>
</tr>
<tr>
<td>Study design filter/limit used</td>
<td>RCT: all languages. SR: English language limit.</td>
</tr>
<tr>
<td>Question specific search strategy</td>
<td>No</td>
</tr>
<tr>
<td>Amendments to search strategy/study design</td>
<td>None</td>
</tr>
</tbody>
</table>
### Review protocols and questions

<table>
<thead>
<tr>
<th>filter</th>
<th>The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Searching other resources</strong></td>
<td>The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage black and minority ethnic [BME]); diagnosis (percentage bipolar I); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.</td>
</tr>
<tr>
<td><strong>The review strategy</strong></td>
<td>Note.</td>
</tr>
</tbody>
</table>

**Note.**
5.2. Pharmacological and nutritional interventions for episodes of bipolar depression in children and young people

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ5.2: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for episodes of bipolar depression? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).</td>
</tr>
<tr>
<td>Objectives</td>
<td>To estimate the efficacy of interventions to treat episodes of bipolar depression.</td>
</tr>
</tbody>
</table>

### Criteria for considering studies for the review

- **Intervention**: All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).
- **Comparator**: Waitlist, no intervention, placebo and other interventions.
- **Types of participants**: Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
- **Outcomes**: 1) Change in symptoms of depression. 2) Response (50% reduction or greater). 3) Discontinuation (due to side effects, other).
- **Time**: The main analysis will include outcomes at the end of the acute treatment phase.
- **Study design**: RCTs and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
- **Dosage**: Fixed or flexible doses within the therapeutic range (BNF recommended).
- **Study setting**: Primary, secondary, tertiary health and social care.

### Search strategy

**Databases searched:**
- RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.
- SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**

**Study design filter/limit used**: RCT: all languages. SR: English language limit.

**Question specific search strategy**: No

**Amendments to search strategy/study design filter**: None

**Searching other resources**: The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
**Review protocols and questions**

<table>
<thead>
<tr>
<th>The review strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.</td>
</tr>
</tbody>
</table>

**Note.**
### 5.3. Pharmacological and nutritional interventions for long-term management of bipolar disorder in children and young people

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ5.3: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for long-term management? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).</td>
</tr>
<tr>
<td>Objectives</td>
<td>To estimate the efficacy of interventions for the long-term management of bipolar disorder.</td>
</tr>
</tbody>
</table>

#### Criteria for considering studies for the review

- **Intervention**: All licensed oral medications (and their combinations) or nutritional intervention delivered for 1 year or more.
- **Comparator**: Pill placebo. Other pharmacological or nutritional interventions.
- **Types of participants**: Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
- **Outcomes**: 1) Relapse (all, mania/mixed, depression), 2) Discontinuation (due to side effects, other), 3) Hospitalisation (rate), 4) Quality of life, 5) Mortality (all-cause, suicides completed), 6) Weight.
- **Time**: At least 1 year after initiating treatment.
- **Study design**: RCTs and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
- **Study setting**: Primary, secondary, tertiary health and social care

#### Search strategy

**Databases searched:**
- RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.
- SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**

**Study design filter/limit used**
- RCT: all languages.
- SR: English language limit.

**Question specific search strategy**
- No

**Amendments to search strategy/study design filter**
- None

**Searching other resources**
- The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
### The review strategy

The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.

*Note.*
### 5.4. Psychological interventions for bipolar disorder in children and young people

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| **Review question(s)**       | RQ5.4: For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for episodes of bipolar depression?  
RQ5.5: For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management?  
What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years)? |
| **Objectives**               | To estimate the efficacy of psychological interventions to manage bipolar disorder in children and young people.                             |
| **Criteria for considering studies for the review** | • Intervention: All psychological and psychosocial interventions (for example, cognitive behavioural therapy) with or without pharmacological interventions.  
• Comparator: Waitlist, no intervention and other interventions.  
• Types of participants: Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.  
• Outcomes:  
  1) Change in symptoms of depression.  
  2) Response (50% reduction or greater).  
  3) Relapse (all, mania/mixed, depression).  
  4) Discontinuation (due to side effects, other).  
• Time: For treatments, the main analysis will include outcomes at the end of the intervention. For long-term management, the main analysis will include outcomes after at least 1 year.  
• Study design: RCTs and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.  
• Study setting: Primary, secondary, tertiary health and social care. |
| **Search strategy**          | **Databases searched:**  
RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.  
**Date limits:**  
| **Study design filter/limit used** | RCT: all languages.  
SR: English language limit. |
<p>| <strong>Question specific search strategy</strong> | No |
| <strong>Amendments to search strategy/study design</strong> | None |</p>
<table>
<thead>
<tr>
<th>filter</th>
<th>The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Searching other resources</strong></td>
<td>The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.</td>
</tr>
</tbody>
</table>

*Note.*
## 5.5. Service-level intervention for bipolar disorder

<table>
<thead>
<tr>
<th>Topic</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question(s)</td>
<td>RQ5.6: For children and young people with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder?</td>
</tr>
<tr>
<td>What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).</td>
<td></td>
</tr>
</tbody>
</table>

### Objectives
To estimate the efficacy of services in treating bipolar disorder.

### Criteria for considering studies for the review

- **Intervention**
  1) Lithium clinics.
  2) Mood clinics.
  3) Collaborative care.

- **Comparator**
  Treatment-as-usual.
  Other services.

- **Types of participants**
  Children and young people (aged 18 years and younger) with suspected bipolar disorder. Special consideration will be given to the groups above.

