

1 Appendices

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Appendix 1: Scope for the development of the clinical guideline

1 *Guideline title*

Depression: the treatment and management of depression in adults (update)

1.1 *Short title*

Depression in adults (update)

2 *Background*

- a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Mental Health to review recent evidence on the treatment and management of depression and to update the existing guideline 'Depression: management of depression in primary and secondary care' (amended) (NICE clinical guideline 23, 2007). The guideline update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

- b) The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care for which a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by NICE after an NSF has been issued have the effect of updating the Framework.

- c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with service users, taking account of their individual needs and preferences, and ensuring that service users (and their carers and families, if appropriate) can make informed decisions about their care and treatment.

3. *Clinical need for the guideline*

- a) Depression refers to a range of mental health disorders characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and

a range of associated emotional, cognitive, physical and behavioural symptoms. It is often accompanied by anxiety, and can be chronic even in milder presentations. People with more severe depression may also develop psychotic symptoms (hallucinations and/or delusions).

- b) The symptoms of depression can be disabling and the effects of the illness pervasive. Depression can have a major detrimental effect on people's personal, social and occupational functioning, placing a heavy burden on individuals and their carers and dependents, as well as placing considerable demands on the healthcare system. Among all diseases, depression is currently the fourth leading cause of burden to society. World Health Organisation projections indicate that it will be the highest ranking cause of disease burden in developed countries by the year 2020.
- c) Each year 6% of adults will experience an episode of depression and over the course of their lifetime more than 15% of the population will experience an episode. The average length of an episode of depression is between 6 and 8 months. For many people the episode will be mild but for more than 30%, the depression will be moderate or severe and have a significant impact on their daily lives. Recurrence rates are high; there is a 50% chance of recurrence after a first episode, rising to 70% and 90% after a second or third episode respectively.
- d) Estimated prevalence rates for men do not vary greatly among ethnic groups but those for women differ remarkably. In the UK significantly higher rates of depression are reported in women of Asian and Oriental family origin or background compared with other groups, with the next highest rates being in white women and the lowest rates in women of West Indian or African family origin or background. However, these estimates are based on relatively small samples.
- e) Depression is the leading cause of suicide, which accounts for just under 1% of all deaths. Nearly two-thirds of deaths by suicide occur in people with depression (that is, about 2600 suicides per year in England alone).
- f) Data from the Prescription Cost Analysis (PCA) system show that in the 12 months to March 2006, antidepressant drugs accounted for 4.1% of all items dispensed in the community in England, at a net ingredient cost of £31 million.

- g) The NICE clinical guideline 'Depression: management of depression in primary and secondary care' (clinical guideline 23) was published in December 2004, and was amended in 2007 to take into account new prescribing advice for venlafaxine. New evidence regarding the care of people with depression involving psychosocial, pharmacological and other physical interventions means that NICE's original guideline on depression needs to be updated.

4. *The guideline*

- a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.
- b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.
- c) 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) Adults (aged 18 years and older) who have a clinical diagnosis of depression established by a recognised diagnostic system such as DSM-IV or ICD-10. The guideline will be relevant to people with mild, moderate and severe major depressive disorders.
- b) People in the above group who also have learning difficulties, acquired cognitive impairments, or language difficulties.

4.1.2 *Groups that will not be covered*

- a) People with chronic physical disorders. A separate guideline on the treatment of depression in people with chronic physical health problems has been commissioned and will be developed in conjunction with this guideline.
- b) People with other primary psychiatric disorders, such as schizophrenia or substance misuse.

4.2 *Healthcare setting*

- a) Primary, secondary and tertiary care. The guidance will be relevant to all healthcare professionals who provide care for people with depression, irrespective of setting.

4.3 *Clinical management*

- a) Recognition, assessment and classification of depression, including variations to the assessment to take account of the needs of people with learning difficulties, acquired cognitive impairments or language difficulties.
- b) Treatment of depressive episodes of differing severity, including the appropriate use of psychosocial interventions (such as guided self-help, formal psychological interventions, support groups and programmes aimed at facilitating employment), pharmacological interventions (including antidepressants and other medication), and physical interventions (such as exercise, and electroconvulsive therapy).
- c) Variations to the systems for accessing and delivering treatment required to take account of the needs of people with learning difficulties, acquired cognitive impairments or language difficulties.
- d) Interventions to reduce the risk of relapse after an acute depressive episode.
- e) Assessment and management of the known side effects and other drawbacks of psychotropic medication, physical interventions, and psychosocial interventions, including long-term side effects and risks of suicide.
- f) Combined psychosocial and pharmacological treatments, the use of combined pharmacological treatments and the sequencing of both pharmacological and psychosocial interventions.
- g) The safe withdrawal/discontinuation of psychotropic medication.
- h) Interactions between psychotropic medication and common prescription and over-the-counter drugs.
- i) The varying approaches of different races and cultures, and issues of internal and external social exclusion.

- j) The role of the families and carers in the treatment and support of people with depression.
- k) The ways in which services are delivered, including models of care such as case management and collaborative care, and the structured delivery of care in primary and secondary care services.
- l) Note that guideline recommendations for pharmacological interventions will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual service users.
- m) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning an intervention for optimal use or changing an approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.
- n) The guideline will not cover:
 - diagnosis of depression
 - primary prevention of depression.

4.4 Status

4.4.1 Scope

This is the final scope.

The guideline will be developed in conjunction with 'Depression: the treatment and management of depression in adults with chronic physical health problems'; together they will update 'Depression: management of depression in primary and secondary care' (amended) (NICE clinical guideline 23 [amended] [2007]).

They will also update and replace the following NICE guidance.

- Computerised cognitive behaviour therapy for depression and anxiety. NICE technology appraisal guidance 97 (2006).
- Guidance on the use of electroconvulsive therapy. NICE technology appraisal guidance 59 (2003).

4.4.2 Guideline

The development of the guideline recommendations will begin in November 2007.

5. Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'.
- 'The guidelines manual'.

These are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix 2: Declarations of interest by Guideline Development

Group members

With a range of practical experience relevant to depression in the GDG, members were appointed because of their understanding and expertise in healthcare for people with depression and support for their families and 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 depression and their families and 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 depression and their families and 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

- 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 depression, holding office in a professional organisation or advocacy group with a direct interest in depression, other reputational risks relevant to depression.

