Depression

Please note: Amendments to recommendations concerning venlafaxine

On 31 May 2006 the MHRA issued revised prescribing advice for venlafaxine*. NICE has made amendments to the NICE guideline, the Quick Reference Guide and the Information for the Public to bring them into line with the new advice but has not made changes to other areas where new evidence may be available. NICE expects to make a decision on a full update later in 2007.

The amended guidance is available at: http://guidance.nice.org.uk/CG23

The full guideline itself (this document) has not been amended.

***see:**
http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023843&ssTargetNodeId+389

National Clinical Practice Guideline Number 23

Depression: Management of depression in primary and secondary care

National Clinical Practice Guideline Number 23

developed by

National Collaborating Centre for Mental Health

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Royal College of Psychiatrists' Research Unit
6th Floor
83 Victoria Street
London
SW1H 0HW

commissioned by National Institute for Clinical Excellence
MidCity Place
London
WC1V 6NA
www.nice.org.uk

published by The British Psychological Society
St Andrews House
48 Princess Road East
Leicester
LE1 7DR
www.bps.org.uk
and
The Royal College of Psychiatrists
17 Belgrave Square
London
SW1X 8PG
www.rcpsych.ac.uk

The British Psychological Society

Contents

Depression Guideline Development Group Members

Professor Sir David Goldberg

Emeritus Professor of Psychiatry, Institute of Psychiatry, King's College, London.
Chair, Guideline Development Group.

Mr Stephen Pilling

Co-Director, National Collaborating Centre for Mental Health.
Director, Centre for Outcomes Research and Effectiveness, University College London.
Consultant Clinical Psychologist, Camden and Islington Mental Health and Social Care Trust.
Facilitator, Guideline Development Group.

Dr Tim Kendall

Co-Director, National Collaborating Centre for Mental Health.
Deputy Director, Royal College of Psychiatrists' Research Unit.
Medical Director and Consultant Psychiatrist, Community Health Sheffield NHS Trust.
Facilitator, Guideline Development Group.

Professor Nicol Ferrier

Head of School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne.
Lead, Topic Group on Pharmacology.

Mr Ted Foster

Patient.
National Advisory Panel Member – Mind Link.

Mr John Gates

Patient.
Trustee, National Mind.
Chair, Redcar & Cleveland Mind.

Professor Paul Gilbert

Professor of Clinical Psychology
Mental Health Research Unit, Kingsway Hospital, University of Derby.
Lead, Topic Group on Psychology.

Dr Paul Harvey

General Practitioner, Devonshire Green Medical Centre, Sheffield.

Dr Ian Hughes

Consultant Clinical Psychologist, Cardiff and Vale NHS Trust.

Mrs Carol Paton

Chief Pharmacist, Oxleas NHS Trust.

Mr Simon Rippon

Programme Co-ordinator, NIMHE Northwest Development Centre.

Mrs Kay Sheldon

Patient.

Dr Douglas Turkington

Senior Lecturer in Liaison Psychiatry, University of Newcastle upon Tyne,
Royal Victoria Infirmary.
Consultant Psychiatrist, Newcastle, North Tyneside and Northumberland Mental Health NHS Trust.

Professor Andre Tylee

Professor of Primary Care Mental Health, Institute of Psychiatry.
Lead, Topic Group on Service Interventions.

National Collaborating Centre for Mental Health staff

Ms Rachel Burbeck, Lead Systematic Reviewer.

Ms Michelle Clark, Project Manager (to September 2003).

Dr Cesar de Oliveira, Systematic Reviewer (November 2002 – October 2003).

Dr Catherine Pettinari, Senior Project Manager (from September 2003).

Ms Preethi Premkumar, Research Assistant.

Dr Judit Simon, Health Economist, Health Economics Research Centre, University of Oxford.

Dr Clare Taylor, Editor.

Ms Lisa Underwood, Research Assistant.

Dr Craig Whittington, Senior Systematic Reviewer.

Ms Heather Wilder, Information Scientist.

1 Introduction

This guideline has been developed to advise on the treatment and management of depression and related conditions. The guideline recommendations have been developed by a multidisciplinary group of healthcare professionals, researchers, patients and their representatives, after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high quality care for those with depression while also emphasising the importance of the experience of care for patients and carers.

1.1 National guidelines

1.1.1 What are clinical practice guidelines?

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

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

- Provide up-to-date evidence-based recommendations for the management of conditions and disorders by healthcare professionals
- Be used as the basis to set standards to assess the practice of healthcare professionals
- Form the basis for education and training of healthcare professionals
- Assist patients and carers in making informed decisions about their treatment and care
- Improve communication between healthcare professionals, patients and carers
- Help to identify priority areas for further research.

1.1.2 Uses and limitations of clinical guidelines

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

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

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

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

1.1.3 Why develop national guidelines?

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

NICE generates guidance in a number of different ways, two of which are relevant here. First, national guidance is produced by the Technology Appraisal Committee to give robust advice about a particular treatment, intervention, procedure or other health technology. Second, NICE commissions the production of national clinical practice

guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE established six National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare.

1.1.4 The National Collaborating Centre for Mental Health

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service-user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and led by a partnership between the Royal College of Psychiatrists' research unit (College Research Unit – CRU) and the British Psychological Society's equivalent unit (Centre for Outcomes Research and Effectiveness – CORE). Members of the NCCMH reference group come from the following organisations:

- Royal College of Psychiatrists (RCPsych)
- British Psychological Society (BPS)
- Royal College of Nursing (RCN)
- National Institute for Social Work (NISW)
- College of Occupational Therapists (COT), now replaced by the Clinical Effectiveness Forum for the Allied Health Professions (CEFAHP)
- Royal College of General Practitioners (RCGP)
- Royal Pharmaceutical Society (RPS)
- Rethink Severe Mental Illness
- Mind
- Centre for Evidence Based Mental Health (CEBMH)
- Centre for Economics in Mental Health (CEMH)
- Institute of Psychiatry (IoP).

The NCCMH reference group provides advice on a full range of issues relating to the development of guidelines, including the membership of experts, professionals, patients and carers within guideline development groups.

1.1.5 From national guidelines to local protocols

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving

commissioners of healthcare, primary care and specialist mental healthcare professionals, patients and carers should undertake the translation of the implementation plan into local protocols. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

1.1.6 Auditing the implementation of guidelines

This guideline identifies key areas of clinical practice and service delivery for local and national audit. Although the generation of audit standards is an important and necessary step in the implementation of this guidance, a more broadly based implementation strategy will be developed. Nevertheless, it should be noted that the Commission for Healthcare, Audit and Improvement (CHAI) will monitor the extent to which Primary Care Trusts (PCTs), trusts responsible for mental health and social care, and Health Authorities have implemented these guidelines.

1.2 The national depression guideline

1.2.1 Who has developed this guideline?

The 'Guideline Development Group' (GDG) was convened by the NCCMH based upon advice from the Centre's reference group representatives, and supported by funding from NICE. The GDG included members from the following professional groups: psychiatry, clinical psychology, pharmacy, nursing and general practice. In addition, the GDG included three patients.

Staff from the NCCMH provided leadership and support throughout the process of guideline development, undertaking systematic searches, information retrieval, appraisal and systematic review of the evidence. Members of the GDG received training in the process of guideline development from the Centre for Evidence-Based Mental Health (CEBMH), and the National Guidelines and Audit Patient Involvement Unit, which has been established by NICE. The National Guidelines Support and Research Unit, also established by NICE, provided advice and assistance regarding all aspects of the guideline development process.

All members of the group made formal declarations of interest at the outset, updated at every GDG meeting. GDG members met a total of 26 times throughout the process of guideline development. For ease of evidence identification and analysis, members of the GDG formed sub-groups, or 'topic groups', covering identifiable treatment approaches. Topic Groups were led by a national expert in the relevant field and supported by the NCCMH technical team, with additional expert advice from special advisers where necessary. Topic groups oversaw the production and synthesis of research evidence before presentation to the wider GDG. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

1.2.2 For whom is this guideline intended?

This guideline will be of relevance to all people with a diagnosis of depression aged 18 and over. This guideline will not explicitly provide guidance on the diagnosis or treatment of people with depression in the context of a separate physical or other primary mental disorder. These may be dealt with in a future guideline.

Although this guideline will briefly address the issue of diagnosis, it will not make evidence-based recommendations or refer to evidence regarding diagnosis, primary prevention or assessment. In sum, this guideline is intended for use by:

- Individuals with a diagnosis of depression aged 18 years and over and their families/carers
- Professional groups who share in the treatment and care for people with a diagnosis of depression, including psychiatrists, clinical psychologists, mental health nurses, community psychiatric nurses, other community nurses, social workers, counsellors, practice nurses, occupational therapists, pharmacists, general practitioners and others
- Professionals in other health and non-health sectors who may have direct contact with or are involved in the provision of health and other public services for those diagnosed with depression. These may include A&E staff, paramedical staff, prison doctors, the police and professionals who work in the criminal justice and education sectors
- Those with responsibility for planning services for people with a diagnosis of depression, and their carers, including directors of public health, NHS trust managers and managers in PCTs.

1.2.3 Specific aims of this guideline

The guideline makes recommendations and good practice points for pharmacological treatments and the use of psychological and service-level interventions in combination with pharmacological treatments in the three phases of care. Specifically it aims to:

- Evaluate the role of specific pharmacological agents in the treatment and management of depression
- Evaluate the role of specific psychological interventions in the treatment and management of depression
- Evaluate the role of specific service delivery systems and service-level interventions in the management of depression
- Integrate the above to provide best practice advice on the care of individuals with a diagnosis of depression through the different phases of illness, including the initiation of treatment, the treatment of acute episodes and the promotion of recovery
- Consider economic aspects of various standard treatments for depression.

1.2.4 Other versions of this guideline

There are other versions of *Depression: Management of Depression in Primary and Secondary Care*, including:

- The NICE guideline, which is a shorter version of this guideline, containing the key recommendations and all other recommendations (see Chapter 4)
- The quick reference guide, which is a summary of the main recommendations in the NICE guideline
- The information for the public, which describes the guidance using non-technical language. It is written chiefly for patients, but may also be useful for family members, advocates, or those who care for people with depression.