- **Outcomes**
  1) Relapse (all, mania/mixed, depression).
  2) Hospitalisation (rate, duration).
  3) Quality of life.
  4) Mortality.

- **Time**
  At least 1 year after initiating treatment.

- **Study design**
  Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.

### Search strategy

**Databases searched:**
- RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO.
- SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO.

**Date limits:**
- RCT: 2005 to 20 January 2014;

**Study design filter/limit used**
- RCT; SR.
  Language restrictions: none.

**Question specific search strategy**
- No

**Amendments to search strategy/study design filter**
- None

**Searching other resources**
- The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.

**The review strategy**
- We will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percentage female); race (percentage BME); diagnosis (percentage...
**Review protocols and questions**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>bipolar I; number of previous episodes; risk of bias.</td>
</tr>
</tbody>
</table>

*Note.*
APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

Scoping searches

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

- BMJ Clinical Evidence
- Canadian Medical Association Infobase (Canadian guidelines)
- Clinical Policy and Practice Program of the New South Wales Department of Health (Australia)
- Clinical Practice Guidelines (Australian Guidelines)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- Excerpta Medica Database (Embase)
- Guidelines International Network
- Health Evidence Bulletin Wales
- Health Management Information Consortium (HMIC)
- HTA database (technology assessments)
- Medical Literature Analysis and Retrieval System Online (MEDLINE/MEDLINE In-Process)
- National Health and Medical Research Council
- National Library for Health Guidelines Finder
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Organizing Medical Networked Information Medical Search
- Scottish Intercollegiate Guidelines Network
- Turning Research Into Practice
- United States Agency for Healthcare Research and Quality

Further information about this process can be found in The Guidelines Manual (NICE, 2012).
Search strategies for the identification of clinical studies

Systematic search

Each search was constructed using the groups of terms set out in Text Box 1. The full set of search terms is documented in sections 1 to 3.23. The selection of search terms was kept broad to maximise retrieval of evidence in a wide range of areas of interest to the GDG.

Text Box 1: Summary of systematic search strategies: search strategy construction

<table>
<thead>
<tr>
<th>Section 1, focused searches</th>
<th>Review area/s</th>
<th>Search type</th>
<th>Search construction</th>
<th>Study design searched</th>
<th>Databases searched</th>
<th>Date range searched</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case identification and assessment</td>
<td>Focused search</td>
<td>[(Population terms version two) AND (((general identification instrument/diagnostic assessment terms ) AND (sensitivity/specificity terms)) OR (named instruments)))]</td>
<td>All study types</td>
<td>General medical databases: Embase, MEDLINE, PreMEDLINE, PsycINFO</td>
<td>Database inception to 20 January 2014</td>
</tr>
</tbody>
</table>
## Section 2, generic searches

<table>
<thead>
<tr>
<th>Review area/s</th>
<th>Search type</th>
<th>Search construction</th>
<th>Study design searched</th>
<th>Databases searched</th>
<th>Date range searched</th>
</tr>
</thead>
</table>
**Search strategies for the identification of clinical studies**

<table>
<thead>
<tr>
<th>Management of physical health</th>
<th>Generic search</th>
<th>General medical databases: [(population terms version 1) AND (RCT/SR terms)]</th>
<th>Topic specific databases: CDSR, CENTRAL, DARE, HMIC, HTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[(population terms)]</td>
<td>Qualitative systematic reviews, randomised controlled studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>General medical databases: CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Topic specific databases: CDSR, CENTRAL, DARE, HMIC, HTA</td>
</tr>
</tbody>
</table>

**Note.** Evidence resulting from generic searches mapped to all review areas.
1 Population search terms – all databases

1.1 STEM – General medical databases
Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

Version 1

1 exp bipolar disorder/ or mania/
2 1 use emez
3 exp bipolar disorder/
4 3 use mesz, prem
5 exp bipolar disorder/ or exp mania/
6 5 use psyh
7 ((bi?polar adj5 (disorder$ or depress$)) or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or hypomani$ or mania$ or manic$ or mixed episode$ or rcbd).ti,ab.
8 or/2,4,6-7

Version 2

1 exp bipolar disorder/ or mania/ or mood disorder/
2 1 use emez
3 exp bipolar disorder/ or mood disorders/
4 3 use mesz, prem
5 affective disorders/ or exp bipolar disorder/ or exp mania/
6 5 use psyh
7 (bi?polar or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or hypomani$ or mania$ or manic$ or mixed episode$ or rcbd).ti,ab,tm.
8 ((affective$ or mood) adj (disorder$ or disturbance$ or dysfunction$ or illness$ or swing$)).ti,ab.tm.
9 or/2,4,6-8

1.2 STEM – topic specific databases
HTA, CDSR, DARE, CENTRAL – Wiley

#1 mesh descriptor bipolar disorder explode all trees

(((bipolar or “bi polar”) near/5 (disorder* or depress*)) or
#2 ((cyclothymi* or rapid or ultradian) near/5 cycl*) or
hypomani* or mania* or manic* or “mixed episode*” or
rcbd):ti,ab,kw

#3 (#1 or #2)
1.3 STEM – topic specific databases
CINAHL – Ebsco

<table>
<thead>
<tr>
<th>s3</th>
<th>s1 or s2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ti ( (((bipolar or “bi polar”) n5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) n5 cycl*) or hypomani* or mania* or manic* or “mixed episode*” or rcbd) ) or ab ( (((bipolar or “bi polar”) n5 (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) n5 cycl*) or hypomani* or mania* or manic* or “mixed episode*” or rcbd) )</td>
</tr>
<tr>
<td>s1</td>
<td>(mh &quot;bipolar disorder&quot;)</td>
</tr>
</tbody>
</table>

1.4 STEM – topic specific databases
HMIC – HDAS
1    hmic  bipolar disorder/
2    hmic  (((bipolar or "bi polar") and (disorder* or depress*)) or ((cyclothymi* or rapid or ultradian) and cycl*) or hypomani* or mania* or manic* or "mixed episode*" or rcbd).ti,ab
3    hmic  1 or 2

2. Question specific search strategies – all databases

2.1 Case identification and assessment

Review questions:

RQ: For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?