<i>Declarations of interest</i>	
Professor Ian Anderson, Chair, Guideline Development Group	
Employment	Professor of Psychiatry, University of Manchester
Personal pecuniary interest	<p>Consultant for Wyeth Ltd Global Depression and Anxiety Strategy Consultant Board (specific), ended August 2007</p> <p>Consultant for Bristol-Myers Squibb Pharmaceuticals Ltd / Otsuka Pharmaceuticals UK Ltd Bipolar Disorder Advisory Board (non-specific), ended August 2007</p> <p>Consultant for Servier Ltd Agomelatine Advisory Board, ended August 2007</p> <p>Honoraria for speaking at non-promotional meetings from the following companies: AstraZeneca, Wyeth, Janssen Cilag, Lundbeck, 2007-2008</p>
Personal family interest	None
Non-personal pecuniary interest	<p>AstraZeneca investigator- initiated grant (specific)</p> <p>Honorarium paid into university research fund by Wyeth Ltd, for speaking at non-promotional meeting</p> <p>Talk on Managing Depression (independent content) at meeting supported by Lilly</p> <p>P1vital commercial study sponsored by Servier</p>
Personal non-pecuniary interest	<p>Member of MHRA Psychiatry Expert Advisory Group</p> <p>Member of Royal College of Psychiatrists Special Committee on ECT</p>
Ms Alison Barnes	
Employment	[to be completed]
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Carolyn Chew-Graham	

Employment	General Practitioner and Senior Lecturer in Primary Care, University of Manchester
Personal pecuniary interest	Mental Health clinical advisor for Manchester Joint Commissioning Team (Manchester Primary care Trust, Central PBC Hub)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Jeremy Clarke	
Employment	Psychological therapist, Lambeth Primary Care Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Research and Development Lead for The Association of Psychoanalytic Psychotherapy in the NHS Member of Expert Reference Group for Improving Access to Psychological Therapies (IAPT)
Ms Catherine Harris	
Employment	Labour Councillor for Haringey
Personal pecuniary interest	Mental health Act Commissioner from April 2008.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Role as Councillor does not entail a portfolio for health issues although the Labour Party campaigns on health issues. Member of Mental health Carers Support Association
Dr Mark Kenwright	
Employment	Consultant Cognitive Behavioural Psychotherapist; Ealing Cognitive Behavioural Therapy Service
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Coordinator of two pilot studies and an RCT on Computerised Cognitive behavioural Therapy (CCBT) Guided Self help for Panic Disorder and Phobias. Formed focus of doctoral thesis and three publications in British Journal of Psychiatry (1999-2002) Manager of Stress Self-Help Clinic research project in first CCBT clinic in primary care which offered CCBT for panic/phobia (Fearfighter), obsessive compulsive disorder (BT Steps) and depression (COPE). Published in Psychological Medicine (2001-2003) Project Lead for Improving Access to Psychological Therapies (IAPT) Pathfinder Site for London and South East (Ealing CBT Service). The service received £200,000 from nation IAPT for the period October 2007 to 2008
Professor Willem Kuyken	
Employment	Professor of Clinical Psychology and Co-Director Mood Disorders Centre, University of Exeter Psychology
Personal pecuniary interest	None
Personal family interest	None

Non-personal pecuniary interest	None
Personal non-pecuniary interest	<p>Co-Director of Mood Disorders Centre, funded by Devon Partnership NHS Trust and Devon Primary Care Trust</p> <p>Co-Principal Investigator, NHS HTA (£1.2 million, 1.7 million with NHS costs). Cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment resistant depression in primary care: a randomised control trial. 2008-2011. (PI Dr Nicola Wiles, University of Bristol)</p> <p>Principal Investigator, Medical Research Council (£233,000). Trial platform: Preventing depression relapse in NHS practice using Mindfulness-based Cognitive Therapy (MBCT) 2005-2007</p>
Professor Glyn Lewis	
Employment	Professor of Psychiatric Epidemiology, University of Bristol
Personal pecuniary interest	Occasional payment from pharmaceutical companies for non-promotional talks, for example, to other departments of psychiatry or at conferences
Personal family interest	None
Non-personal pecuniary interest	Colleagues in Department on Bristol University received funds from pharmaceutical industry to carry our research which I am not involved in.
Personal non-pecuniary interest	None
Mr Brendan Masterson	
Employment	Clinical Nurse Leader, Affective Disorders Unit, Bethlem Royal Hospital
Personal pecuniary interest	Presented a session on NICE guidelines for bipolar disorder at a study day sponsored by Janssen Cilag, February 2007)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Alan Meudell	
Employment	Healthy Minds at Work
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	<p>Member of Mind Expert Policy Group on Psychiatric Medicine and other Therapies</p> <p>Member of Pwyllgor Cymru (Governance body of Mind Cymru, Mind Wales)</p> <p>Member of Caerphilly Borough Council Mental Health Strategy Group</p> <p>Member of Adult Mental Health NSF Implementation Advisory Group (WAG)</p>
Dr Alex Mitchell	
Employment	Consultant Psychiatrist and Honorary lecturer in

	liaison psychiatry, University of Leicester
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Richard Moore	
Employment	Clinical Psychologist, Cambridge
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Interest in effectiveness of treatments for depression including taking part in related RCTs and the production of a treatment manual for treatment of chronic depression
Ms Carol Paton	
Employment	Chief Pharmacist, Oxleas NHS Foundation Trust
Personal pecuniary interest	Eli Lilly Advisory Board and consultancy for duloxetine antidepressant. Involvement has been since phase three trials and is not ongoing (2003 - 2007) Attendance at European Congress of neuropsychopharmacology (ECNP) 2007, sponsored by Janssen Cilag, without personal financial gain Eli Lilly Advisory Board on other products currently subject to clinical trials on depot IM olanzapine and novel drugs in phase two studies. None of these drugs were currently licensed and none were intended to treat depression (February 2008)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-author of paper describing clinical use of depot antipsychotics in the United Kingdom, to be published in BMJ supplement. The supplement is funded by Eli Lilly who have no influence over the content. No personal payment has been or will be received for this (April 2008)
Dr Thomas Shackleton	
Employment	General Practitioner, Suffolk
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Jane Wood	
Employment	Nurse, Strategic Development Manager, Mental Health, Leeds Primary Care Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

National Collaborating Centre for Mental Health staff	
Dr Steve Pilling – Facilitator, Guideline Development Group	
Employment	Joint Director, National Collaborating Centre for Mental Health Director, Centre for Outcomes Research and Effectiveness, University College London.
Personal pecuniary interest	In receipt of funding from NICE to develop clinical guidelines
Personal family interest	None
Non-personal pecuniary interest	Randomised controlled trial to evaluate multi-systemic therapy. Principal investigator is Professor Peter Fonagy. Department of Health funding of £1,000,000. (2008-2012)
Personal non-pecuniary interest	None
Ms Rachel Burbeck	
Employment	Systematic Reviewer, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Victoria Bird	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Matthew Dyer	
Employment	Health Economist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Sarah Hopkins (2007-2008)	
Employment	Project Manager, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Angela Lewis	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Ryan Li (2008)	

Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Nick Meader	
Employment	Systematic Reviewer, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Suffiya Omarjee	
Employment	Health Economist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Peny Retsa	
Employment	Health Economist (until 2008), National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Maria Rizzo	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Christine Sealey	
Employment	Centre Manager, National Collaborating Centre for Mental Health
Personal pecuniary interest	On secondment from National Institute for Health and Clinical Excellence.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Rob Saunders	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Beth Shackleton	
Employment	Project Manager, National Collaborating Centre for Mental Health (until 2008)
Personal pecuniary interest	None
Personal family interest	None

Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Sarah Stockton	
Employment	Information Scientist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Clare Taylor	
Employment	Editor, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Appendix 3: Special advisors to the Guideline Development Group