2 Depression

This guideline is concerned with the treatment and management of people with depression in primary and secondary care. Although the terminology and diagnostic criteria used for this heterogeneous group of related disorders has changed over the years, this guidance relates only to those identified by *The ICD-10 Classification of Mental and Behavioural Disorders* (ICD-10) (WHO, 1992), namely, depressive episode (F32), recurrent depressive episode (F33) and mixed anxiety and depressive disorder (F41.2). It should be noted that a sizeable quantity of the research forming the evidence base from which much of this guideline is drawn has used a similar classificatory system – the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (DSM-IV) (APA, 1994). The guideline does not address the management of related affective disorders such as bipolar disorder or dysthymia, nor does it provide specific guidance for post-natal depression.

2.1 The disorder

2.1.1 Symptoms, presentation and pattern of illness

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Distinguishing the mood changes between major depression and those occurring 'normally' remains problematic: persistence, severity, the presence of other symptoms and the degree of functional and social impairment form the basis of that distinction.

Commonly, mood and affect in a major depressive illness are unreactive to circumstance, remaining low throughout the course of each day, although for some people mood varies diurnally, with gradual improvement throughout the day only to return to a low mood on waking. Arguably as common, a person's mood may be reactive to positive experiences and events, although these elevations in mood are not sustained, with depressive feelings re-emerging, often quickly (Andrews & Jenkins, 1999).

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

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

Major depression is generally diagnosed when a persistent and unreactive low mood and an absence of positive affect are accompanied by a range of symptoms, the number and combination needed to make a diagnosis being operationally defined (ICD-10, WHO, 1992; DSM-IV, APA, 1994), although some people show an atypical presentation with reactive mood, increased appetite, weight gain and excessive sleepiness (Quitkin *et al.*, 1991).

In addition, those with a more severe and typical presentation, including marked physical slowness (or marked agitation) and a range of somatic symptoms, are often referred to as melancholic depressions, or depression with melancholia.

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

2.1.2 Course and prognosis

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

Although it is generally thought that depression is usually a time-limited disorder lasting up to six months with complete recovery afterwards, in the WHO study of mental disorders in 14 centres across the world, 66% of those suffering from depression were still found to satisfy criteria for a mental disorder a year later, and for 50% the diagnosis was depression. It is probable that widely differing rates between the clinics studied in these countries reflect true differences in prevalence in these clinics rather than differing concepts of depression between countries (Simon *et al.*, 2002). In the WHO study, episodes of depression that were either untreated by the GP or missed entirely had the same outlook as treated episodes of depression; however, they were milder at index consultation (Goldberg *et al.*, 1998). In a meta-analysis of 12 studies of depressed older adults, the outcomes for people with depression in the community were on average poor:

after two years, 20% had died and nearly 40% were still depressed (Cole *et al.*, 1999).

While around half of those affected by depression will have no further episodes, depressive illnesses, as with many other mental health problems such as schizophrenia, have a strong tendency for recurrence. At least 50% of people following their first episode of major depression will go on to have at least one more episode (Kupfer, 1991), with early onset depression (at or before 20 years of age) particularly associated with a significantly increased vulnerability to relapse (Giles *et al.*, 1989).

After the second and third episodes, the risk of further relapse rises to 70% and 90% respectively (Kupfer, 1991). Thus, while the outlook for a first episode is good, the outlook for recurrent episodes over the long term can be poor, with many patients suffering symptoms of depression over many years (Akiskal, 1986). Sometimes, recurrent episodes of depression will follow a seasonal pattern, receiving the label seasonal affective disorder.

The term 'treatment-resistant depression', used to describe depression that has failed to respond to two or more antidepressants at an adequate dose for an adequate duration given sequentially, is not especially helpful. It does not take into account depressive subtypes, makes no distinction between chronicity, relapse or recurrence, and fails to take into account what psychosocial factors may be preventing recovery or indeed whether the patient has had an adequate course of an appropriate psychotherapeutic treatment (Andrews & Jenkins, 1999).

2.1.3 Impairment and disability

Depression is the most common mental disorder in community settings, and is a major cause of disability across the world. In 1990 it was the fourth most common cause of loss of disability-adjusted life years in the world, and by 2020 it is projected to become the second most common cause (World Bank, 1993). In 1994 it was estimated that about 1.5 million disability-adjusted life years were lost each year in the west as a result of depression (Murray *et al.*, 1994). It is even more common in the developing world (for review, see Institute of Medicine *et al.*, 2001).

Apart from the subjective suffering experienced by people who are depressed, the impact on social and occupational functioning, physical health and mortality is substantial. The impact on physical health puts depression on a par with all the major chronic and disabling physical illnesses such as diabetes, arthritis and hypertension (Cassano & Fava, 2002). Depressive illnesses substantially reduce a person's ability to work effectively, with losses in personal and family income (and, therefore, tax revenues), and unemployment (with loss of skills from the workplace). Wider social effects include: greater dependence upon welfare and benefits with the inevitable impact upon self-esteem and self-confidence; social impairments, including reduced ability to communicate during the illness; disturbed relationships during and subsequent to an episode; and longer term changes in social functioning, especially for those who have a recurrent disorder. The stigma associated with mental health problems generally (Sartorius, 2002), and the public view that depression suggests a person is unbalanced, neurotic and irritating (Priest *et al.*, 1996), may account for the reluctance of depressed people to seek help (Bridges & Goldberg, 1987).

Mental disorders account for as much of the total disability in the population as physical disorders (Ormel & Costa e Silva 1995), and there is a clear dose-response relationship between illness severity and the extent of disability (ibid.). Depression and disability show synchrony of change (Ormel *et al.*, 1993), and onsets of depression are associated with onsets of disability, with an approximate doubling of both social and occupational disability (Ormel *et al.*, 1999).

Depression can also exacerbate the pain and distress associated with physical diseases, as well as adversely affecting outcomes. For example, in people with myocardial infarction (MI), death rates are significantly greater for those who are depressed following an MI, not only in the immediate post-MI period, but for the subsequent year (Lesperance & Frasure-Smith, 2000). In one community study, patients with cardiac disease who were depressed had an increased risk of death from cardiac problems compared with those without depression, and depressed people without cardiac disease also had a significantly increased risk of cardiac mortality (Pennix *et al.*, 2001). Similar findings for a range of physical illnesses also suggest an increased risk of death when comorbid depression is present (Cassano & Fava, 2002).

Suicide accounts for just under 1% of all deaths, and nearly two-thirds of this figure occur in depressed people (Sartorius, 2001). Sometimes depression may also lead to acts of violence against others, and may even include homicide. However, more common, and a greater cause of disability for people who are depressed, is the impact of depressive illnesses on social and occupational function (Ormel *et al.*, 1999). Marital and family relationships are frequently negatively affected, and parental depression may lead to neglect of children and significant disturbances in children (Ramachandani & Stein, 2003). The vocational consequences are discussed below.

2.2 Incidence and prevalence

The estimated point prevalence for major depression among 16- to 65-year-olds in the UK is 21/1000 (males 17, females 25), but, if the less specific and broader category of 'mixed depression and anxiety' (F41.2, ICD-10, WHO, 1992) was included, these figures rise dramatically to 98/1000 (males 71, females 124). In mixed depression and anxiety, it can be seen that the gender ratio is more skewed to females (Meltzer *et al.*, 1995a and b).

Prevalence rates are greatly influenced by gender, age and marital status. In the same survey, for example, female preponderance was marked during the reproductive years, but after the age of 55 the sex ratio actually reverses. Prevalence is highest among the separated (56/1000 female, 111/1000 male), next highest among widowed males (70/1000) and divorced females (46/1000), with the lowest prevalence among the married (17/1000 and 14/1000 respectively). Female prevalence is higher among the single and cohabiting than among the married, but male rates are low for all of these. Lone parents have higher rates than couples, and couples with children higher rates than those without (ibid.).

Ethnic status and gender also interact: prevalence rates for males from minority ethnic groups were not greatly different from those for white males, but female rates differed remarkably, the highest rates being found amongst Asians and Orientals (51/1000), the next highest for whites (24/1000) and the lowest rates for West Indians or Africans

(6/1000) (Meltzer *et al.*, 1995a). However, these estimates are based on relatively small samples of people from minority ethnic groups.

Gender and a number of socio-economic factors also significantly affect prevalence rates differentially: unemployed women have over twice the prevalence of depression of unemployed men (56/1000 vs 27/1000), whereas the rates are low for both sexes in full-time employment (11/1000 vs 12/1000 respectively), with part-time women workers in between (22/1000). Social classes 3 and below have higher rates than classes 1 and 2 for both sexes, and those living in rented accommodation have substantially higher rates than those living in their own home. There are clear trends for years of education for males, with those finishing education later having progressively lower rates for depression; these effects are less for females. Rates are higher in town than country, with 'semi-rural' being intermediate (Meltzer, 1995a and b).

Rates for the homeless living in leased accommodation and hostels are very high indeed, with prevalence rates of 130/1000 for ICD depression, and 270/1000 for all forms of depression (Meltzer, 1995b). Another study, of the roofless homeless, showed that 60% were depressed (Gill *et al.*, 1996). Those who are depressed consume no more alcohol than the non-depressed, but their cigarette consumption is higher (Meltzer *et al.*, 1995b). It should be emphasised that the direction of causality in these associations is unclear. Depression also affects asylum seekers, with one-third of asylum seekers in Newham being diagnosed with depression (Gammell *et al.*, 1993), considerably higher than the rate in the population.

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

The rates for depression considered so far have looked at depression at a point in time. Annual period prevalence produces much higher figures, with male rates ranging between 24 and 34/1000 and females rates between 33 and 71/1000 in Puerto Rico, Edmonton, Canada, and Christchurch, New Zealand (Jenkins *et al.*, 2003). Even higher rates are obtained for one-year prevalence using the International Composite Interview Schedule in the US of 77/1000 for males, and 129/1000 for females (Kessler *et al.*, 1994). It is probable that widely differing rates between the clinics studied in these countries reflect true differences in prevalence in these clinics rather than differing concepts of depression between countries (Simon *et al.*, 2002). In any event, the evidence overwhelmingly supports the view that the prevalence of depression, however it is defined, varies considerably according to gender and a wide range of social, ethnic and economic factors.