RQ: For children (less than 13 years) and young people (13 to 18 years) at risk of or suspected of having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?

RQ: For people with possible bipolar disorder, what are the key components of, and the most effective structure for, diagnostic assessment?

What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) people of different genders, (iii) children and young people, (iv) older adults?
2.11 General medical databases
Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

1 checklist/ or clinical assessment tool/ or clinical assessment/ or clinical evaluation/ or exp computer assisted diagnosis/ or exp diagnostic test/ or functional assessment/ or geriatric assessment/ or measurement/ or needs assessment/ or nursing assessment/ or outcome assessment/ or patient assessment/ or predictive value/ or exp psychologic test/ or psychometry/ or rating scale/ or risk assessment/ or scoring system/ or screening test/ or self evaluation/ or semi structured interview/ or "speech and language assessment"/ or structured interview/ or structured questionnaire/ or summated rating scale/

2 1 use emez

3 checklist/ or exp diagnosis, computer-assisted/ or diagnostic tests, routine/ or diagnostic, self evaluation/ or geriatric assessment/ or interview, psychological/ or mass screening/ or needs assessment/ or exp nursing assessment/ or "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or exp personality assessment/ or "predictive value of tests"/ or exp psychiatric status rating scales/ or exp psychological tests/ or exp questionnaires/ or risk assessment/

4 3 use mesz, prem

5 attitude measurement/ or exp attitude measures/ or comprehension tests/ or computer assisted diagnosis/ or geriatric assessment/ or group testing/ or individual testing/ or exp inventories/ or measurement/ or needs assessment/ or exp perceptual measures/ or performance tests/ or exp personality measures/ or exp preference measures/ or pretesting/ or professional examinations/ or exp psychiatric evaluation/ or exp psychodiagnostic interview/ or exp psychological assessment/ or psychometrics/ or exp questionnaires/ or exp rating scales/ or exp reading measures/ or exp retention measures/ or risk assessment/ or exp screening tests/ or exp selection tests/ or self evaluation/ or sensorimotor measures/ or sociometric tests/ or "speech and hearing measures"/ or standardized tests/ or subtests/ or symptom checklists/ or exp testing/ or testing methods/ or exp test scores/ or verbal tests/

6 5 use psyh

7 (index or instrument$ or interview$ or inventor$ or item$ or measure$1 or questionnaire$ or rate$ or rating or scale$ or score$ or screen$ or (self adj (assess$ or report$)) or subscale$ or survey$ or test$ or tool$).tw.

8 or/2,4,6-7

9 di.fs. or exp diagnosis/ or exp mass screening/ or screening test/

10 9 use emez
Search strategies for the identification of clinical studies

di.fs. or exp diagnosis/ or mass screening/ or nursing diagnosis/
11 use mesz, prem
exp diagnosis/ or exp health screening/ or screening/ or exp screening
tests/
13 use psyh
(assess$ or detect$ or diagnos$ or evaluat$ or identif$ or psychodiagnos$ or recogni$ or screen$).tw.
or/10,12,14-15
8 and 16
(casefind$ or ((case or tool$) adj (find$ or identif$))).tw.
or/17-18
"area under the curve"/ or predictive validity/ or receiver operating
characteristic/ or reliability/ or "sensitivity and specificity"/ or test retest
reliability/ or validity/
20 use emez
"area under curve"/ or "predictive value of tests"/ or "reproducibility of
results"/ or roc curve/ or "sensitivity and specificity"/ or validation
studies/
22 use mesz, prem
test reliability/ or test validity/
24 use psyh
(accurac$ or accurat$ or area under curve or auc value$ or (likelihood adj3
ratio$) or (diagnostic adj2 odds ratio$) or ((pretest or pre test or posttest or
post test) adj2 probabilit$) or (predict$ adj3 value$) or receiver operating
characteristic or (roc adj2 curv$) or reliabl$ or sensitiv$ or specificit$ or
valid$).tw.
or/21,23,25-26
19 and 27
((altman adj (selfrat$ or self rat$) adj mania adj2 scale$) or arsm).tw.
(bipolar spectrum diagnostic scale$ or bsds).tw.
((bipolarity or bi polarity) adj index).tw.
((child mania rating scale) or cmrs).ti,ab,tm.
(clinician-administered rating scale for mania or carsm or cars m).tw.
((connor$ abbreviated adj3 parent$ adj3 question$) or CAPQ).ti,ab,tm.
(hypomania checklist or hcl 32 or hcl32 or hcl32r1).tw.
(hypomanic personality adj (questionnaire$ or scale$)).tw.
((screening assessment adj2 (depression adj2 polarity)) or sadp or sad
p).tw.
((parent adj4 young mania rating scale) or pymrs or p ymrs).tw.
(composite international diagnostic interview or cidi or cidi1 or cidi2 or
cidi3 or cidisc).tw.
(general behavio?r inventory or gbi15 or gbi 15 or pgbi or p gbi).tw.
life chart.tw.
Search strategies for the identification of clinical studies