[To be completed after consultation]

**Appendix 4: Stakeholders and experts who submitted comments
in response to the consultation draft of the guideline**

Stakeholders

[To be completed after consultation]

Experts

[To be completed after consultation]

Appendix 5: Stakeholders and experts who submitted comments in response to the pre-publication check

Stakeholders

[To be completed after consultation]

Experts

[To be completed after consultation]

Appendix 6: Researchers contacted to request information about unpublished or soon-to-be published studies

Dr Allan Abbass
Prof Anthony Bateman
Professor Crits-Christoph
Dr John Eagles
Dr Robert Golden
Professor Hayes
Dr Hilsenroth
Prof Peter Fonagy
Professor Kenneth Wilson
Mr Leichsenring
Dr Chris Martell
Professor Parry
Professor Stratton

Appendix 7: Clinical questions

Clinical Questions for Depression Update

		<i>CQ in CG23</i>
A	<i>Service configuration for people with depression</i>	
A1	What methods are effective in identifying people with depression in primary care and community settings, including sexual health clinics, emergency departments, and drug and alcohol services? In which populations (excluding those with chronic physical health problems) should identification methods be used?	A1
A2	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), which models of care produce the best outcomes? - collaborative care - stepped care - case management - stratified (matched) care - attached professional model Are different models appropriate to the care of people in different phases of the illness, such as treatment resistant depression and relapse prevention?	A5
B	<i>Psychology/psychosocial interventions for people with depression</i>	
B1	In depression, does guided self-help improve outcomes compared to other interventions?	A2
B2	Does computerised CBT improve patient outcomes compared to other treatments?	A3
B3	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), do any of the following improve outcomes compared with other interventions: - exercise - support including groups, befriending, and non-statutory provision - programmes to facilitate employment	A4
B4	Do non-statutory support groups improve outcomes?	A6
B5	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), do any of the following	B1

(either alone or in combination with pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual): B2

- CBT
- BT/behavioural activation
- counseling/ person-centred therapy
- problem-solving
- psychodynamic psychotherapy
- family interventions/ couples therapy
- ACT (Acceptance and commitment therapy)
- systemic interventions
- psychoeducation
- CAT
- solution-focused therapy
- self-help, including guided self-help
- CCBT

Does mode of delivery (group-based or individual) impact on outcomes?

Are there specific therapist characteristics which improve outcomes?

Are there specific patient characteristics (eg anxiety, previous episodes) which predict outcomes?

Are brief interventions (eg 6-8 weeks) effective?

Are psychological interventions harmful?

- B6 Following poor response to treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), which psychological or psychosocial interventions are appropriate?
- B7 In people whose depression has responded to treatment, what psychological and psychosocial strategies are effective in preventing relapse (including maintenance treatment)?

C Pharmacological/physical Interventions

- C1 In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), which drugs (either not covered by the original guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo: C1
- TCAs
 - duloxetine
 - desvenlafaxine
 - escitalopram
 - agomelatine
 - St John's wort
 - antipsychotics (eg quetiapine)
- C2 In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), to what extent do the following factors affect the choice of drug: C2
- adverse events (in particular, cardiotoxicity), including long-term adverse events
 - discontinuation problems
- C3 In the pharmacological treatment of depression, what are the most effective strategies for treating patients experiencing treatment side-effects, including sexual dysfunction and weight gain?

- C4 In people whose depression has responded to treatment, what strategies are effective in preventing relapse (including maintenance treatment)? C3
C6
- C5 In people whose depression has atypical features, what are the most effective treatment strategies? C6
- C6 In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), do any of the following improve outcomes compared with other interventions: C7
A9
- ECT
 - TMS (integrate NICE IP)
 - light therapy
 - VNS
 - neurosurgery (don't review but mention)
 - deep brain stimulation
- C7 For people with depression (major depressive disorder, dysthymia etc), who are receiving pharmacological treatment, does therapeutic drug monitoring improve outcomes?
- C8 What are appropriate ways to promote adherence? (Link to forthcoming NICE guideline)
- C9 In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and minor depression), how can equal access to services for all be ensured? [what promotes access to effective care particularly for people with learning difficulties, acquired cognitive impairment and language difficulties?] A9

D General

- D1 In the treatment of depression, which patient characteristics predict response and relapse? Eg childhood trauma, age of onset, number of previous episodes, gender
- D2 In the treatment of depression, are there specific clinician approaches which improve outcomes?

Appendix 8: Search strategies for the identification of clinical studies

1. General search strategies

a. MEDLINE, EMBASE, PsycINFO, CINAHL - Ovid interface

- 1 (depression or depressive disorder or depression, postpartum or depressive disorder, major or dysthymic disorder or mood disorders or seasonal affective disorder).sh,id.
- 2 (affective disorders or depression or depression, postpartum or depression, reactive or dysthymic disorder or seasonal affective disorder).sh,id.
- 3 (depression or agitated depression or atypical depression or depressive psychosis or dysphoria or dysthymia or endogenous depression or involuntional depression or major depression or masked depression or melancholia or mood disorder or mourning syndrome or organic depression or postoperative depression or premenstrual dysphoric disorder or pseudodementia or puerperal depression or reactive depression or recurrent brief depression or seasonal affective disorder).sh,id. or "mixed anxiety and depression "/ or "mixed depression and dementia "/
- 4 (affective disorders or anaclitic depression or dysthymic disorder or endogenous depression or major depression or postpartum depression or reactive depression or recurrent depression or treatment resistant depression or atypical depression or pseudodementia or sadness or seasonal affective disorder).sh,id. or "depression (emotion)"/
- 5 (depress\$ or dysphori\$ or dysthym\$ or melanchol\$ or seasonal affective disorder\$).tw.
- 6 or/1-5

b. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials - Wiley Interscience interface

- #1 MeSH descriptor Depression, this term only
- #2 MeSH descriptor Depressive Disorder explode all trees
- #3 MeSH descriptor Mood Disorders, this term only
- #4 (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ti or (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ab
- #5 (#1 OR #2 OR #3 OR #4)

[note: with respect to 1b as outlined above - this search was generated for the DCHP team and was sifted for relevance to the clinical areas of both this and the DCHP guideline.]