2.3 Diagnosis

Diagnostic criteria and methods of classification of depressive illnesses have changed substantially over the years, although the advent of operational diagnostic criteria has improved the reliability of diagnosis. ICD-10 uses an agreed list of 10 depressive symptoms, and divides the common form of major depressive episode into four groups: not depressed (fewer than four symptoms), mild (four symptoms), moderately depressed (five to six symptoms), and severe (seven symptoms or more, with or without various psychotic symptoms). Symptoms must be present for at least two weeks. These definitions have been used in the report that follows. The more severe the episode of depression, the less likely it is that remission will occur spontaneously. Patients with mild episodes in primary care settings will frequently remit, but such episodes may well be persistent, and may also be a transitional state as a more severe illness develops. Mild depression is also a vulnerability factor, rendering patients more likely to develop a more severe illness in the presence of life stress. However, it is doubtful whether the severity of a depressive illness can realistically be captured in a single symptom count although there is some evidence for this (Faravelli *et al.*, 1996): clinicians will wish to consider family and previous history, as well as the degree of associated disability, in making this assessment. In addition, some symptoms may have greater weight than others in establishing severity levels (Faravelli *et al.*, 1996).

Although reliability of diagnosis has improved, there has been no parallel improvement in the validity of diagnosis (Dohrenwend, 1990), partly as a result of the breadth of the diagnostic category – major depression – partly the result of the lack of physical tests available to confirm a diagnosis of depression, and partly because our understanding of the aetiology and underlying mechanisms of depression remain putative and lacking in specificity.

The symptom-focused, diagnostic approach adopted in much contemporary research, and which underpins the evidence base for this guideline, will distinguish between types of depression (e.g. unipolar versus bipolar), severity (mild, moderate and severe), chronicity, recurrence and treatment resistance. However, depressed people also vary greatly in their personalities, premorbid 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 diagnosis, such as anxiety, social phobia, panic and various personality disorders (Brown *et al.*, 2001). As noted above, gender, ethnic 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. Indeed, there is increasing concern that 'depression' may be too heterogeneous in biological, psychological and social terms to enable clarity on which specific interventions will be effective – for which problem, for which person, and in which context.

Differential diagnosis of depression can be difficult; of particular concern are patients with bipolar disorder presenting with depression. The issue of differential diagnosis in this area will be dealt with in the forthcoming NICE guideline on bipolar disorder.

2.4 Aetiology

The enormous variation in the presentation, course and outcomes of depressive illnesses is reflected in the breadth of theoretical explanations for their aetiology, including genetic (Kendler & Prescott, 1999), biochemical and endocrine (Goodwin, 2000), psychological (Freud, 1917), and social (Brown & Harris, 1978) processes and/or factors. No doubt an emphasis upon physical, and especially endocrine, theories of causation has been encouraged by the observation that some physical illnesses do increase the risk of depression, including diabetes, cardiac disease, hyperthyroidism, hypothyroidism, Cushing's syndrome, Addison's disease and hyperprolactinaemic amenorrhea (Cassano & Fava, 2002).

Whatever theories of causation have gained credence none has been convincingly accepted. Most now believe that all these factors influence an individual's vulnerability to depression, although it is likely that for different people living in different circumstances, precisely how these factors interact and influence that vulnerability will vary between individuals (Harris, 2000). Nevertheless, the factors identified as likely to increase a person's vulnerability to depression include gender (see above), genetic and family factors, adverse childhood experiences, and personality factors. In the stress-vulnerability model (Nuechterlein & Dawson, 1984), these 'vulnerability factors' interact with current social circumstances, such as poverty and social adversity, with stressful life events acting as the trigger for a depressive episode (Harris, 2000). Physical illness is also regarded as an important stressful life event.

A family history of depressive illness accounts for around 39% of the variance of depression in both sexes (Kendler *et al.*, 2001), and early life experiences such as a poor parent–child relationship, marital discord and divorce, neglect, physical abuse and sexual abuse almost certainly increase a person's vulnerability to depression in later life (Fava & Kendler, 2000). Personality traits such as 'neuroticism' also increase the risk of depression when faced with stressful life events (Fava & Kendler, 2000). However, different personalities have different expectancies of stressful life events, and some personalities have different rates of dependent life events, which are directly related to their personality – such as breaking up a relationship (Hammen *et al.*, 2000).

The role of current social circumstances in increasing the risk of depression, such as poverty, homelessness, unemployment and chronic physical or mental illness cannot be doubted even from a brief examination of the epidemiology of depression (see above). However, in the UK, predictive factors for depression in women in Camberwell, south-east London, include: having three or more children under the age of 14 years living at home; not having a confiding relationship with another person; and having no paid employment outside the home (Brown & Harris, 1978).

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

2.5 Use of health service resources and other costs

As the most common psychiatric disorder, and one that has a strong tendency for recurrence and chronicity, depression is ranked as the fourth leading cause of burden among all diseases and is expected to show a rising trend during the coming 20 years (WHO, 2001). One in four women and one in ten men in the UK are likely to suffer a period of depression serious enough to require treatment (National Depression Campaign, 1999). Due to its high prevalence and treatment costs, its role as probably the most important risk factor for suicide (Knapp & Ilson, 2002), and the cost of antidepressant drug overdose and its great impact on the productivity of people with the disease, depression places enormous economic burden not just on the health care system but also on the broader society. On average, depressed patients lose 11 days over a six-month period, compared with two to three days for individuals without this condition (Lepine *et al.*, 1997). It is also of interest that the cost of health and social service utilisation is almost 1.5-fold higher for older adults with depression compared with their younger counterparts (Hughes *et al.*, 1997).

A recent review identified three studies that investigated the economic burden of depression in the UK (Berto *et al.*, 2000). The study by Jonsson and Bebbington (1993) focused only on the direct costs of depression in the UK without giving detailed breakdown of the results. They calculated the direct costs of depression to be about £222 million in 1990, but this is likely to be a substantial underestimate. For example, West (1992) estimated the direct costs of depression in the UK to be £333 million at 1990 prices, of which £55 million are drug costs, £250 million hospitalisation costs, and £28 million are GP surgery consultation costs based on data from England and Wales.

In the third study reviewed, Kind and Sorensen (1993), using a different methodology, calculated the cost of depression for England and Wales in the year 1990 from a broader societal perspective. They estimated the direct care costs at £417 million, of which £47 million were drug treatment costs, £143 million were primary healthcare costs, £40 million were social services costs, £177 million were inpatient care costs, and outpatient attendances accounted for £9 million. For hospital admissions they included reasons such as depression, attempted suicide, poisoning and mental illness. These authors also went a step further by attempting to measure productivity forgone due to premature deaths and morbidity arising as a consequence of depression. They estimated that 155 million working days were lost in 1990 at a cost of £2.97 billion.

In a study comparing community-based and hospital-based treatment of anxious depression in Manchester (Goldberg *et al.*, 1996), lost productivity costs due to morbidity were on average £2,574 per patient to be compared with £424 for total service costs during six months. This study included lost marketed output as well as lost domestic output. It is of interest that the indirect costs were six times as great as the direct costs to the NHS.

These studies highlight the important facts that drug costs account for only approximately 11 to 19% of the direct costs and that the cost of lost productivity due to depression far outweighs the health service costs.

Although no recent economic burden estimates exist for the UK, it is likely that the overall economic impact of depression has increased substantially over the last decade: statistics reveal that the age-standardised prevalence of treated depression in primary

care grew from 19.9/1000 males and 50.5/1000 females in 1994 to 29.0/1000 males and 70.1/1000 females in 1998 (Office for National Statistics, 2000) and that the number of GP consultations for depressive disorders more than doubled from four million to nine million during these years (National Depression Campaign Survey, 1999). Also the number of prescriptions for antidepressants increased by 11.2% between 1998 and 1999 (Compufile Ltd, 1999). This may reflect increasing trends in the prevalence and/or in the recognition and treatment of major depressive disorder.

In 1993, Henry reported that the majority of cases of major depression were diagnosed by general practitioners, who issued 95% of all prescriptions for antidepressants (Henry, 1993). Freemantle & Mason (1995) and Freemantle (1998) calculated that 76.5% of the GP antidepressant prescribing volume was for TCAs and related drugs, which accounted for 36.7% of the total cost of prescription for depression in primary care in England in the year 1993/94. In the same period, SSRIs accounted for 23.2% of the total volume of prescribing at 62.6% of the total cost. Both the sale and cost shares of MAOIs were less than 1%. In 1996, GPs prescribed 160 million pounds' worth of antidepressants. This figure has further increased as newer and more expensive antidepressants have become available (Eccles *et al.*, 1999).

Without doubt, depression places a major direct economic burden on patients, carers and the healthcare system, and its indirect economic consequences are shown to be even greater. Furthermore, its healthcare costs continue to increase substantially. Efficient service provision could greatly reduce this burden and ensure that best care is delivered within the budget constraint.

2.6 Treatment and management in the NHS

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

2.6.1 Detection, recognition and referral in primary care

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

Of the 80 depressed people per 1000 population who do consult their GP, 49 are not recognised as depressed, mainly because most such patients are consulting for a somatic symptom, and do not consider themselves mentally unwell, despite the presence of symptoms of depression (Kisely *et al.*, 1995). This group also have milder illnesses (Goldberg *et al.*, 1998; Thompson *et al.*, 2001). And of those that are recognised as

depressed, most are treated in primary care and about one in four or five are referred to secondary mental health services. There is considerable variation between individual GPs in their referral rates to the mental illness services, but those seen by the mental illness service are a highly selected group – they are skewed towards those who do not respond to antidepressants, more severe illnesses, single women and those below the age of 35 (Goldberg & Huxley, 1980).