3 Study design filters – all databases

3.1 Quantitative systematic review study design filters

3.11 Quantitative systematic review study design filter, general medical databases

Embase, MEDLINE, MEDLINE In-Process, PsycINFO – OVID SP

1 meta analysis/ or systematic review/
2 1 use emez
3 meta analysis.sh,pt. or "meta-analysis as topic"/ or "review literature as topic"/
4 3 use mesz, prem
5 (literature review or meta analysis).sh,md. or systematic review.id,md.
6 5 use psyh
7 (exp bibliographic database/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)
8 7 use emez
9 (exp databases, bibliographic/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)
10 9 use mesz, prem
11 (computer searching.sh,id. or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,pt. or systematic$.ti,ab.)
12 11 use psyh
Search strategies for the identification of clinical studies

13 ((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$) adj2 (overview$ or review$)).tw. or ((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$).ti. and review$.ti,pt.) or (systematic$ adj2 search$).ti,ab.

14 (metaanal$ or meta anal$).ti,ab.

15 (research adj (review$ or integration)).ti,ab.

16 reference list$.ab.

17 bibliograph$.ab.

18 published studies.ab.

19 relevant journals.ab.

20 selection criteria.ab.

21 (data adj (extraction or synthesis)).ab.

22 (handsearch$ or ((hand or manual) adj search$)).ti,ab.

23 (mantel haenszel or peto or dersimonian or der simonian).ti,ab.

24 (fixed effect$ or random effect$).ti,ab.

25 ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.

26 or/2,4,6,8,10,12-25

3.12 Qualitative systematic review study design filter, topic specific databases
CINAHL – EBSCO HOST

s33  s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s22 or s23 or s26 or s27 or s28 or s29 or s30 or s31 or s32
s32  ti ( analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantitativ* n5 review* or systematic* n5 review* ) or ab ( analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantitativ* n5 review* or systematic* n5 review* )

s31  ti ( analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantitativ* n5 overview* or systematic* n5 overview* ) or ab ( analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantitativ* n5 overview* or systematic* n5 overview* )

s30  ti ( pool* n2 results or combined n2 results or combining n2 results ) or ab ( pool* n2 results or combined n2 results or combining n2 results )

s29  ti ( pool* n2 studies or combined n2 studies or combining n2 studies ) or ab ( pool* n2 studies or combined n2 studies or combining n2 studies )
Search strategies for the identification of clinical studies

s28  ti ( pool* n2 trials or combined n2 trials or combining n2 trials ) or ab ( pool* n2 trials or combined n2 trials or combining n2 trials )
s27  ti ( pool* n2 data or combined n2 data or combining n2 data ) or ab ( pool* n2 data or combined n2 data or combining n2 data )
s26  s24 and s25
s25  ti review* or pt review*
s24  ti analy* or assessment* or evidence* or methodol* or quantativ* or systematic*
s23  ti “systematic* n5 search*” or ab “systematic* n5 search*”
s22  (s17 or s18 or s19) and (s20 or s21)
s21  ti systematic* or ab systematic*
s20  tx review* or mw review* or pt review*
s19  (mh "cochrane library")
s18  ti ( bids or cochrane or index medicus or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science ) or ab ( bids or cochrane or index medicus or “isi citation” or psyclit or psychlit or scisearch or “science citation” or web n2 science )
s17  ti ( “electronic database*” or “bibliographic database*” or “computer?ed database*” or “online database*” ) or ab ( “electronic database*” or “bibliographic database*” or “computer?ed database*” or “online database*” )
s16  (mh "literature review")
s15  pt systematic* or pt meta*
s14  ti ( “fixed effect*” or “random effect*” ) or ab ( “fixed effect*” or “random effect*” )
s13  ti ( “mantel haenszel” or peto or dersimonian or “der simonian” ) or ab ( “mantel haenszel” or peto or dersimonian or “der simonian” )
s12  ti ( handsearch* or "hand search*" or "manual search*" ) or ab ( handsearch* or "hand search*" or "manual search*" )
s11  ab "data extraction" or "data synthesis"
s10  ab "selection criteria"
s9   ab "relevant journals"
s8   ab "published studies"
s7   ab bibliograph*
s6   ab "reference list*"
s5   ti ( “research review*” or “research integration” ) or ab ( “research review*” )
Search strategies for the identification of clinical studies

or “research integration”

s4 ti (metaanal* or “meta anal*”) or ab (metaanal* or “meta anal*”)

s3 (mh "meta analysis")

s2 (mh "systematic review")

s1 (mh "literature searching+")

3.2 Randomised controlled trial filters

3.21 Randomized controlled trial study design filter, general medical databases
Embbase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

1 exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/

2 1 use emez

3 exp clinical trial/ or exp “clinical trials as topic”/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/

4 3 use mesz, prem

5 (clinical trials or placebo or random sampling).sh,id.

6 5 use psyh

7 (clinical adj2 trial$).ti,ab.

8 (crossover or cross over).ti,ab.