2. *Systematic review search filters*

a. MEDLINE, EMBASE, PsycINFO, CINAHL - Ovid interface

- 1 (literature searching or (systematic review\$ or metaanal\$ or metaanal\$)).sh,id.
- 2 ((analy\$ or assessment\$ or evidence\$ or methodol\$ or qualitativ\$ or quantativ\$ or systematic\$) adj5 (overview\$ or review\$)).tw. or ((analy\$ or assessment\$ or evidence\$ or methodol\$ or quantativ\$ or qualitativ\$ or systematic\$).ti. and review\$.ti,pt.) or (systematic\$ adj5 search\$).ti,ab.
- 3 ((electronic database\$ or bibliographic database\$ or computeri?ed database\$ or online database\$).tw,sh. or (bids or cochrane or index medicus or isi citation or psyclit or psychlit or scisearch or science citation or (web adj2 science)).tw. or cochrane\$.sh.) and (review\$.ti,ab,sh,pt. or systematic\$.ti,ab.)
- 4 (metaanal\$ or meta anal\$ or metasynthes\$ or meta synthes\$).ti,ab.
- 5 (research adj (review\$ or integration)).ti,ab.
- 6 reference list\$.ab.
- 7 bibliograph\$.ab.
- 8 published studies.ab.
- 9 relevant journals.ab.
- 10 selection criteria.ab.
- 11 (data adj (extraction or synthesis)).ab.
- 12 (handsearch\$ or ((hand or manual) adj search\$)).ti,ab.
- 13 (mantel haenszel or peto or dersimonian or der simonian).ti,ab.
- 14 (fixed effect\$ or random effect\$).ti,ab.
- 15 (systematic\$ or meta\$).pt. or (literature review or meta analysis or systematic review).md.
- 16 ((pool\$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
- 17 or/1-16

3. *Randomised controlled trial search filters*

a. MEDLINE, EMBASE, PsycINFO, CINAHL - Ovid interface

- 1 exp clinical trial/ or exp clinical trials/ or exp clinical trials as topic/ or exp controlled clinical trials/
- 2 (placebo\$1 or random allocation or random assignment or random sample or random sampling or randomization).sh,id.
- 3 (double blind\$ or single blind\$ or triple blind\$).sh,id.
- 4 (crossover procedure or crossover design or cross over studies).sh,id.
- 5 (clinical adj2 trial\$).tw.
- 6 (crossover or cross over).tw.
- 7 (((single\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$ or dummy)) or (singleblind\$ or doubleblind\$ or trebleblind\$)).tw.
- 8 (placebo\$ or random\$).mp.

- 9 (clinical trial\$ or controlled clinical trial\$ or random\$).pt. or treatment outcome\$.md.
- 10 animals/ not (animals/ and human\$.mp.)
- 11 animal\$/ not (animal\$/ and human\$/)
- 12 (animal not (animal and human)).po.
- 13 (or/1-9) not (or/10-12)

Details of additional searches undertaken to support the development of this guideline are available on request.

Appendix 9: Clinical study data extraction form

Topic Area:		Report reference ID:			
Comparisons:					Total N
Ref List checked		Rev Man		Study Dbase	
Data Checked		Reference Manager updated		Excluded (record reason in Notes below)	

Randomised?		Blind?			
Age:		Young/Elderly (mean age over 65)	Mean Age	% women	
Setting:		In/Out/Mixed/Primary Care (80% patients)			
Analysis:		Completer/ITT (continuous data)			
Diagnosis				% comorbid Axis I	
				% cormobid Axis II	
Mean baseline					

Trial length:
Interventions (Dose):
1
2
3

Notes:

Appendix 10: Quality checklists for clinical studies and reviews

Completed by:						Report reference ID:						
1 TREATMENT GROUP:												
Leaving treatment early (any reason)			Leaving treatment early (side effects)			Side Effects (total number reporting)			Remission [non-remission]			
<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		
Definition of remission												
Definition of response												
Post-treatment means												
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
Other data	Response [non-response]											
	<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>

2 TREATMENT GROUP:												
Leaving treatment early (any reason)			Leaving treatment early (side effects)			Side Effects (total number reporting)			Remission [non-remission]			
<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		
Definition of remission												
Definition of response												
Post-treatment means												
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
Other data												
	<i>n</i>	<i>N</i>		<i>n</i>	<i>N</i>		<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>

Comparisons entered:

3 TREATMENT GROUP:												
Leaving treatment early (any reason)		Leaving treatment early (side effects)			Side Effects (total number reporting)			Remission [non-remission]				
<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	
Definition of remission												
Definition of response												
Post-treatment means												
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
Other data												
	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>		

4 TREATMENT GROUP:												
Leaving treatment early (any reason)		Leaving treatment early (side effects)			Side Effects (total number reporting)			Remission [non-remission]				
<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	
Definition of remission												
Definition of response												
Post-treatment means												
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>
Other data												
	<i>n</i>	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>		

Appendix 11: The classification of depression and depression rating scales/questionnaires

Background

This paper sets out an approach to the classification of depression that was used in the development of the guideline (including the analysis of the evidence, the development of recommendations) and will be of value in routine clinical use.

Depression is a heterogeneous disorder in which a number of underlying presentations may share a common phenomenology but have different aetiologies. Despite considerable work on the aetiology of depression including neurobiological, genetic and psychological studies no reliable classificatory system has emerged which links either to the underlying aetiology or which has proven strongly predictive of response to treatment. A number of classification systems/sub-groupings have been used including reactive and endogenous depression, melancholia, atypical depression, seasonal affective disorder and dysthymia. These have been based on varying combinations of the nature, number, severity, pattern and duration of symptoms, and in some cases the assumed aetiology. Over time pragmatic definitions have emerged, enshrined in the current two major classification systems, DSM-IV (American Psychiatric Association 2000a) and ICD-10 (World Health Organisation 1992). These have defined a threshold of severity of clinical significance with further classification in terms of severity (e.g. mild, moderate or severe as adopted in DSM-IV with regard to major depressive disorder), duration and course of the disorder (e.g. recurrent, presence of residual symptoms) and subtype based on symptom profile (e.g. melancholic, atypical). Other aspects of depression such as response to treatment (e.g. treatment resistant, refractory) and aetiology (e.g. preceding life events) do not feature specifically in the classifications and lack accepted definitions, although are used in clinical practice. The classification has some use in describing likely outcome and course (Van et al 2008; Jackson et al 2007; Barrett et al 2001; Sullivan et al 2003; Khan et al 1991; Holma et al 2008; Conradi et al 2007; Blom et al 2007) although social support, social impairment or personality factors also need to be taken into account. Lower severity and duration of a depressive episode predicts, to some extent, a greater likelihood of spontaneous or earlier and eventual improvement whereas greater severity, chronicity and number of previous episodes predict a higher chance of subsequent relapse.

The lack of a highly reliable or valid classificatory system has significant and practical clinical consequences, particularly in primary care where the full range of depression presents. A major concern is whether depression should be classified using dimensions or categories. Categories help distinguish cases

from non-cases, whilst dimensions help identify severe disorder from mild (Cole et al, 2008). Clinicians are often required to make a categorical decisions – for example to treat with antidepressants or not, to refer for further interventions or not - and consequently there can be pressure to interpret data on a single dimension in a categorical way e.g. treat or not treat based solely on a symptom severity rating (e.g. a PHQ-9 score alone). This conflicts with the recognised need to take multiple factors/ dimensions into consideration within a consultation, including the patient view on the cause of symptoms and acceptable treatment, and in the guideline update a major challenge has been to provide a useful categorisation which adequately captures the complexity.