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

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

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

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

2.6.2 Assessment and co-ordination of care

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

2.6.2.1 All healthcare professionals involved in diagnosis and management should have a demonstrably high standard of consultation skills, so that a structured approach can be taken to the diagnosis and subsequent management of depression. (GPP)

2.6.2.2 In older adults with depression, their physical state, living conditions, and social isolation should be assessed. The involvement of more than one agency is recommended where appropriate. (GPP)

2.6.2.3 When depressive symptoms are accompanied by anxious symptoms, the first priority should usually be to treat the depression. Psychological treatment for depression often reduces anxiety, and many antidepressants also have sedative/anxiolytic effects. When the patient has anxiety without depression, the NICE guideline on management of anxiety should be followed. (GPP)

2.6.2.4 In deciding on a treatment for a depressed patient, the healthcare professional should discuss alternatives with the patient, taking into account other factors such as past or family history of depression, response of any previous episodes to intervention, and the presence of associated problems in social or interpersonal relationships. (GPP)

2.6.2.5 Healthcare professionals should always ask patients with depression directly about suicidal ideas and intent. (GPP)

2.6.2.6 When a patient with depression is assessed to be at high risk of suicide, the use of additional support such as more frequent direct contacts with primary care staff or telephone contacts should be considered. (C)

2.6.2.7 Healthcare professionals should advise patients and carers to be vigilant for changes in mood, negativity and hopelessness, and suicidal ideas, particularly during high-risk periods, such as during initiation of and changes to medication and increased personal stress. Patients and carers should be advised to contact the appropriate healthcare practitioner if concerned. (GPP)

2.6.2.8 Healthcare professionals should assess whether patients with suicidal ideas have adequate social support and are aware of sources of help. They should advise them to seek appropriate help if the situation deteriorates. (GPP)

2.6.2.9 Where a patient presents considerable immediate risk to self or others, urgent referral to a specialist mental health service should be arranged. (GPP)

2.6.2.10 When a patients' depression has failed to respond to various strategies for augmentation and combination treatments, referral to a clinician with a specialist interest in treating depression should be considered. (GPP)

2.6.2.11 The assessment of patients with depression referred to specialist mental health services should include a full assessment of their symptom profile and suicide risk and, where appropriate, previous treatment history. Assessment of psychosocial stressors, personality factors and significant relationship difficulties should also be undertaken, particularly where the depression is chronic or recurrent. (GPP)

2.6.2.12 In specialist mental health services, after a thorough review of previous treatments for depression has been undertaken, consideration should be given to re-introducing previous treatments that have been inadequately delivered or adhered to. (GPP)

2.6.2.13 Medication in secondary-care mental health services should be initiated under the supervision of a consultant psychiatrist. (GPP)

2.6.2.14 Inpatient treatment should be considered for people with depression who are at significant risk of suicide or self-harm. (C)

2.6.2.15 Where a patients' depression has resulted in loss of work or disengagement from other social activities over a longer term, a rehabilitation programme addressing these difficulties should be considered. (C)

The nature and course of depression is significantly affected by psychological, social and physical characteristics of the patient and their circumstances. These factors have a significant impact upon both the initial choice of treatment and the probability of a patient benefiting from that intervention.

2.6.2.16 When assessing a person with depression, healthcare professionals should consider the psychological, social, cultural and physical characteristics of the patient and the quality of interpersonal relationships. They should consider the impact of these on the depression and the implications for choice of treatment and its subsequent monitoring. (GPP)

The need for more effective assessments for people who are depressed also requires that healthcare professionals must have the requisite level of skill and ensure continued competence in the use of those skills.

2.6.2.17 Healthcare professionals should ensure they maintain their competence in risk assessment and management. (GPP)

This is particularly important if an individual receives help and treatment in both primary and secondary care.

2.6.2.18 Where a patient's management is shared between primary and secondary care, there should be clear agreement between individual healthcare professionals on the responsibility for the monitoring and treatment of that patient, and the treatment plan should be shared with the patient and, where appropriate, families and carers. (GPP)

2.6.3 Non-specific effects of treatment and the placebo

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

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

Although there is insufficient space to allow proper discussion, the placebo effect in trials of psychiatric drugs is often so large that specific pharmacological effects can be hard to identify, especially when given to people who fall into one of the larger, more heterogeneous diagnostic categories. The treatment of depression is a clear example of this (Kirsch *et al.*, 2002a). Drug, and some other, treatments for depression, when compared with wait list controls in the treatment of mild to moderate depression, all produce a substantial and roughly equal fall in depressive symptoms. But, when antidepressants are compared with placebo for this diagnostic group, the clinical improvements resulting from antidepressants over and above that for placebo is not clinically significant (Kirsch *et al.*, 2002b). Given the recent focus upon publication bias, especially with regard to drug company funded trials (Lexchin *et al.*, 2003; Melander *et al.*, 2003) there is the possibility that some drug (or other) treatments for depression may offer no advantage, on average, over placebo, for patients with mild depression. Nevertheless, it is likely that with greater definition of subgroups of people with depression, benefits over placebo may well be demonstrable. Further discussion of the placebo effect in the treatment of depression can be found in the evidence chapters.

2.6.4 Pharmacological treatments

The mainstay of the pharmacological treatment of depression for the last 40 or more years has been antidepressants. Tricyclic antidepressants (TCAs) were introduced in the 1950s, the first being imipramine (Kuhn, 1958). The mode of action of this class of drugs thought to be responsible for their mood-elevating properties is their ability to block the synaptic reuptake of monoamines, including noradrenaline (NA), 5-hydroxytryptymine (5HT) and dopamine (DA). In fact the TCAs predominantly affect the reuptake of NA and 5HT rather than DA (Mindham, 1982). The antidepressant properties of MAOIs were discovered by chance in the 1950s in parallel with TCAs.

Although the introduction of the TCAs was welcome, given the lack of specific treatments for people with depression, the side effects resulting from their ability to influence anticholinergics, histaminergic and other receptor systems reduced their acceptability. Moreover, overdose with TCAs (with the exception of lofepramine) carries a high mortality and morbidity, particularly problematic in the treatment of people with suicidal intentions.

In response to the side effect profile and the toxicity of TCAs in overdose, new classes of antidepressants have been developed, including: the specific serotonin reuptake inhibitors (SSRIs) such as fluoxetine; drugs chemically related to, but different from, the TCAs, such as trazodone; and a range of other chemically unrelated antidepressants including mirtazapine (*BNF*, 4.3). Their effects and side effects vary considerably, although their mood-elevating effects are again thought to be mediated through increasing intra-synaptic levels of monoamines, some primarily affecting NA, some 5HT and others affecting both to varying degrees and in different ways.

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

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

2.6.5 Psychological treatments

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

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

2.6.6 Service-level and other interventions

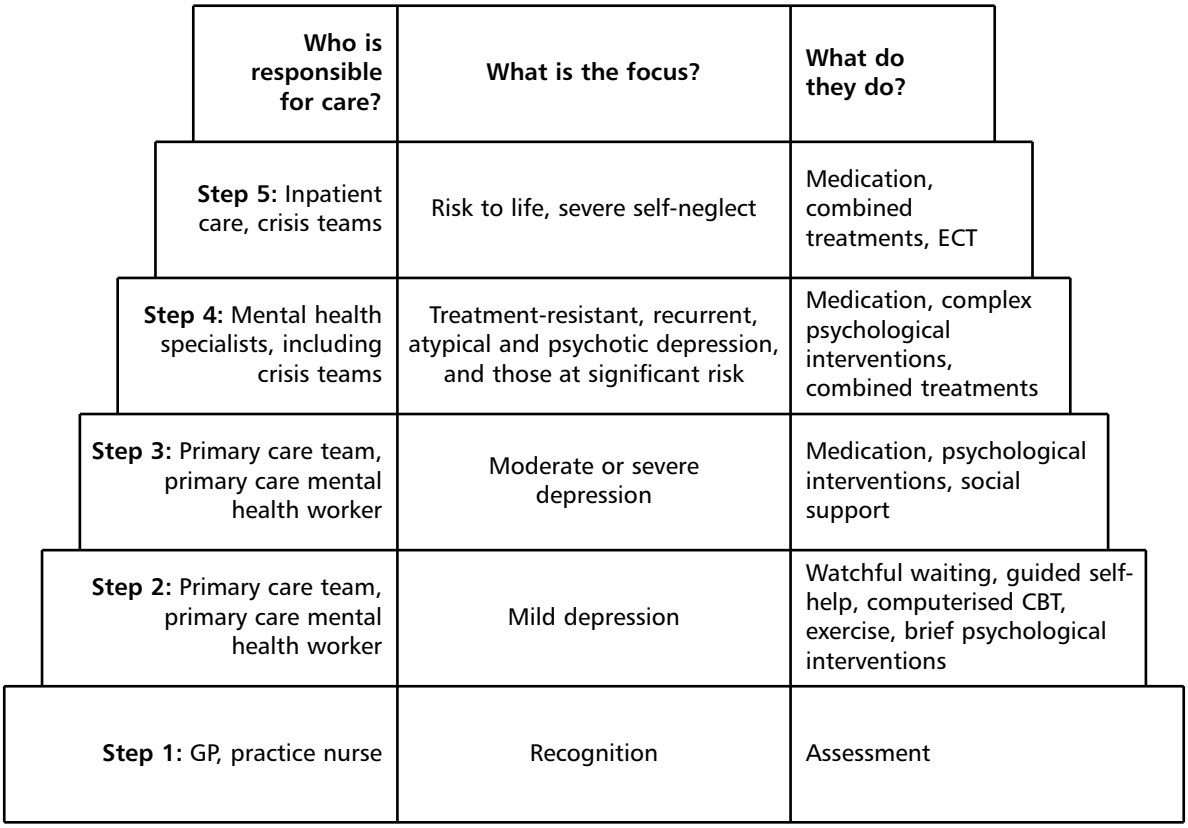
Given the complexity of healthcare organisations, and the variation in the way care is delivered (inpatient, outpatient, day hospital, community teams, etc.), choosing the right service configuration for the delivery of care to specific groups of people has gained increasing interest with regard to both policy (for example, see Department of Health, 1999b), and research (e.g. evaluating day hospital treatment, Marshall *et al.*, 2001). Research using RCT designs has a number of difficulties; for example, using comparators such as 'standard care' in the US make the results difficult to generalise or apply to countries with very different types of 'standard care'.

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

2.6.7 Stepped care

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

Figure 1: The stepped care model.



Of those people whom primary healthcare professionals recognise as having depression, some prefer to avoid medical interventions, and others will improve in any case without them. Thus, in depressions of only mild severity, many GPs prefer a 'watchful waiting' approach, which can be accompanied by general advice on such matters as restoring natural sleep rhythms and getting more structure into the day. However, other people prefer to accept, or indeed require, medical, psychological or social interventions, and these patients are therefore offered more complex interventions. Various interventions are effective, delivered by a range of workers in primary care.

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

Finally, there are a few patients who will need admission to an inpatient psychiatric bed. Here they can receive round the clock nursing care and various special interventions.