9 (((single$ or double$ or treble$ or triple$) adj2 blind$) or mask$ or dummy or doubleblind$ or singleblind$ or trebleblind$ or tripleblind$).ti,ab.

10 (placebo$ or random$).ti,ab.

11 treatment outcome$.md. use psyh

12 animals/ not human$.mp. use emez

13 animal$/ not human$/ use mesz, prem

14 (animal not human).po. use psyh

15 (or/2,4,6-11) not (or/12-14)

3.23 Randomized controlled trial study design filter, topic specific databases
CINAHL– EBSCO Host

s10 s9 not s8
Search strategies for the identification of clinical studies

s9  s1 or s2 or s3 or s4 or s5 or s6 or s7
s8  (mh "animals") not (mh "human")
s7  (pt "clinical trial") or (pt "randomized controlled trial")
s6  ti ( placebo* or random* ) or ab ( placebo* or random* )
s5  ti ( single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* ) or ab ( single blind* or double blind* or treble blind* or mask* or dummy* or singleblind* or doubleblind* or trebleblind* )
s4  ti ( crossover or cross over ) or ab ( crossover or cross over )
s3  ti clinical n2 trial* or ab clinical n2 trial*
s2  (mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")
s1  (mh "clinical trials+")
APPENDIX 9: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMICS EVIDENCE

Scoping searches

A broad preliminary search of the literature was undertaken in August 2011 to obtain an overview of the issues likely to be covered by the scope, and to help define key areas. Searches were limited to full and partial economic evaluations, and quality of life studies.

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

Further information about this process can be found in The Guidelines Manual (NICE, 2012).
Systematic search

Each search was constructed using the groups of terms set out in Text Box 2. The full set of search terms is documented in sections 1 to 3.1. The selection of search terms was kept broad to maximise retrieval of evidence in a wide range of areas of interest to the GDG.

Text Box 2: Summary of systematic search strategies: Search strategy construction

<table>
<thead>
<tr>
<th>Review area/s</th>
<th>Search type</th>
<th>Search construction</th>
<th>Study design searched</th>
<th>Databases searched</th>
<th>Date range searched</th>
</tr>
</thead>
</table>
### Section 2, generic searches

<table>
<thead>
<tr>
<th>Review area/s</th>
<th>Search type</th>
<th>Search construction</th>
<th>Study design searched</th>
<th>Databases searched</th>
<th>Date range searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological and medical interventions for acute episodes</td>
<td>Generic search</td>
<td>General medical databases: [(population terms version 1) AND (HE/QoL terms)]</td>
<td>Full and partial economic evaluations, quality of life studies</td>
<td>General medical databases: Embase, MEDLINE, PreMEDLINE, PsycINFO</td>
<td>2005 to 20 January 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topic specific databases: [(population terms)]</td>
<td></td>
<td>Topic specific databases: HTA, NHS EED</td>
<td></td>
</tr>
<tr>
<td>Pharmacological and medical interventions for long-term management</td>
<td>Generic search</td>
<td>General medical databases: [(population terms version 1) AND (HE/QoL terms)]</td>
<td>Full and partial economic evaluations, quality of life studies</td>
<td>General medical databases: Embase, MEDLINE, PreMEDLINE, PsycINFO</td>
<td>2005 to 20 January 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topic specific databases: [(population terms)]</td>
<td></td>
<td>Topic specific databases: HTA, NHS EED</td>
<td></td>
</tr>
<tr>
<td>Psychosocial interventions for adults</td>
<td>Generic search</td>
<td>General medical databases: [(population terms version 1) AND (HE/QoL terms)]</td>
<td>Full and partial economic evaluations, quality of life studies</td>
<td>General medical databases: Embase, MEDLINE, PreMEDLINE, PsycINFO</td>
<td>2005 to 20 January 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topic specific databases: [(population terms)]</td>
<td></td>
<td>Topic specific databases: HTA, NHS EED</td>
<td></td>
</tr>
</tbody>
</table>
### Search strategies for the identification of health economics evidence

<table>
<thead>
<tr>
<th>Management of physical health</th>
<th>Generic search</th>
<th>General medical databases: [(population terms version 1) AND (HE/QoL terms)]</th>
<th>Full and partial economic evaluations, quality of life studies</th>
<th>General medical databases: Embase, MEDLINE, PreMEDLINE, PsycINFO</th>
<th>2005 to 20 January 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Topic specific databases: [(population terms)]</td>
<td></td>
<td>Topic specific databases: HTA, NHS EED</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Evidence resulting from generic searches mapped to all review areas.
Search strategies for the identification of health economics evidence

1 Population search terms – all databases

1.1 STEM – general medical databases
Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

Version 1

1  exp bipolar disorder/ or mania/
2  1 use emez
3  exp bipolar disorder/
4  3 use mesz, prem
5  exp bipolar disorder/ or exp mania/
6  5 use psyh
7  ((bi?polar adj5 (disorder$ or depress$)) or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or hypomani$ or mania$ or manic$ or mixed episode$ or rcbd).ti,ab.
8  or/2,4,6-7

Version 2

1  exp bipolar disorder/ or mania/ or mood disorder/
2  1 use emez
3  exp bipolar disorder/ or mood disorders/
4  3 use mesz, prem
5  affective disorders/ or exp bipolar disorder/ or exp mania/
6  5 use psyh
7  (bi?polar or ((cyclothymi$ or rapid or ultradian) adj5 cycl$) or hypomani$ or mania$ or manic$ or mixed episode$ or rcbd).ti,ab,tm.
8  ((affective$ or mood) adj (disorder$ or disturbance$ or dysfunction$ or illness$ or swing$)).ti,ab.tm.
9  or/2,4,6-8