Classification of Depression and NICE Guidance

The approach adopted in the 2004 NICE depression guideline was based on ICD-10 and rested on a dimensional approach based on a symptom count further elaborated by taking into account the presence of social role impairment and the duration of both symptoms and social impairment. The subsequent categorisation of depression into mild, moderate and severe has led to a number of concerns in practice. First this classification appears to have often been implemented with an emphasis on a symptom count alone with other important factors such as duration and social impairment ignored (although it should be noted that in general there is a relationship between the number of symptoms and severity of functional impairment (Faravelli et al, 1996). Second it implies that the different symptoms experienced are equivalent, although in fact, symptom patterns may be important and, third, it does not take into account illness duration and course. This tendency may be exacerbated by the use of measures such as the Patient Health Questionnaire (PHQ-9, Kroenke et al 2001) or Hospital Anxiety and Depression Scale (HADS Zigmond & Snaith 1983) under the Quality and Outcomes Framework (Department of Health 2004).

A drawback inherent in using ICD-10 depression criteria is that most of the treatment research on which the guideline has to be based uses DSM-IV or previous, essentially similar, versions of DSM (DSM-III, and DSM-III-R).criteria. As discussed below, the criteria are similar but not identical, and this has particular relevance for the ‘threshold’ of the diagnosis of clinically significant depressive episode and therefore what is considered subthreshold or minor depression.

Diagnosis of a depressive/ major depressive episode

The criteria for diagnosing depressive episodes in ICD-10 and DSM-IV overlap considerably but have some differences of emphasis. In ICD-10 the patient must have two of the first three symptoms (depressed mood, loss of interest in everyday activities, reduction in energy) plus at least 2 of the remaining 7 symptoms, whilst in DSM-IV the patient must have five or more

out of 9 symptoms with at least at least one from the first two (depressed mood and loss of interest). Both diagnostic systems require symptoms to have been present for at least 2 weeks to make a diagnosis (but can be shorter in ICD10 if symptoms are unusually severe or of rapid onset). In both ICD-10 and DSM-IV the symptoms must result in impairment of functioning which increases with the episode severity. Table 1 compares the symptoms required in ICD-10 and DSM-IV.

Table 1 Comparison of depression symptoms in ICD-10 and DSM-IV

ICD-10	DSM-IV major/minor depressive disorder
Depressed mood*	Depressed mood by self-report or observation made by others*
Loss of interest*	Loss of interest or pleasure*
Reduction in energy*	Fatigue/loss of energy
Loss of confidence or self-esteem	Worthlessness/excessive or inappropriate guilt
Unreasonable feelings of self-reproach or inappropriate guilt	
Recurrent thoughts of death or suicide	Recurrent thoughts of death, suicidal thoughts or actual suicide attempts
Diminished ability to think/concentrate or indecisiveness	Diminished ability to think/concentrate or indecisiveness
Change in psychomotor activity with agitation or retardation	Psychomotor agitation or retardation
Sleep disturbance	Insomnia/hypersomnia
Change in appetite with weight change	Significant appetite and/or weight loss

* core symptoms

Determining severity of a depressive/major depressive episode

Both ICD-10 and DSM-IV classify clinically significant depressive episodes as mild, moderate and severe based on the number, type and severity of symptoms present and degree of functional impairment. Table 2 shows the number of symptoms required by each diagnostic system which are less specific DSM-IV. The prescriptive symptom counting approach of ICD-10 tends to lend itself to using symptom counting alone to determine severity.

Table 2 Number of symptoms required in ICD-10 and DSM-IV for a diagnosis of depressive episode/major depression (but note they also need assessment of severity and functional impairment to ascertain diagnosis and severity)

	ICD-10 depressive episode	DSM-IV major depression
Mild	4	Minimal above the minimum (5)
Moderate	5-6	Between mild and severe

Severe	7+	Several symptoms in excess of 5
--------	----	---------------------------------

As ICD-10 requires only 4 symptoms for a diagnosis of a mild depressive episode, it can identify more people as having a depressive episode compared with a DSM-IV major depressive episode. One study in primary care in Europe identified 2 to 3 times more people as depressed using ICD-10 criteria compared with DSM-IV (11.3% v 4.2%) (Wittchen et al., 2001). However another study in Australia (Andrews et al 2008) found similar rates using the two criteria (6.8% v 6.3%) but slightly different populations were identified (83% concordance) which appears to be related to the need for only one of 2 core symptoms for DSM-IV but 2 out of 3 for ICD-10. These studies emphasise that, although similar, the two systems are not identical and that this is particularly apparent at the threshold taken to indicate clinical significance.

Diagnosis of minor depressive disorder

Given how common milder forms of depression are, and the problems inherent in defining a 'threshold' of clinical significance given the diagnostic system differences and the lack of any natural discontinuity identifying a critical threshold (Andrews et al 2008), the current guideline has broadened its scope to include depression that is 'subthreshold', ie does not meet the full criteria for a depressive/major depressive episode. A further reason is that it has been increasingly recognised as causing considerable morbidity and human and economic costs and is more common in those with a history of major depression and is a risk factor for future major depression (Rowe & Rapaport, 2006).

There is no accepted classification for this in the current diagnostic systems with the closest being minor depression, a research diagnosis in DSM-IV. At least two but less than 5 symptoms are required of which one must be depressed mood or diminished interest. This includes ICD-10 depressive episode with 4 symptoms and, given the practical difficulty and inherent uncertainty in deciding thresholds for significant symptom severity and disability, there is no natural discontinuity between minor depression and mild major depression in routine clinical practice.

Both DSM-IV and ICD-10 do have the category of dysthymia, which consists of depressive symptoms which are sub-threshold for major depression but which persist (by definition for more than 2 years). There appears to be no empirical evidence that dysthymia is distinct from minor depression apart from duration of symptoms.

ICD10 has a category of mixed anxiety and depression, which is less clearly defined than minor depression, and is largely a diagnosis of exclusion in those with anxiety and depressive symptoms sub-threshold for specific

disorders. Not unexpectedly it appears to be a heterogeneous category with a lack of diagnostic stability over time (Barkow et al 2004; Wittchen et al 2001). For this reason it has not been included in this guideline.

Duration

The duration of a depressive episode can vary considerably between individuals. The average course of an untreated depressive episode is between 6 and 8 months with much of the improvement occurring in the first 3 months, and 80% recovered by one year (Coryell et al, 1994). There is evidence to suggest that patients who do not seek treatment for their depression may recover more quickly than those who seek but do not receive treatment (Posternak et al 2006). There is also some evidence to suggest that people who do not seek help have a shorter mean duration of depressive episode (Posternak et al 2006).

Traditionally the minimum duration of persistent symptoms for major depression is 2 weeks and for chronic depression (or dysthymia) 2 years. These conventional definitions have been adopted in the absence of good evidence as there is only a modest empirical base for the minimum duration (e.g. Angst & Merikangas, 2001) and none that we could find for the 'cut-off' between acute and chronic depression. As with severity, duration is better thought of as a dimension with a decreased likelihood of remission with increasing chronicity over a given time frame (Van et al 2008). The conventional criteria are therefore better viewed as guides rather than cut-offs. It is likely that the minimum duration after which therapy provides more benefit than occurs by spontaneous improvement is somewhat longer than 2 weeks (possibly 2-3 months, Posternak et al 2006) but this has never been tested empirically. By 2 years it does appear that outcome is poorer supporting consideration of chronicity in describing the disorder; nevertheless the point at which acute becomes chronic is not clear, and indeed may not be a meaningful question. There is some evidence that outcome is poorer after about 1 year (eg Khan et al 1991). However there seems little to be gained by redefining duration for the guideline as long as it is recognised that the conventional definitions are merely signposts to include consideration of duration in relation to outcome and need for treatment.