2.6.7.1 For patients with mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, a further assessment should be arranged, normally within two weeks ('watchful waiting'). (C)

2.6.7.2 Healthcare professionals should make contact with patients with depression who do not attend follow-up appointments. (C)

2.6.7.3 Patients with mild depression may benefit from advice on sleep hygiene and anxiety management. (C)

2.7 The experience of depression

For any guideline on the treatment of depression to be credible it has to be informed at every stage of its development by the perspective of patients. Intensive patient input has led to the development of the tiered and multifaceted management cascade described in this guideline ('stepped care'). Patients are keen to be given much more explanation and information about depression and to be offered a range of possible treatment choices. The patient view is that healthcare professionals have previously been over-reliant on the prescribing of antidepressant medications often without adequate psychological support (Smith, 1995; Singh, 1995). A patient narrative is described overleaf.

2.7.1 A personal perspective

The following is a personal account of an experience of long-term depression.

> *'Happily, my experience of taking antidepressants was not too unpleasant. I had been suffering from recurrent periodic bouts of depression for quite a long time without realising it. Various medications were prescribed for short-term use, which alleviated the condition for a while, although I was, and still am, averse to becoming dependent on them. Sometimes the side effects were extremely unpleasant – at times I felt almost suicidal and felt that the treatment was actually making me worse. I started to doubt my doctor's competence, feeling that he didn't understand or care.*
>
> *'The really effective treatment only began when I consulted a GP who knew my and my family history, not just my medical history. He took time to explain what was happening, described the possible side effects, the interaction with alcohol and other medications, but, most importantly, assured me that depression did not necessarily have to be a "life sentence".*
>
> *'After a short period on antidepressants we explored alternative therapies and identified practical steps that I could take in order to develop a coping strategy without recourse to antidepressants. This was done in a spirit of equal partnership between the GP and myself, with me being able to make informed choices.*
>
> *'By far the worst thing about my depression was not knowing what was happening to me, the feeling that life had nothing to offer me, the lack of interest and loss of motivation, in short, the feeling of helplessness and hopelessness.*
>
> *'I still suffer bouts of depression, but now understand what is happening, and know how to cope and seek help, as I know I can, and will, come out of it.*
>
> *'The provision of alternative therapies is paramount, instead of the reliance on medication as an ongoing first line defence. It is of extreme importance that patients feel that they will get well, and feel that they can contribute to the economy instead of feeling that they are a burden on it.*
>
> *'In summary, the main priorities should be the provision of understanding, time, choice and above all, hope. These are not as cost prohibitive as some of the alternatives.'*

Patients have, through their involvement in the preparation of this guideline, made tangible changes to the suggested management of depression, particularly in primary care settings. They have endorsed the use of the term 'patient', where appropriate, to refer to people with depression.

2.8 Patient preference, information, consent and mutual support

There is now a wide range of different possible treatments, each with their own combination of general and specific effects, side effects and mechanisms of action, and variation in the NHS sites at which healthcare may be provided for people who are depressed and their carers. With this in mind, the provision of comprehensive information, using clear and understandable language, is increasingly necessary. Written material in the language of the patient, and access to interpreters for those whose first language is other than English, is essential in order for people to be able to express their preferences. This is especially the case when a range of broadly equivalent treatments is available for people with mild to moderate depression. Patients and carers need a good understanding of the treatment options and the risks involved before treatment is initiated.

The principle of informed consent should be followed even when a person has severe depression, or when a person is being treated under the Mental Health Act. When a person with recurrent depressive illness is sometimes unable to give consent, consideration should be given to the development and recording of advance directives.

In addition, given the emotional, social and economic cost that depression usually entails, patients and their families may need help in contacting support groups and self-help groups. This is also important to promote understanding and collaboration between patients, their carers and healthcare professionals at all levels of primary and secondary care.

2.8.1.1 A number of different treatment approaches may be equally effective for patients who are depressed, especially for those with mild and moderate depression who are not considered to be at substantial risk of self-harm. Patient preference and the experience and outcome of previous treatment(s) should be considered when deciding on treatment. (GPP)

2.8.1.2 Common concerns about taking medication should be addressed. For example, patients should be advised that craving and tolerance do not occur, and that taking medication should not be seen as a sign of weakness. (GPP)

2.8.1.3 Patients and, where appropriate, families and carers should be provided with information on the nature, course and treatment of depression including the use and likely side-effect profile of medication. (GPP)

2.8.1.4 When talking to patients and carers, healthcare professionals should use everyday, jargon-free language. If technical terms are used they should be explained to the patient. (GPP)

2.8.1.5 Where possible, all services should provide written material in the language of the patient, and independent interpreters should be sought for people whose preferred language is not English. (GPP)

2.8.1.6 Where available, consideration should be given to providing psychotherapies and information about medications in the patient's own language if this is not English. (GPP)

2.8.1.7 Healthcare professionals should make all efforts necessary to ensure that a patient can give meaningful and properly informed consent before treatment is initiated. This is especially important when a patient has a more severe depression or is subject to the Mental Health Act. (GPP)

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

2.8.1.9 Patients, families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate. (GPP)

3 Methods used to develop this guideline

3.1 Overview

The development of this guideline drew upon methods outlined by NICE (NICE, 2001; Eccles & Mason, 2001). A team of experts, professionals and patients, known as the Guideline Development Group (GDG), with support from NCCMH staff, undertook the development of a patient-centred, evidence-based guideline. There are six basic steps in the process of developing a guideline:

- Define the scope, which sets the parameters of the guideline and provides a focus and steer for the development work
- Define clinical questions considered important for practitioners and patients
- Develop criteria for evidence searching and search for evidence
- Design validated protocols for systematic review and apply to evidence recovered by search
- Synthesise and (meta-) analyse data retrieved, guided by the clinical questions, and produce evidence statements
- Answer clinical questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are, therefore, derived from the most up-to-date and robust evidence base for the clinical and cost effectiveness of the treatments and services used in the management of depression. In addition, to ensure a patient and carer focus, the concerns of patients and carers regarding clinical practice have been highlighted and addressed by good practice points and recommendations agreed by the whole GDG. The evidence-based recommendations and good practice points are the core of this guideline.

3.2 The Guideline Development Group

The GDG consisted of patients, and professionals and academic experts in psychiatry, clinical psychology and general practice. NCCMH staff undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to the drafting of the guideline.

3.2.1 Guideline Development Group meetings

Twenty-six GDG meetings were held between November 2001 and October 2003. During each day-long GDG meeting clinical evidence was reviewed and assessed to develop

statements and recommendations. At each meeting all GDG members declared any potential conflict of interests. Patient and carer concerns were routinely discussed as part of a standing agenda.

3.2.2 Topic groups

The GDG divided its workload along clinically relevant lines in order to deal with the large volume of evidence efficiently. GDG members formed three topic groups: the Service topic group covered questions relating to the presentation of services to users, including screening, exercise and guided self-help; the Pharmacology topic group covered pharmacological treatments for depression; and the Psychology topic group covered psychotherapies. Each topic group was chaired by a GDG member with expert knowledge of the topic area. Topic groups refined the clinical definitions of treatment interventions, reviewed and prepared the evidence with the NCCMH review team. Topic group leaders reported the status of their group's work as part of the GDG standing agenda. They also assisted in drafting the section of the guideline relevant to the work of each topic group.

3.2.3 Patients and carers

Individuals with direct experience of services gave an integral patient focus to the GDG and the guideline. The GDG included three patients. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology associated with depression, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to the editing of the first draft of the guideline's introduction and identified good practice points from the patient and carer perspective; their suggestions were incorporated before distributing the draft to the GDG for further review.

3.2.4 Special advisers

Special advisers who had specific expertise in one or more aspects of treatment and management relevant to the guideline assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 2 lists those who agreed to act as special advisers.

3.2.5 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the evidence base for the guideline. Appendix 5 lists researchers who were contacted.

3.3 Clinical questions

Clinical questions were used to guide the identification and interrogation of the evidence base. The questions were developed using a modified nominal group technique. The process began by asking each member of the GDG to submit as many questions as possible. The questions were then collated and refined by the review team. At a subsequent meeting, the guideline chair facilitated a discussion to further refine the questions. At this point, the GDG members were asked to rate each question for importance. The results of this process were then discussed and consensus reached about which questions would be of primary importance and which would be secondary. The GDG aimed to address all primary questions, while secondary questions would only be covered time permitting. Appendix 6 lists the clinical questions.

3.4 Systematic clinical literature review

The aim of the clinical literature review was to identify and synthesise systematically all relevant evidence in order to answer the clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence-based as far as possible.

Where an existing NICE Technology Appraisal addressed one of the clinical questions, the GDG was obliged to adopt the relevant existing recommendations. If evidence was not available, then informal consensus methods were used (see Section 3.4.4) and the need for future research was specified.

A stepwise, hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed the methodology for this process with advice from the National Guidelines Support and Research Unit (NICE) and after considering recommendations from a range of other sources. These included:

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

3.4.1 The review process

Since most of the clinical questions for this guideline concerned interventions, much of the evidence base was formed from high quality randomised controlled trials (RCTs). Although there are a number of difficulties with the use of RCTs in the evaluation of interventions in mental health, this research design remains the most important method for establishing treatment efficacy (see introductions to later chapters for fuller discussions of this issue).

The review process involved:

- Developing search filters
- Searching for existing systematic reviews
- Searching for new RCTs
- Selecting studies
- Synthesising the evidence.

3.4.1.1 Developing search filters

The review team developed search filters to search electronic databases that combined subject headings with free-text phrases. A filter was developed for the general topic 'depression', which was combined with specific filters for each clinical question. These were also combined with filters developed for 'systematic reviews' or 'RCTs' (or other research designs as appropriate) (Appendix 7).

3.4.1.2 Searching for existing systematic reviews

The NCCMH review team undertook searches for existing systematic reviews of RCTs published in English since 1995 (an arbitrary cut-off date to reduce the number of references found and to ensure recency), which would answer the clinical questions posed by the GDG. The initial searches were undertaken in December 2001 and January 2002, with update searches being carried out every two months until May 2002. A search of PubMed (MEDLINE) was also undertaken weekly beginning in April 2003 until the end of the guideline development process. The following databases were searched: EMBASE, MEDLINE, PsycINFO, Cochrane Library, CINAHL, Web of Science.