1.2 STEM – topic specific databases
HTA, CDSR, DARE, CENTRAL – Wiley

Version 1

#1 mesh descriptor bipolar disorder explode all trees

  (((bipolar or “bi polar”) near/5 (disorder* or depress*)) or
#2 ((cyclothymi* or rapid or ultradian) near/5 cycl*) or
  hypomani* or mania* or manic* or “mixed episode**” or
  rcbd):ti,ab,kw

#3 (#1 or #2)
Version 2

#1 mesh descriptor bipolar disorder explode all trees
#2 mesh descriptor mood disorders this tree only

- (((bipolar or “bi polar”) near/5 (disorder* or depress*)) or
- ((cyclothymi* or rapid or ultradian) near/5 cycl*)) or
- hypomani* or mania* or manic* or “mixed episode*” or
- rcbd):ti,ab,kw

#3

#4 ((affective* or mood) near/1 (disorder* or disturbance* or
- illness* or swing*)):ti,ab.

#5 (#1 or #2 or #3 or #4)

2. Question specific search strategies – all databases

2.1 Case identification and assessment

<table>
<thead>
<tr>
<th>Review questions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RQ: For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?</td>
</tr>
<tr>
<td>RQ: For children (less than 13 years) and young people (13 to 18 years) at risk of or suspected of having bipolar disorder, what identification instruments when compared with a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (that is, clinically useful with good sensitivity and specificity) and reliability?</td>
</tr>
<tr>
<td>RQ: For people with possible bipolar disorder, what are the key components of, and the most effective structure for, diagnostic assessment?</td>
</tr>
<tr>
<td>What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) people of different genders, (iii) children and young people, (iv) older adults?</td>
</tr>
</tbody>
</table>

2.11 General medical databases

Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

1 checklist/ or clinical assessment tool/ or clinical assessment/ or clinical evaluation/ or exp computer assisted diagnosis/ or exp diagnostic test/ or functional assessment/ or geriatric assessment/ or measurement/ or needs assessment/ or nursing assessment/ or outcome assessment/ or patient assessment/ or predictive value/ or exp psychologic test/ or psychometry/ or rating scale/ or risk assessment/ or scoring system/ or screening test/ or self evaluation/ or semi structured interview/ or "speech and language assessment"/ or structured interview/ or structured questionnaire/ or summated rating scale/
Search strategies for the identification of health economics evidence

2 1 use emez
3 checklist/ or exp diagnosis, computer-assisted/ or diagnostic tests, routine/ or diagnostic, self evaluation/ or geriatric assessment/ or interview, psychological/ or mass screening/ or needs assessment/ or exp nursing assessment/ or "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or exp personality assessment/ or "predictive value of tests"/ or exp psychiatric status rating scales/ or exp psychological tests/ or exp questionnaires/ or risk assessment/
4 3 use mesz, prem
5 attitude measurement/ or exp attitude measures/ or comprehension tests/ or computer assisted diagnosis/ or geriatric assessment/ or group testing/ or individual testing/ or exp inventories/ or measurement/ or needs assessment/ or exp perceptual measures/ or performance tests/ or exp personality measures/ or exp preference measures/ or pretesting/ or professional examinations/ or exp psychiatric evaluation/ or exp psychodiagnostic interview/ or exp psychological assessment/ or psychometrics/ or exp questionnaires/ or exp rating scales/ or exp reading measures/ or exp retention measures/ or risk assessment/ or exp screening tests/ or exp selection tests/ or self evaluation/ or sensorimotor measures/ or sociometric tests/ or "speech and hearing measures"/ or standardized tests/ or subtests/ or symptom checklists/ or exp testing/ or testing methods/ or exp test scores/ or verbal tests/
6 5 use psyh
7 (index or instrument$ or interview$ or inventor$ or item$ or measure$ or questionnaire$ or rate$ or rating or scale$ or score$ or screen$ or (self adj (assess$ or report$))) or subscale$ or survey$ or test$ or tool$).tw.
8 or/2,4,6-7
9 di.fs. or exp diagnosis/ or exp mass screening/ or screening test/
10 9 use emez
11 di.fs. or exp diagnosis/ or mass screening/ or nursing diagnosis/
12 11 use mesz, prem
13 exp diagnosis/ or exp health screening/ or screening/ or exp screening tests/
14 13 use psyh
15 (assess$ or detect$ or diagnosis$ or evaluat$ or identifi$ or psychodiagnosis$ or recogni$ or screen$).tw.
16 or/10,12,14-15
17 8 and 16
18 (casefind$ or ((case or tool$) adj (find$ or identifi$))).tw.
19 or/17-18
20 "area under the curve"/ or predictive validity/ or receiver operating characteristic/ or reliability/ or "sensitivity and specificity"/ or test retest reliability/ or validity/
21 20 use emez
22 "area under curve"/ or "predictive value of tests"/ or "reproducibility of results"/ or roc curve/ or "sensitivity and specificity"/ or validation studies/
23 22 use mesz, prem
Search strategies for the identification of health economics evidence