Course of Depression

An influential model of the course of major depression proposes that the onset of an episode of depression consist of a worsening of symptoms in a continuum going from depressive symptoms through to major depression. Phases of improvement with treatment consist of response (significant improvement) to remission (absence of depressive symptoms) which if stable for 4-6 months results in (symptomatic) recovery, meaning that the episode is over (Frank et al., 1991). It is important to distinguish this use of recovery from more recent concepts related to quality and meaning of life in spite of

continued symptoms. After recovery a further episode of depression is viewed as a recurrence to distinguish it from a relapse of the same episode. There has been no consensus as to how long a period of remission is needed to declare recovery; different definitions result in different definitions of episode length and time to full or sub-threshold depressive recurrence (Furukawa et al 2008). In practice it can therefore be difficult to distinguish between relapse and recurrence, particularly when people have mild residual symptoms. Follow-up studies of people with depression have shown that overall more time is spent with sub-threshold depressive symptoms than in major depression and there is a variable individual pattern ranging from persisting chronic major depression, through significant but not full improvement (partial remission), to full remission and recovery (Judd et al 1998). DSM-IV defines full remission when there has been an absence of symptoms for at least two months. For partial remission, full criteria for a major depressive episode are no longer met, or there are no substantial symptoms but two months have not yet passed. DSM-IV specifies 'With Full Inter-episode Recovery' if full remission is attained between the two most recent depressive episodes and 'Without Full Inter-episode Recovery' if full remission is not attained. In DSM-IV therefore separate episodes are distinguished by at least 2 months of not meeting major depression criteria which is in contrast to the more stringent ICD-10 requirements of 2 months without any significant symptoms. There is therefore some ambiguity as to whether full remission is required to define separate episodes.

Nevertheless the number of episodes and degree of symptom resolution have important implications for considering the course of an individual patient's depressive disorder. The risk of a further episode of major depression within a given time frame is greater with an increasing number of previous episodes (Solomon et al., 2000; Kessing & Andersen, 2005) and also if there has not been full remission/symptomatic recovery (Paykel et al., 1995; Kanai et al., 2003; Dombrowski et al., 2007). If someone presents with minor depressive symptoms it is therefore crucial to determine whether or not this directly follows an episode of major depression.

Depression subtypes

Different symptom profiles have been described and are included in the classification systems. In DSM-IV severe major depression can be without or with psychosis (psychotic depression) and there are specifiers which include melancholia, atypical features, catatonia, seasonal pattern (Seasonal Affective Disorder) and post-partum onset. ICD-10 also provides specifiers for psychotic and somatic symptoms, the latter similar to DSM-IV melancholia. These subtypes do not however form distinct categories (e.g. Kendell, 1968; Angst et al., 2007) and they add a further complexity to the diagnosis of depression. The Guideline Development Group judged that these specifiers are best considered where appropriate after the diagnosis of a depressive

disorder is made and we do not discuss them in detail here. Some specifiers, particularly psychosis and seasonal pattern, have potential treatment implications and are considered in the Guideline where evidence is available.

Classification of Depression in the Depression Guideline Update

The depression classification system adopted for the Depression Guideline update had to meet a number of criteria:

- The use of a system that reflects the non-categorical, multidimensional nature of depression
- The use of a system which makes best use of the available evidence on both efficacy and effectiveness
- The use of a system that could be distilled down for practical day-to-day use in healthcare settings without potentially harmful oversimplification or distortion
- The use of terms that can be easily understood and are not open to misinterpretation by a wide range of healthcare staff and service users
- The use of a system which would facilitate the generation of clinical recommendations

These criteria led the Guideline Development Group to the adoption of a classificatory system for depression based on DSM-IV criteria. When assessing an individual it is important to assess 3 dimensions to diagnose a depressive disorder, a) severity (symptomatology and social impairment), b) duration, and c) course as linked, but separate, factors. In addition there was recognition that a single dimension of severity was insufficient to fully capture its multidimensional nature.

As discussed above the following depressive symptoms require assessment to determine the presence of major depression. **They need to be experienced to a sufficient degree of severity and persistence to be counted as definitely present.** At least one core symptom is required; both core symptoms would be expected in moderate and severe major depression.

Core symptoms of depression

- 1) depressed mood most of the day, nearly every day
- 2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day

Somatic symptoms

- 3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- 4) insomnia or hypersomnia nearly every day

- 5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- 6) fatigue or loss of energy nearly every day

Other symptoms

- 7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- 8) diminished ability to think or concentrate, or indecisiveness, nearly every day
- 9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism) or better accounted for by Bereavement.

There is evidence that doctors have difficulty in remembering the nine DSM-IV depressive symptoms (Krupinski & Tiller, 2001; Rapp & Davis, 1989) which has important implications for the application of these criteria. In addition there is need to be able consistently diagnose depression in patients where physical symptoms may be due to medical illness. Zimmermann et al (2006) and Andrews et al (2008) have demonstrated that, compared with the diagnosis using the full DSM-IV criteria, there is a high agreement (94%-97%) and good sensitivity (93%) and specificity (95-98%) when a cut-down list (excluding the 4 somatic symptoms) is used with a requirement for 3 out of the remaining 5 symptoms.

It is therefore possible to use an abridged list, first asking about the two core symptoms of depression:

- 1) Persistent depressed mood
- 2) Markedly diminished interest or pleasure

Then if either or both are present going on to ask about:

- c) Feelings of worthlessness or guilt
- d) Impaired concentration
- e) Recurrent thoughts of death or suicide

Three or more symptoms indicate a very high probability of major depression. This does not however replace the need to go on to assess somatic symptoms as an aid to determining severity and to help judge subsequent response to treatment. This limits the usefulness of the abridged list in practice and it may be most useful when there are confounding somatic symptoms due to physical illness.

a) Severity

While recognising that severity is not a unitary dimension it is practically useful to make a judgement of severity consisting at least of number of symptoms, severity of individual symptoms and functional impairment. This leads to a classification of depression into the following severity groupings based on DSM-IV criteria which should be viewed as exemplars not discrete categories. In the guideline the term depression refers to major depression except where qualified by the term minor:

- 1) **minor** depression typically consisting of 2-4 symptoms with maintained function.
- 2) **mild** depression where there are few, if any, symptoms in excess of those required to make the diagnosis and symptoms result in only minor functional impairment.
- 3) **moderate** depression where symptoms or functional impairment are between 'mild' and 'severe'. Some symptoms would be expected to be marked.
- 4) **severe** depression where there are several symptoms in excess of those required to make the diagnosis and the symptoms markedly interfere with functioning. Some symptoms would be expected to be severe.