Systematic reviews were assessed for quality and eligibility (Appendices 8 and 9) before being assessed by the GDG for relevance to a clinical question. Searches were undertaken for RCTs published too late to be included in chosen systematic reviews beginning two years before the publication date of the review in question. Where authors stated the date searches had been undertaken, the NCCMH review team undertook new searches from the beginning of that year. Each study included in an existing review was subjected to the same quality checks as those located through NCCMH searches, and the data were re-extracted according to NCCMH protocols (see below). Where existing reviews had been undertaken using Review Manager (any version) authors were approached for data sets, although any used were checked for accuracy. For clinical questions where no existing systematic review was identified, searches were undertaken for all relevant evidence.

3.4.1.3 Searching for RCTs

For Service and Pharmacology topic area clinical questions, searches for RCTs were undertaken for each clinical question individually. However, RCTs to answer the clinical questions posed by the Psychology topic group were searched for together.
For all questions the following electronic databases were searched: EMBASE, MEDLINE, PsycINFO, Cochrane Library, CINAHL. For the pharmacological review of St John's Wort, AMED was also searched. In addition, hand searches were also made of the reference lists of all eligible RCTs, as well as of the list of evidence submitted by registered stakeholders (Appendix 3). Known experts in the field (see Appendix 5), based both on the references identified in earlier steps and on advice from GDG members, were approached for unpublished RCTs.[1] Studies were considered provided a full trial report was available. Studies published in languages other than English were used provided a native speaker was available.

If no RCTs were found to answer a clinical question the GDG adopted a consensus process (see Section 3.4.4). Future guidelines will be able to update and extend the usable evidence base starting from the evidence collected, synthesised and analysed for this guideline.

3.4.1.4 Study selection

All references located in searches of electronic databases were downloaded into Reference Manager (ISI ResearchSoft, 2002) and searched liberally to exclude irrelevant papers. The titles of excluded papers were double-checked by a second reviewer. All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility. Appendix 8 lists the standard inclusion and exclusion criteria. Additional eligibility criteria were developed to assess trials of pharmacotherapy, and these are listed in Chapter 7. All eligible papers were critically appraised for methodological quality (see Appendix 10). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

For some clinical questions, it was necessary to prioritise the evidence with respect to the UK context. To make this process explicit, the topic group members took into account the following factors when assessing the evidence:

- Participant factors (e.g. gender, age, ethnicity)
- Provider factors (e.g. model fidelity, the conditions under which the intervention was performed, the availability of experienced staff to undertake the procedure)
- Cultural factors (e.g. differences in standard care, differences in the welfare system).

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each clinical question in light of the UK context, and then decide how they should modify their recommendations.

[1] Unpublished full trial reports were accepted where sufficient information was available to judge eligibility and quality.

3.4.2 Synthesising the evidence

3.4.2.1 Outcomes

The vast majority of data extracted were scores on the Hamilton Rating Scale for Depression (HRSD), Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) at the end of treatment and, where available, at follow-up. Both continuous (e.g. mean endpoint scores) and dichotomised data (e.g. number of people achieving below the cut-off for remission) were extracted. The GDG felt it was important to extract a variety of measures since relying on only one can be misleading. For example, dichotomising scores into remission and non-remission creates an artificial boundary, with patients just over the cut-off score often being clinically indistinguishable from those just under the cut-off. The GDG would also have liked to have been able to use quality of life measures as outcomes, but these are rarely reported.

In addition, where possible, sub-analyses were performed for severity of depression. Because very few studies gave information about participants' baseline severity of depression in terms of number of symptoms using the ICD classification (see Chapter 2), the mean depression score at baseline (most commonly an HRSD score) was used as a proxy measure. Scores were categorised mild, moderate, severe or very severe according to American Psychiatric Association criteria (APA, 2000a). Where necessary different versions of the HRSD were standardised using the method for prorating suggested by Walsh *et al.* (2002). The GDG used these categories with caution, mindful of the problematic nature of this proxy measure, in particular the variation in the standard deviation around baseline mean scores. Details of the categories and further information about the depression rating scales are in Appendix 13. When drawing up recommendations the GDG related the APA categories to ICD categories. This method does not take account of the severity of individual symptoms but is nonetheless a rough approximation to clinical severity.

3.4.2.2 Data extraction

Where possible, outcome data from all eligible studies that met quality criteria were extracted using a data extraction form (Appendix 11) and input into Review Manager 4.2 (Cochrane Collaboration, 2003). Where trial reports contained incomplete data and it was possible to contact the original authors, additional information was sought. Where mean endpoint or change scores were extracted and trial reports did not provide standard deviations, standard conversion formulas were used (see Appendix 12).

All dichotomous outcomes were calculated on an intention-to-treat basis (i.e. a 'once-randomised-always-analyse' basis). This assumes that those participants who ceased to engage in the study – from whatever group – had an unfavourable outcome. The effects of high attrition rates (defined as more than 50% of participants in a particular group leaving treatment early) were examined with sensitivity analyses, and studies were removed from efficacy outcomes if the possibility of bias was detected.

Consultation was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer directly into Review Manager and checked by a second reviewer. Where consensus could not be reached, a third reviewer was consulted. Masked assessment (i.e. blind to the journal from which the article comes, the authors, the institution, and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad *et al.*, 1996; Berlin, 1997).

Information describing each study was also extracted and input into Review Manager 4.2. This was used to generate evidence tables (see Appendix 17 on the CD).

3.4.2.3 Meta-analysis

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

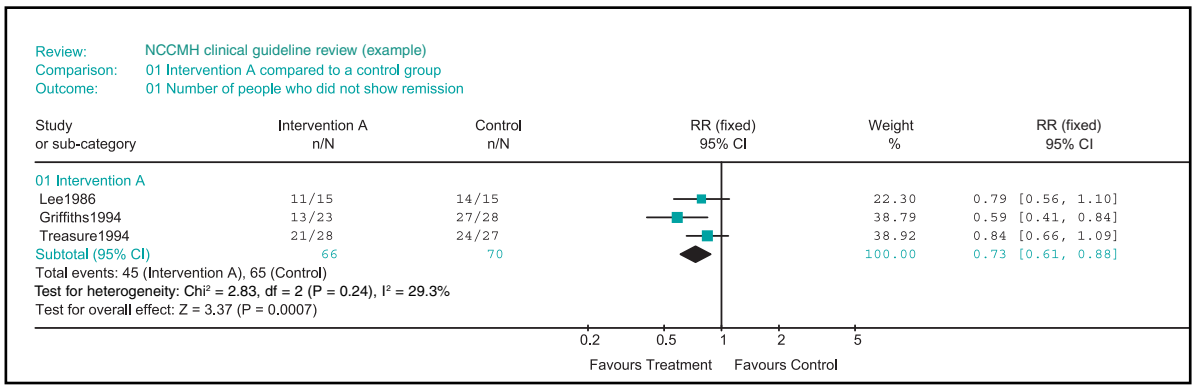
The GDG was given a graphical presentation of the results using forest plots generated with Review Manager. Each forest plot displayed the effect size and 95% confidence interval (CI) for each study as well as the overall summary statistic with its 95% CI. The graphs were organised so that the display of data in the area to the left of the 'line of no effect' indicated a 'favourable' outcome for the treatment in question.[2]

Dichotomous outcomes were presented as relative risks (RR) with the associated 95% CI (see Figure 1). A relative risk (or risk ratio) is the ratio of the treatment event rate to the control event rate. A RR of 1 indicates no difference between treatment and control. In Figure 1, the overall RR of 0.73 indicates that the event rate (i.e. non-remission rate) associated with intervention A is about half of that with the control intervention, or in other words, intervention A reduces non-remission rates by 27%. In addition, the 95% CI around the RR does not cross the 'line of no effect' indicating that this is a statistically significant effect. The CI shows with 95% certainty the range within which the true treatment effect should lie.

It had been planned to calculate the number needed to treat (NNT) (or number needed to harm (NNH)) for dichotomous outcomes with statistically significant effect sizes. However, when the baseline risk (i.e. control group event rate (CER)) or length of follow-up varies, NNT is a poor summary of the treatment effect, especially with low risk or where the CER is dissimilar across studies in a meta-analysis (Deeks, 2002). Since it was not possible to calculate the baseline risk for most outcomes NNT and NNH have not been calculated.

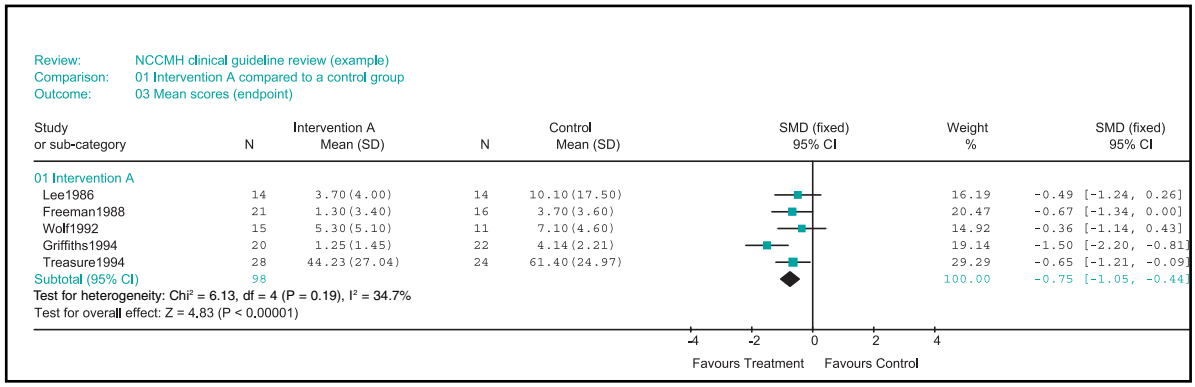
Continuous outcomes were analysed as weighted mean differences (WMD) or standardised mean differences (SMD) when different measures (or different versions of the same measure) were used in different studies to estimate the same underlying effect (see Figure 2).

Figure 1: Example of a forest plot displaying dichotomous data.



[2] The exceptions to this are: the review of amitriptyline, for which the GDG were provided with a data set for an existing systematic review (Barbui & Hotopf, 2001), and the overview of TCA data.

Figure 2: Example of a forest plot displaying continuous data.