24 test reliability/ or test validity/
25 24 use psyh
26 (accurac$ or accurat$ or area under curve or auc value$ or (likelihood adj3 ratio$) or (diagnostic adj2 odds ratio$) or ((pretest or pre test or posttest or post test) adj2 probabilit$) or (predict$ adj3 value$) or receiver operating characteristic or (roc adj2 curv$) or reliabil$ or sensitiv$ or specificit$ or valid$).tw.
27 or/21,23,25-26
28 19 and 27
29 ((altman adj (selfrat$ or self rat$) adj mania adj2 scale$) or arsm).tw.
30 (bipolar spectrum diagnostic scale$ or bsds).tw.
31 ((bipolarity or bi polarity) adj index).tw.
32 ((child mania rating scale) or cmrs).ti,ab,tm.
33 (clinician-administered rating scale for mania or carsm or cars m).tw.
34 ((conner$ abbreviated adj3 parent$ adj3 question$) or CAPQ).ti,ab,tm.
35 (hypomania checklist or hcl 32 or hcl32 or hcl32r1).tw.
36 (hypomonic personality adj (questionnaire$ or scale$)).tw.
37 ((screening assessment adj2 (depression adj2 polarity)) or sadp or sad p).tw.
38 ((parent adj4 young mania rating scale) or pymrs or p ymrs).tw.
39 (composite international diagnostic interview or cidi or cidi1 or cidi2 or cidi3 or cidisc).tw.
40 (general behavio?r inventory or gbi15 or gbi 15 or pgbi or p gbi).tw.
41 life chart.tw.
42 ((m3 or m 3) adj (checklist$ or screen$)).tw.
43 (((miniinternational or mini international) adj neuropsychiatric interview) or mini or miniplus).tw.
44 (mood swings questionnaire or msq).tw.
45 (mood disorder questionnaire or mdq).tw.
46 (provisional diagnostic instrument or pdi4 or pdi 4).tw.
47 or/29-46
48 or/28,47

3 Study design filters – all databases

3.1 Health economic and quality of life study design filter
Embase, MEDLINE, PreMEDLINE, PsycINFO – OVID SP

1 budget/ or exp economic evaluation/ or exp fee/ or funding/ or exp health care
cost/ or health economics/ or exp pharmaceconomics/ or resource allocation/
2 1 use emez
   exp budgets/ or exp “costs and cost analysis”/ or economics/ or exp economics,
hospital/ or exp economics, medical/ or economics, nursing/ or economics,
pharmaceutical/ or exp “fees and charges”/ or exp resource allocation/ or value
of life/
Search strategies for the identification of health economics evidence

4 3 use mesz, prem
exp "costs and cost analysis"/ or "cost containment"/ or economics/ or finance/
or funding/ or health care economics/ or pharmacoeconomics/ or exp
professional fees/ or resource allocation/

5 5 use psyh
(cost$ or economic$ or pharmacoeconomic$ or pharmaco economic$).ti. or (cost$ adj2
(effective$ or utilit$ or benefit$ or minimi$)).ab. or economic modell$.tw. or (budget$ or
fee or fees or financ$ or price or prices or pricing or resource$ allocat$ or (value adj2
(money or money))).ti,ab.
decision theory/ or decision tree/ or monte carlo method/ or *nonbiological
model/ or (statistical model/ and exp economic aspect/) or stochastic model/ or
*theoretical model/

6 8 use emez
exp decision theory/ or markov chains/ or exp models, economic/ or *models,
organizational/ or *models, theoretical/ or monte carlo method/

7 11 use mesz, prem
12 exp decision theory/ or exp stochastic modeling/
13 12 use psyh
((decision adj (analy$ or model$ or tree$)) or economic modell$ or markov or
monte carlo).ti,ab.
quality adjusted life year/ or "quality of life index"/ or short form 12/ or short
form 20/ or short form 36/ or short form 8/ or sickness impact profile/

8 15 use emez
17 quality-adjusted life years/ or sickness impact profile/
18 17 use mesz, prem
19 "*quality of life"
20 19 use psyh
((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab.
22 (disutili$ or (utilit$ adj1 (health or score$ or value$ or weigh$))).ti,ab.
23 (health year equivalent or hve or hies).ti,ab.
24 (daly or qal or qald or qale or qaly or qtime$ or qwb$).ti,ab.
25 discrete choice.ti,ab.
26 (euroqol$ or euro qol$ or eq5d$ or eq 5d$).ti,ab.
27 (hui or hui1 or hui2 or hui3).ti,ab.
((quality adj2 (wellbeing or well being)) or quality adjusted life or qwb or (value adj2
(money or monetary))).ti,ab.
29 (qol or hql$ or hqol$ or hrqol or hr qol or hr ql or hrql$).ti,ab.
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APPENDIX 10: RESEARCH RECOMMENDATIONS

The GDG has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. Psychological interventions for young people with bipolar depression

What is the clinical and cost effectiveness of structured psychological interventions for young people with bipolar depression?

Why this is important

There has been very little research regarding the clinical effectiveness of structured individual and group psychological interventions for children and young people with bipolar disorder. Research on unipolar depression in children and young people supports the effectiveness of cognitive behavioural therapy (CBT), interpersonal therapy (IPT) and short-term family therapy. However, there have been no published trials investigating clinical and functional outcomes for young people with bipolar depression. Given the increasing emphasis on early interventions in related conditions such as psychosis and unipolar depression, it is important to know the form of psychological therapy that can benefit young people with bipolar disorder.