In addition psychotic symptoms can occur and are usually associated with severe depression.

Symptom severity and degree of functional impairment correlate highly (e.g. Zimmerman et al 2007) but in individual cases this may not be the case and some mildly symptomatic individuals may have marked functional impairment while some people who are severely symptomatic may, at least for a time, maintain good function, employment etc.

b) Duration

By convention the duration of persistent symptoms is required to be at least 2 weeks and once they have persisted for 2 years or more they are called chronic in the case of major depression or dysthymia in the case of minor depression. While the specific values may not be particularly helpful there are insufficient empirical data to change these.

- 1) **Acute** - meeting one of the severity criteria for a minimum of 2 weeks and not longer than 2 years
- 2) **Chronic** - meeting one of the severity criteria for longer than 2 years

Given that the cut-off of 2 years is arbitrary it is best in practice to consider the specific duration and degree of persistence of symptoms for an individual in the context of the severity and course of the disorder

c) Course

This was not explicitly considered as a classificatory issue in the last guideline but it has important treatment implications, particularly for the likelihood of relapse/recurrence.

1) Number of lifetime depressive episodes and the interval between recent episodes. The number varies from a single/first episode to increasingly frequent recurrences. At least two months of full or partial remission is required to distinguish episodes.

2) Stage of episode. This refers to where an individual is in the course of their depression. In an episode it is useful to determine if the depression is worsening, static or improving and whether mild depressive symptoms reflect minor depression or partial remission from prior major depression.

Conventionally classification has distinguished between a single episode and two or more episodes (recurrent depression) irrespective of how long there has been between episodes and how many recurrences have occurred. However someone who has had two episodes separated by decades has a different clinical course to someone with three episodes in a few years and therefore noting the number of episodes and their recent pattern is important. There is uncertainty as to how long, and how well, an individual needs to be to distinguish between different episodes of depression and a fluctuating course of a single episode. In practice this is less important than recognising the risk of persistent symptoms and of major depressive relapse/recurrence.

Classification in relation to depression rating scales and questionnaires.

Depression rating scales and questionnaires give ranges that are proposed to describe different severities of depression. Some of these were described in the previous guideline (Appendix 13). In reconsidering this for the update it quickly became apparent, not only that there is no consensus for the proposed ranges, but also that the ranges in different rating scales and questionnaires do not correspond with each other. In addition there is a variable degree of correlation between different scales which indicates that they do not measure precisely the same aspects of depression. When these factors are added to the need to consider more than symptoms in determining severity, and more than severity in considering diagnosis, the guideline development group was concerned not to perpetuate a spurious precision in relating scores in depression rating scales and questionnaires to the diagnosis or severity of depression which must in the end be a clinical judgement.

Nevertheless it is necessary try and translate trial evidence (which may only provides rating scales or questionnaire scores) into a meaningful clinical context as well as relating this guideline update to the previous guideline which used the American Psychiatric Association (APA 2000b) cut-offs. The change to DSM-IV-based diagnosis and the inclusion of minor depression in the update means that the descriptors of ranges previously given are no longer tenable. Table 3 gives the descriptors and ranges used in this guideline update, with the important caveat that these must not be taken as clear cut-offs or a short-cut to classify people with depression.

Table 3: Levels of depression in relation to HRSD and BDI in the guideline update compared with those suggested by APA 2000.

17-item Hamilton Rating Scale for Depression					
Guideline update	Not depressed	Minor	Mild	Moderate	Severe
APA 2000b ¹	Not depressed	Mild	Moderate	Severe	Very Severe
Score	0-7	8-13	14-18	19-22	23+
Beck Depression Inventory					
Guideline update	Not depressed	Minor	Mild to Moderate	Moderate to Severe	
APA 2000b ¹	Not depressed	Mild	Moderate	Severe	
Guideline update	0-9	10-16	17-29	30+	

¹ Used in the last guideline

Implications of the proposed classification

An important implication is that symptom counts alone (e.g. using the PHQ-9) should not be used to determine the presence or absence of a depressive disorder although this is an important part of the assessment. The score on a rating scale or questionnaire can contribute to the assessment of depression and rating scales are also useful to monitor treatment progress.

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

Diagnosis using the three aspects listed above (severity, duration, course) necessarily only provides a partial description of the individual experience of depression. Depressed people vary in the pattern of symptoms they experience, their family history, personalities, pre-morbid difficulties (e.g. sexual abuse), psychological mindedness and current relational and social problems – all of which may significantly affect outcomes. It is also common for depressed people to have a comorbid psychiatric diagnosis, such as anxiety, social phobia, panic and various personality disorders (Brown et al., 2001), and physical co-morbidity, or for the depression to occur in the context of bipolar disorder (not considered in this guideline). Gender and socio-economic factors account for large variations in the population rates of depression, and few studies of pharmacological, psychological or indeed other treatments, for depression control for or examine these variations. This emphasises that choice of treatment is a complex process and involves negotiation and discussion with patients, and, given the current limited knowledge about what factors are associated with better antidepressant or psychotherapy response, most decisions will rely upon clinical judgement and patient preference until we have further research evidence. Trials of treatment in unclear cases may be warranted but the uncertainty needs to be discussed with the patient and benefits from treatment carefully monitored.

References

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Appendix 12: Search strategies for the identification of health economics evidence

Search strategies for the identification of health economics and quality-of-life studies.

1. General search strategies

a. MEDLINE, EMBASE, PsycINFO, CINAHL – Ovid interface

- 1 (depression or depressive disorder or depression, postpartum or depressive disorder, major or dysthymic disorder or mood disorders or seasonal affective disorder).sh,id.
- 2 (affective disorders or depression or depression, postpartum or depression, reactive or dysthymic disorder or seasonal affective disorder).sh,id.
- 3 (depression or agitated depression or atypical depression or depressive psychosis or dysphoria or dysthymia or endogenous depression or involuntional depression or major depression or masked depression or melancholia or mood disorder or mourning syndrome or organic depression or postoperative depression or premenstrual dysphoric disorder or pseudodementia or puerperal depression or reactive depression or recurrent brief depression or seasonal affective disorder).sh,id. or "mixed anxiety and depression "/ or "mixed depression and dementia "/
- 4 (affective disorders or anaclitic depression or dysthymic disorder or endogenous depression or major depression or postpartum depression or reactive depression or recurrent depression or treatment resistant depression or atypical depression or pseudodementia or sadness or seasonal affective disorder).sh,id. or "depression (emotion)"/
- 5 (depress\$ or dysphori\$ or dysthym\$ or melanchol\$ or seasonal affective disorder\$).tw.
- 6 or/1-5

b. NHS Economic Evaluation Database, Health Technology Assessment Database – Wiley interface

- #1 MeSH descriptor Depression, this term only
- #2 MeSH descriptor Depressive Disorder explode all trees
- #3 MeSH descriptor Mood Disorders, this term only
- #4 (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ti or (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ab
- #5 (#1 OR #2 OR #3 OR #4)

c. OHE HEED – Wiley interface

- 1 AX=depress*
- 2 AX=dysthym*
- 3 AX=dysphori*
- 4 AX=seasonal AND affective AND disorder*
- 5 CS=1 OR 2 OR 3 OR 4