To check for heterogeneity between studies, both the I^2 test of heterogeneity and the chi-squared test of heterogeneity ($p<0.10$), as well as visual inspection of the forest plots, were used. The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins & Thompson, 2002). An I^2 of less than 30% was taken to indicate mild heterogeneity and a fixed effects model was used to synthesise the results. This assumes that the underlying effect is the same (Egger *et al.*, 2001). An I^2 of more than 50% was taken as notable heterogeneity. In this case, an attempt was made to explain the variation. If studies with heterogeneous results were found to be comparable, a random effects model was used to summarise the results (DerSimonian & Laird, 1986). In the random effects analysis, heterogeneity is accounted for both in the width of CIs and in the estimate of the treatment effect. With decreasing heterogeneity the random effects approach moves asymptotically towards a fixed effects model. An I^2 of 30% to 50% was taken to indicate moderate heterogeneity. In this case, both the chi-squared test of heterogeneity and a visual inspection of the forest plot were used to decide between a fixed and random effects model.

To explore the possibility that the results entered into each meta-analysis suffered from publication bias, data from included studies were entered, where there were sufficient data, into a funnel plot. Asymmetry of the plot was taken to indicate possible publication bias and was investigated further.

3.4.3 Developing statements and graded recommendations

The summary statistics (effect sizes (ES)) and evidence tables formed the basis for developing clinical statements and recommendations.

3.4.3.1 Developing statements

For each outcome a clinical statement describing the evidence found was developed. To do this both the statistical and the clinical significance (i.e. the likely benefit to patients) of the summary statistic were taken into account.

Assessing statistically significant summary statistics

To assess clinical significance where a statistically significant summary was obtained (after controlling for heterogeneity) the GDG adopted the following 'rules of thumb', in addition to taking into account the trial population and nature of the outcome:

For dichotomous outcomes a RR of 0.80 or less was considered clinically significant (see Section 3.4.2.3).

For continuous outcomes for which an SMD was calculated (for example, when data from different versions of a scale are combined), an effect size of ~0.5 (a 'medium' effect size; Cohen, 1988) or higher was considered clinically significant. Where a WMD was calculated, a between group difference of at least three points (two points for treatment-resistant depression) was considered clinically significant for both BDI and HRSD.

Once clinical significance had been established the strength of the evidence was assessed by examining the 95% CIs surrounding the ES. For level I evidence, where the effect size was judged clinically important for the full range of plausible estimates, the result was characterised as 'strong evidence' (i.e. S1, Flowchart 1: Guideline Statement Decision Tree). For non-level I evidence or in situations where the CI also included clinically unimportant effects, the result was characterised as 'some evidence' (i.e. S2).

Where an ES was statistically significant, but *not* clinically significant and the CI excluded values judged clinically important, the result was characterised as 'unlikely to be clinically significant' (S3). Alternatively, if the CI included clinically important values, the result was characterised as 'insufficient to determine clinical significance' (S6).

Assessing non-statistically significant summary statistics

Where a non-statistically significant ES was obtained, the GDG reviewed the trial population, nature of the outcome, size of the effect and, in particular, the CI surrounding the result. If the CI was narrow and excluded a clinically significant ES, this was seen as indicating evidence of 'no clinically significant difference' (S4), but where the CI was wide this was seen as indicating 'insufficient evidence' to determine if there was a clinically significant difference or not (S5).

In order to facilitate consistency in generating and drafting the clinical statements the GDG utilised a statement decision tree (see Flowchart 1 overleaf). The flowchart was designed to assist with, but not replace, clinical judgement.

3.4.3.2 Developing graded recommendations

Once all evidence statements relating to a particular clinical question were finalised and agreed by the GDG, the associated recommendations were produced and graded. Recommendations were graded A to C based on the level of associated evidence, or noted as coming from a previous NICE guideline or health technology appraisal (see Table 1 overleaf).

Grading allowed the GDG to distinguish between the level of evidence and the strength of the associated recommendation. It is possible that a statement of evidence would cover only one part of an area in which a recommendation was to be made or would cover it in a way that would conflict with other evidence. In order to produce more comprehensive recommendations suitable for people in England and Wales, there were times when the GDG had to extrapolate from the available evidence based on their combined clinical experience. The resulting recommendations were then graded with a lower grade (e.g. a 'B' grade where data were based upon Level I evidence).
This allowed the GDG to moderate recommendations based on factors other than the

Flowchart 1: Guideline Statement Decision Tree.

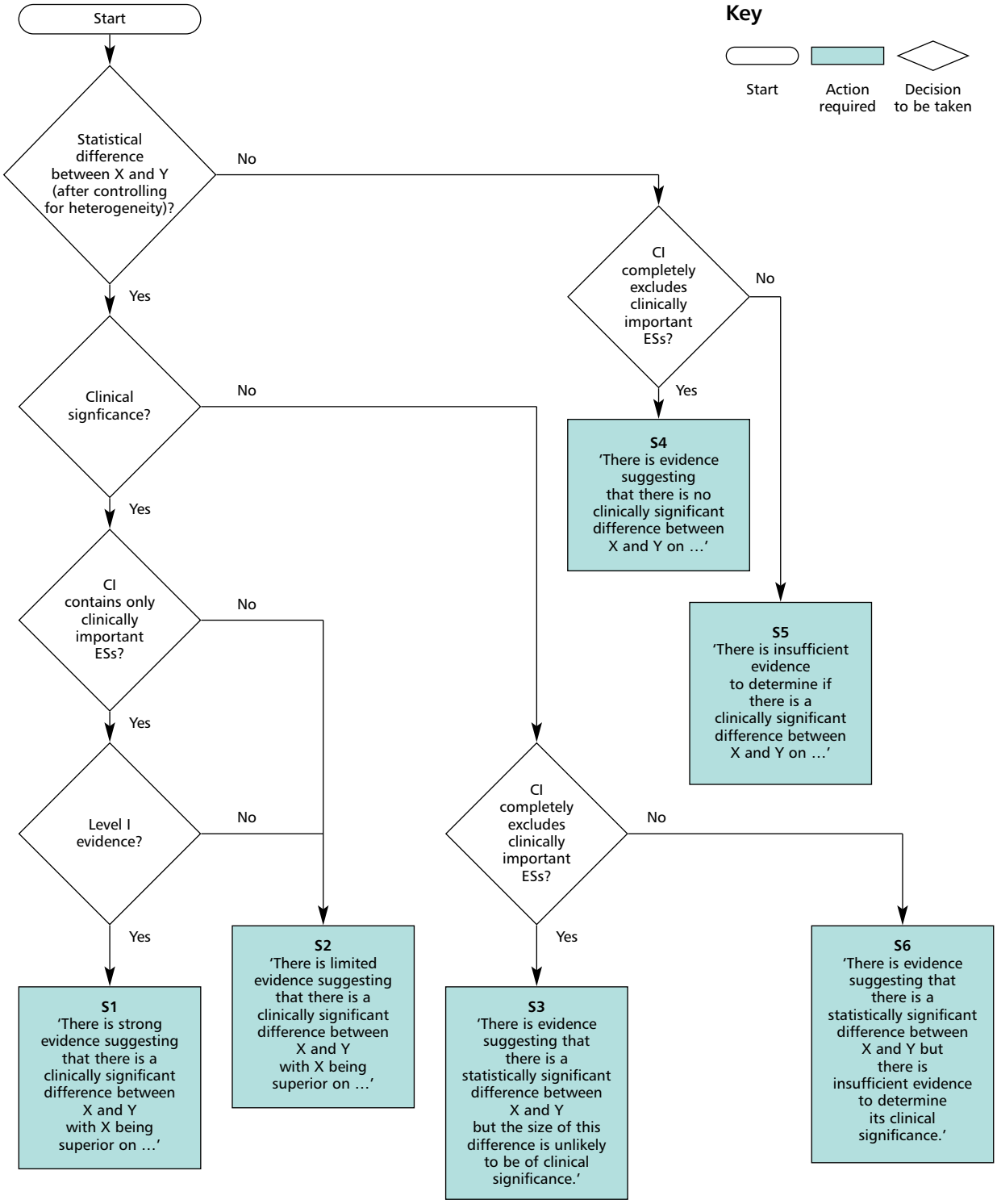


Table 1: Hierarchy of evidence and recommendations grading scheme.

Level	Type of evidence	Grade	Evidence
I	Evidence obtained from a single randomised controlled trial or a meta-analysis of randomised controlled trials	**A**	At least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level I) without extrapolation
IIa	Evidence obtained from at least one well-designed controlled study without randomisation	**B**	Well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels II or III); or extrapolated from level I evidence
IIb	Evidence obtained from at least one other well-designed quasi-experimental study		
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies		
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities	**C**	Expert committee reports or opinions and/or clinical experiences of respected authorities (evidence level IV) or extrapolated from level I or II evidence. This grading indicates that directly applicable clinical studies of good quality are absent or not readily available
		GPP	Recommended good practice based on the clinical experience of the GDG
NICE	Evidence from NICE guideline or Technology Appraisal	**NICE**	Evidence from NICE guideline or Technology Appraisal

Adapted from Eccles, M. & Mason, J. (2001), How to develop cost-conscious guidelines. *Health Technology Assessment, 5*(16); Department of Health (1996), *Clinical Guidelines: Using clinical guidelines to improve patient care within the NHS*. Leeds: NHS Executive.

strength of evidence. Such considerations include the applicability of the evidence to the people in question, economic considerations, values of the development group and society, or the group's awareness of practical issues (Eccles *et al.*, 1998).

3.4.4 Method used to answer a clinical question in the absence of appropriately designed, high-quality research

In the absence of level I evidence (or a level that is appropriate to the question), or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there was unlikely to be such evidence, an informal consensus process was adopted. This process focused on those questions that the GDG considered a priority.

3.4.4.1 Informal consensus

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

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

1. A description of what is known about the issues concerning the clinical question was written by one of the topic group members.

2. Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question.

3. Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the clinical question but were thought to contain relevant data.

4. If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) was identified, a full systematic review was done.

5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question was developed.

6. Following this, on occasions and as deemed appropriate by the development group, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.