A high-quality, non-inferiority randomised controlled trial (RCT) should recruit young people during an acute episode of bipolar depression who are treated with structured psychological interventions (CBT compared with IPT). Interventions should be offered over 6–9 months, with a 9-month follow-up period. Key outcomes should include clinical recovery, symptom change, personal recovery or functional outcomes at the end of treatment and at 9-month follow-up, and cost effectiveness.

2. Maintenance treatment

In the maintenance treatment of bipolar disorder, what is the relative effect on quality of life of lithium, an antipsychotic (haloperidol, olanzapine, quetiapine or risperidone), or a combination of lithium and an antipsychotic?

Why this is important

Lithium and antipsychotic medication are known to reduce the risk of relapse when used long term in people with bipolar disorder. Relapses do still occur and the response is usually to add another mood-stabilising drug. However, lithium and antipsychotics are associated with a number of side effects, some of which can adversely affect physical health. The relative effects of lithium, an antipsychotic or a combination of these drugs, regarding efficacy, tolerability, cost effectiveness and quality of life are unknown. Such information is important to people with bipolar disorder to help them make an informed choice about the treatment options available to them, and to the NHS to inform the best use of resources.
The suggested programme of research should involve a pragmatic -arm RCT comparing lithium monotherapy with antipsychotic monotherapy (haloperidol, olanzapine, quetiapine or risperidone) and a combination of lithium and an antipsychotic. The study should last at least 1 year with the primary outcome being quality of life. Symptom control, relapse, function and economic outcomes should also be measured.

3. **Antidepressants combined with antimanic medication in bipolar depression**

What is the clinical and cost effectiveness of fluoxetine combined with olanzapine versus an alternative selective serotonin reuptake inhibitor (SSRI) combined with olanzapine in the treatment of moderate to severe bipolar depression?

**Why this is important**

Bipolar depression occurs three times more frequently than mania and is associated with suicide and impaired function and quality of life. The Guideline Development Group found that the combination of fluoxetine and olanzapine was the most clinically- and cost-effective treatment for bipolar depression. Antidepressants (imipramine, paroxetine and moclobemide) alone were ineffective compared with placebo. Olanzapine alone was an effective treatment for bipolar depression, but not as effective as olanzapine and fluoxetine in combination. However, for many people some antidepressants are ineffective or cannot be tolerated. For these people the NICE clinical guideline on depression in adults\(^3\) recommends changing to another antidepressant from the same or a different class.

A two-arm non-inferiority RCT of the combination of fluoxetine and olanzapine within BNF therapeutic levels compared with an alternative SSRI and olanzapine for moderate or severe bipolar depression with a 12-week follow-up period should be carried out. The primary clinical outcome should be depression response. Secondary outcomes should be depression remission, function, anxiety symptoms, emergent mania or hypomania symptoms, other adverse outcomes, quality of life and cost effectiveness.

4. **A specialised collaborative care service for people with bipolar disorder**

What is the clinical and cost effectiveness of a specialised collaborative care service for people admitted to hospital with bipolar disorder compared with usual treatment delivered by generic care services?

**Why this is important**

There is moderate-quality evidence of the effectiveness of a specialised collaborative care service compared with usual treatment in reducing hospitalisation in two studies (from Denmark and the US). There is no overall evidence of an effect on

\(^3\) NICE. Depression in Adults: The Treatment and Management of Depression in Adults. NICE clinical guideline 90. London: NICE; 2009. Available from: www.nice.org.uk/CG90
relapse or other outcomes. An economic analysis from one study showed that better clinical outcomes were achieved at two-thirds of the overall cost of usual treatment. If similar results were obtained in England, then better care for a substantially reduced cost might be achieved.

A two-arm multicentre RCT of a specialist collaborative care service for people admitted to hospital with bipolar disorder compared with usual treatment, with follow-up of at least 2 years, is needed. Community alternatives to hospitalisation should be included. The specialist intervention should be based on collaborative care principles, including group or other psychoeducation to promote self-management, care coordination and algorithm-derived psychotropic medication (in line with this guideline) under the direction of a psychiatrist. Feasibility and acceptability development work should involve collaborating with people with bipolar disorder and professionals to demonstrate sustainable service delivery and recruitment, and identify and address possible barriers to such a service. Clinical outcomes should include time to next bipolar episode, mania and depression symptoms, function, recovery and quality of life. Economic outcomes should consider health, social care and personal costs.

5. **Cognitive behavioural therapy for the long-term management of bipolar disorder**

What is the clinical and cost effectiveness of face-to-face cognitive behavioural therapy (CBT) compared with internet-facilitated CBT in the long-term management of bipolar disorder?

**Why this is important**

The Guideline Development Group found that individual structured psychological interventions are clinically effective. Studies support the efficacy of individual CBT, but evidence for long-term benefits of internet-based interventions is less conclusive. Internet-facilitated CBT has the potential to deliver the key components of face-to-face CBT in a more cost-effective and accessible format. If this proves to be the case then increased access to cost-effective psychological care could be rapidly achieved. The proposed research programme would have 2 phases: (1) software development of internet-facilitated CBT including alpha, beta and feasibility and acceptability testing to confirm that the intervention is safe, acceptable and used by potential patients; (2) a two-arm non-inferiority RCT comparing internet-facilitated CBT with individual face-to-face CBT designed for bipolar disorder. Participants should be aged 16 years and over and be in a state of euthymia when recruited. The primary outcomes should be personal recovery and quality of life at 12-month follow-up. Secondary outcomes should be time to relapse, social and occupational functioning, and cost effectiveness.