2 Health economics and quality-of-life search filters

a. MEDLINE, EMBASE, PsycINFO, CINAHL – Ovid interface

- 1 (budget\$ or cost\$ or economic\$ or expenditure\$ or fee\$1 or fees\$ or financ\$ or health resource\$ or money or pharmaco-economic\$ or socioeconomic\$).hw,id.
- 2 (health care rationing or health priorities or medical savings accounts or quality adjusted life years or quality of life or resource allocation or value of life).sh,id. or "deductibles and coinsurance"/ or "health services needs and demand"/
- 3 (budget\$ or cost\$ or econom\$ or expenditure\$ or financ\$ or fiscal\$ or funding or pharmaco-economic\$ or price or prices or pricing).tw.
- 4 (QALY\$ or lifeyear\$ or life year\$ or ((qualit\$3 or value) adj3 (life or survival))).tw.
- 5 ((burden adj3 (disease or illness)) or (resource adj3 (allocation\$ or utilit\$)) or (value adj5 money)).tw.
- 6 ec.fs.
- 7 (or/1-6)

[note: with respect to 2a above - search request 6 was ANDed with or/1-4 from the general search strategy only.]

Appendix 13: Quality checklist for economic studies

Author:

Date:

Title:

		Yes	No	NA
Study design				
1	The research question is stated	<input type="checkbox"/>	<input type="checkbox"/>	
2	The economic importance of the research question is stated	<input type="checkbox"/>	<input type="checkbox"/>	
3	The viewpoint(s) of the analysis are clearly stated and justified	<input type="checkbox"/>	<input type="checkbox"/>	
4	The rationale for choosing the alternative programmes or interventions compared is stated	<input type="checkbox"/>	<input type="checkbox"/>	
5	The alternatives being compared are clearly described	<input type="checkbox"/>	<input type="checkbox"/>	
6	The form of economic evaluation is stated	<input type="checkbox"/>	<input type="checkbox"/>	
7	The choice of form of economic evaluation used is justified in relation to the questions addressed	<input type="checkbox"/>	<input type="checkbox"/>	
Data collection				
1	The source of effectiveness estimates used is stated	<input type="checkbox"/>	<input type="checkbox"/>	
2	Details of the design and results of effectiveness study are given (if based on a single study)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	The primary outcome measure(s) for the economic evaluation are clearly stated	<input type="checkbox"/>	<input type="checkbox"/>	
5	Methods to value health states and other benefits are stated	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Details of the subjects from whom valuations were obtained are given	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Indirect costs (if included) are reported separately	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	The relevance of indirect costs to the study question is discussed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Quantities of resources are reported separately from their unit costs	<input type="checkbox"/>	<input type="checkbox"/>	
10	Methods for the estimation of quantities and unit costs are described	<input type="checkbox"/>	<input type="checkbox"/>	
11	Currency and price data are recorded	<input type="checkbox"/>	<input type="checkbox"/>	
12	Details of currency, price adjustments for inflation or currency conversion are given	<input type="checkbox"/>	<input type="checkbox"/>	
13	Details of any model used are given	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14	The choice of model used and the key parameters on which it is based are justified	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Analysis and interpretation of results

- | | | | | |
|----|---|--------------------------|--------------------------|--------------------------|
| 1 | The time horizon of costs and benefits is stated | <input type="checkbox"/> | <input type="checkbox"/> | |
| 2 | The discount rate(s) is stated | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 | The choice of rate(s) is justified | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4 | An explanation is given if costs or benefits are not discounted | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5 | Details of statistical tests and confidence intervals are given for stochastic data | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6 | The approach to sensitivity analysis is given | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7 | The choice of variables for sensitivity analysis is given | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8 | The ranges over which the variables are varied are stated | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9 | Relevant alternatives are compared | <input type="checkbox"/> | <input type="checkbox"/> | |
| 10 | Incremental analysis is reported | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11 | Major outcomes are presented in a disaggregated as well as aggregated form | <input type="checkbox"/> | <input type="checkbox"/> | |
| 12 | The answer to the study question is given | <input type="checkbox"/> | <input type="checkbox"/> | |
| 13 | Conclusions follow from the data reported | <input type="checkbox"/> | <input type="checkbox"/> | |
| 14 | Conclusions are accompanied by the appropriate caveats | <input type="checkbox"/> | <input type="checkbox"/> | |

Validity score: Yes/No/NA:

Appendix 14: Data extraction form for economic studies

Reviewer:

Date of Review:

Authors:

Publication Date:

Title:

Country:

Language:

Economic study design:

- | | |
|------------------------------|------------------------------|
| <input type="checkbox"/> CEA | <input type="checkbox"/> CCA |
| <input type="checkbox"/> CBA | <input type="checkbox"/> CA |
| <input type="checkbox"/> CUA | |
| <input type="checkbox"/> CMA | |

Modelling:

- No Yes

Source of data for effect size measure(s):

- | | |
|--|--|
| <input type="checkbox"/> RCT | <input type="checkbox"/> Meta-analysis |
| <input type="checkbox"/> Quasi experimental study | <input type="checkbox"/> RCT |
| <input type="checkbox"/> Cohort study | <input type="checkbox"/> Quasi experimental study |
| <input type="checkbox"/> Mirror image (before-after) study | <input type="checkbox"/> Cohort study |
| <input type="checkbox"/> Expert opinion | <input type="checkbox"/> Mirror image (before-after) study |

Comments _____

Primary outcome measure(s) (please list):

Interventions compared (please describe):

Treatment: _____

Comparator: _____

Setting (please describe):

Patient population characteristics (please describe):

Perspective of analysis:

- Societal
- Patient and family
- Health care system
- Health care provider
- Third party payer
- Other: _____

Time frame of analysis: _____

Cost data:

- Primary
- Secondary

If secondary please specify: _____

Costs included:

- | Direct medical | Direct non-medical | Lost productivity |
|---|--|--|
| <input type="checkbox"/> direct treatment illness | <input type="checkbox"/> social care | <input type="checkbox"/> income forgone due to illness |
| <input type="checkbox"/> inpatient death | <input type="checkbox"/> social benefits | <input type="checkbox"/> income forgone due to death |
| <input type="checkbox"/> outpatient caregiver | <input type="checkbox"/> travel costs | <input type="checkbox"/> income forgone by caregiver |
| <input type="checkbox"/> day care | <input type="checkbox"/> caregiver out-of-pocket | |
| <input type="checkbox"/> community health care | <input type="checkbox"/> criminal justice | |
| <input type="checkbox"/> medication | <input type="checkbox"/> training of staff | |

Or

- staff

- medication
- consumables
- overhead
- capital equipment
- real estate

Others: _____

Currency: _____

Year of costing: _____

Was discounting used?

Yes, for benefits and costs

Yes, but only for costs

No

Discount rate used for costs: _____

Discount rate used for benefits: _____