7. Recommendations were then developed and could also be sent for further external peer review.

8. After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.5 Evidence on safety and harm

In the UK the licensing and post-licensing safety monitoring of medicines is undertaken by the Medicines and Healthcare products Regulatory Agency (MHRA). During the development of this guideline the safety of some drugs used to treat depression (selective serotonin reuptake inhibitors (SSRIs), mirtazapine and venlafaxine) was formally reviewed by the MHRA on behalf of the Committee on Safety of Medicines (CSM). The CSM convened a working group to look at this issue (the SSRI Expert Working Group (EWG)). The EWG's findings were made available to the GDG, and used in addition to the efficacy and safety data reviewed during the guideline development process in drawing up recommendations. In particular, data on discontinuation/withdrawal symptoms, cardiotoxicity, dose, and suicidality and self-harm, were used, together with information on changes to produce licences as a result of the EWG's report to the CSM (MHRA, 2004). The Marketing Authorisation Holder (the pharmaceutical company responsible for the drug in question) analysed data from clinical trials for each relevant drug, in accordance with a protocol specified by the EWG. These reviews formed the basis of the EWG's deliberations, and it should be noted that not all trial data were made available to the EWG (MHRA, 2004). The EWG used other data, including a number of analyses of the General Practice Research Database (for example, Jick *et al.*, 2004), along with spontaneous reporting of adverse drug reactions (via the MHRA's Yellow Card scheme).

3.6 Health economics review strategies

The aim of the health economics review was to contribute to the guideline development process data on the economic burden of depression. Evidence of the cost-effectiveness of different treatment options for depression was collected and assessed in order to help the decision-making process. See Chapter 9, Health economics evidence, for the detailed review strategies.

3.7 Stakeholder contributions

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

- Patient/carer stakeholders: the national patient and carer organisations that represent people whose care is described in this guideline

- Professional stakeholders: the national organisations that represent healthcare professionals who are providing services to patients
- Commercial stakeholders: the companies that manufacture medicines used in the treatment of depression
- Primary Care Trusts
- Department of Health and Welsh Assembly Government.

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

- Commenting on the initial scope of the guideline and attended a briefing meeting held by NICE
- Contributing lists of evidence to the GDG
- Commenting on the first and second drafts of the guideline.

3.8 Validation of this guideline

This guideline has been validated through two consultation exercises. Drafts of the full and NICE versions of the guideline were submitted to the NICE Guidelines Review Panel and posted on the NICE website (www.nice.org.uk). Stakeholders and other reviewers nominated by the GDG were then informed that the documents were available.

The GDG reviewed comments from stakeholders, the NICE Guidelines Review Panel, a number of health authority and trust representatives and a wide range of national and international experts from the first round of consultation. The GDG then responded to all comments and prepared final consultation drafts of all three versions of the guideline – the full guideline, the NICE guideline, and the information for the public. These were made available on the NICE website, and stakeholders were informed. Following consultation, the drafts were amended and responses to any comments were made. The final drafts were then submitted to NICE to be signed off after review by the Guidelines Review Panel.

4 Summary of recommendations

Key priorities for implementation

Screening in primary care and general hospital settings

- Screening should be undertaken in primary care and general hospital settings for depression in high-risk groups – for example, those with a past history of depression, significant physical illnesses causing disability, or other mental health problems, such as dementia.

Watchful waiting

- For patients with mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, a further assessment should be arranged, normally within two weeks ('watchful waiting').

Antidepressants in mild depression

- Antidepressants are not recommended for the initial treatment of mild depression, because the risk–benefit ratio is poor.

Guided self-help

- For patients with mild depression, healthcare professionals should consider recommending a guided self-help programme based on cognitive behavioural therapy (CBT).

Short-term psychological treatment

- In both mild and moderate depression, psychological treatment specifically focused on depression (such as problem-solving therapy, brief CBT and counselling) of six to eight sessions over 10 to 12 weeks should be considered.

Prescription of an SSRI

- When an antidepressant is to be prescribed in routine care, it should be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects.

Tolerance and craving, discontinuation/withdrawal symptoms

- All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly.

Initial presentation of severe depression

- When patients present initially with severe depression, a combination of antidepressants and individual CBT should be considered as the combination is more cost-effective than either treatment on its own.

Maintenance treatment with antidepressants

- Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for two years.

Combined treatment for treatment-resistant depression

- For patients whose depression is treatment resistant, the combination of antidepressant medication with CBT should be considered.

CBT for recurrent depression

- CBT should be considered for patients with recurrent depression who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions.

The following guidance is evidence-based. The grading scheme used for the recommendations (A, B, C, Good Practice Points (GPP) or NICE) is described in Chapter 3 (3.4.3.2); the evidence on which the guidance is based is provided in the full guideline (Chapters 5 through 9).

Guidance

This guideline makes recommendations for the identification, treatment and management of depression for adults aged 18 years and over, in primary and secondary care. Depression is a broad and heterogeneous diagnostic grouping, central to which is depressed mood or loss of pleasure in most activities. Depressive symptoms are frequently accompanied by symptoms of anxiety, but may also occur on their own. ICD-10 uses an agreed list of 10 depressive symptoms, and divides the common form of major depressive episode into four groups: not depressed (fewer than four symptoms), mild depression

(four symptoms), moderate depression (five to six symptoms), and severe depression (seven or more symptoms, with or without psychotic symptoms). Symptoms should be present for a month or more and every symptom should be present for most of every day.

For the purposes of this guideline, the treatment and management of depression has been divided into the following descriptions as defined by ICD-10:

- mild depression
- moderate depression
- severe depression
- severe depression with psychotic symptoms.

However, it is doubtful whether the severity of the depressive illness can realistically be captured in a single symptom count. Clinicians will wish to consider family and previous history as well as the degree of associated disability in making this assessment.

We also make recommendations using the following descriptions, which are defined in the text:

- recurrent depression
- treatment-resistant depression
- chronic depression
- atypical depression
- psychotic depression.

The guideline draws on the best current available evidence for the treatment and management of depression. However, there are some significant limitations to the current evidence base, which have considerable implications for this guideline. These include very limited data on both long-term outcomes for most, if not all, interventions, and outcomes generally for the type of severe depression that often presents major challenges in secondary care mental health services. In part, these limitations arise from the problems associated with the randomised control trial methodology for all interventions, but particularly for psychological and service interventions.

However, the most significant limitation is with the concept of depression itself. The view of the Guideline Development Group is that it is too broad and heterogeneous a category, and has limited validity as a basis for effective treatment plans. A focus on symptoms alone is not sufficient because a wide range of biological, psychological and social factors have a significant impact on response to treatment and are not captured by the current diagnostic systems.

The guideline makes good practice points and evidence-based recommendations for the psychological, pharmacological, service-level and self-help interventions appropriate to each section.

4.1 Good practice points relevant to the care of all people with depression

4.1.1 Depression and anxiety

4.1.1.1 When depressive symptoms are accompanied by anxious symptoms, the first priority should usually be to treat the depression. Psychological treatment for depression often reduces anxiety, and many antidepressants also have sedative/anxiolytic effects. When the patient has anxiety without depression, the NICE guideline on management of anxiety should be followed. (GPP)

4.1.2 Providing good information, informed consent and mutual support

The provision of information and support is important in promoting understanding and collaboration between patients, their families and carers and healthcare professionals.

4.1.2.1 Patients and, where appropriate, families and carers should be provided with information on the nature, course and treatment of depression including the use and likely side-effect profile of medication. (GPP)

4.1.2.2 Healthcare professionals should make all efforts necessary to ensure that a patient can give meaningful and properly informed consent before treatment is initiated. This is especially important when a patient has a more severe depression or is subject to the Mental Health Act. (GPP)

4.1.2.3 Patients, families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate. (GPP)

4.1.2.4 Primary Care Trusts and mental health communities should collate information on local self-help groups for practitioners. (GPP)

4.1.3 Language

4.1.3.1 When talking to patients and carers, healthcare professionals should use everyday, jargon-free language. If technical terms are used they should be explained to the patient. (GPP)

4.1.3.2 Where possible, all services should provide written material in the language of the patient, and independent interpreters should be sought for people whose preferred language is not English. (GPP)

4.1.3.3 Where available, consideration should be given to providing psychotherapies and information about medications in the patient's own language if this is not English. (GPP)

4.1.4 Advance directives

4.1.4.1 Although there are limitations with advance directives about the choice of treatment for people who are depressed, it is recommended that they are

developed and documented in care plans, especially for people who have recurrent severe or psychotic depression, and for those who have been treated under the Mental Health Act. (GPP)

4.1.5 Patient preference

4.1.5.1 A number of different treatment approaches may be equally effective for patients who are depressed, especially for those with mild and moderate depression who are not considered to be at substantial risk of self-harm. Patient preference and the experience and outcome of previous treatment(s) should be considered when deciding on treatment. (GPP)

4.1.6 Assessment and co-ordination of care

The effective assessment of a patient (including where appropriate, a comprehensive review of physical, psychological and social needs and a risk assessment) and the subsequent co-ordination of his or her care may contribute significantly to improved outcomes. This is particularly important if the patient receives care in both primary and secondary care. The nature and course of depression are significantly affected by psychological, social and physical characteristics of the patient and his or her environment. These factors can have a significant impact on both the initial choice of intervention and the probability of the patient benefiting from that intervention.

4.1.6.1 When assessing a person with depression, healthcare professionals should consider the psychological, social, cultural and physical characteristics of the patient and the quality of interpersonal relationships. They should consider the impact of these on the depression and the implications for choice of treatment and its subsequent monitoring. (GPP)

4.1.6.2 In older adults with depression, their physical state, living conditions and social isolation should be assessed. The involvement of more than one agency is recommended where appropriate. (GPP)

4.1.6.3 In deciding on a treatment for a depressed patient, the healthcare professional should discuss alternatives with the patient, taking into account other factors such as past or family history of depression, response of any previous episodes to intervention, and the presence of associated problems in social or interpersonal relationships. (GPP)

4.1.6.4 Healthcare professionals should always ask patients with depression directly about suicidal ideas and intent. (GPP)

4.1.6.5 Healthcare professionals should advise patients and carers to be vigilant for changes in mood, negativity and hopelessness, and suicidal ideas, particularly during high-risk periods, such as during initiation of and changes to medication and increased personal stress. Patients and carers should be advised to contact the appropriate healthcare practitioner concerned. (GPP)

4.1.6.6 Healthcare professionals should assess whether patients with suicidal ideas have adequate social support and are aware of sources of help. They should advise them to seek appropriate help if the situation deteriorates. (GPP)

4.1.6.7 Where a patient's management is shared between primary and secondary care, there should be clear agreement between individual health care professionals on the responsibility for the monitoring and treatment of that patient, and the treatment plan should be shared with the patient and, where appropriate, with families and carers. (GPP)

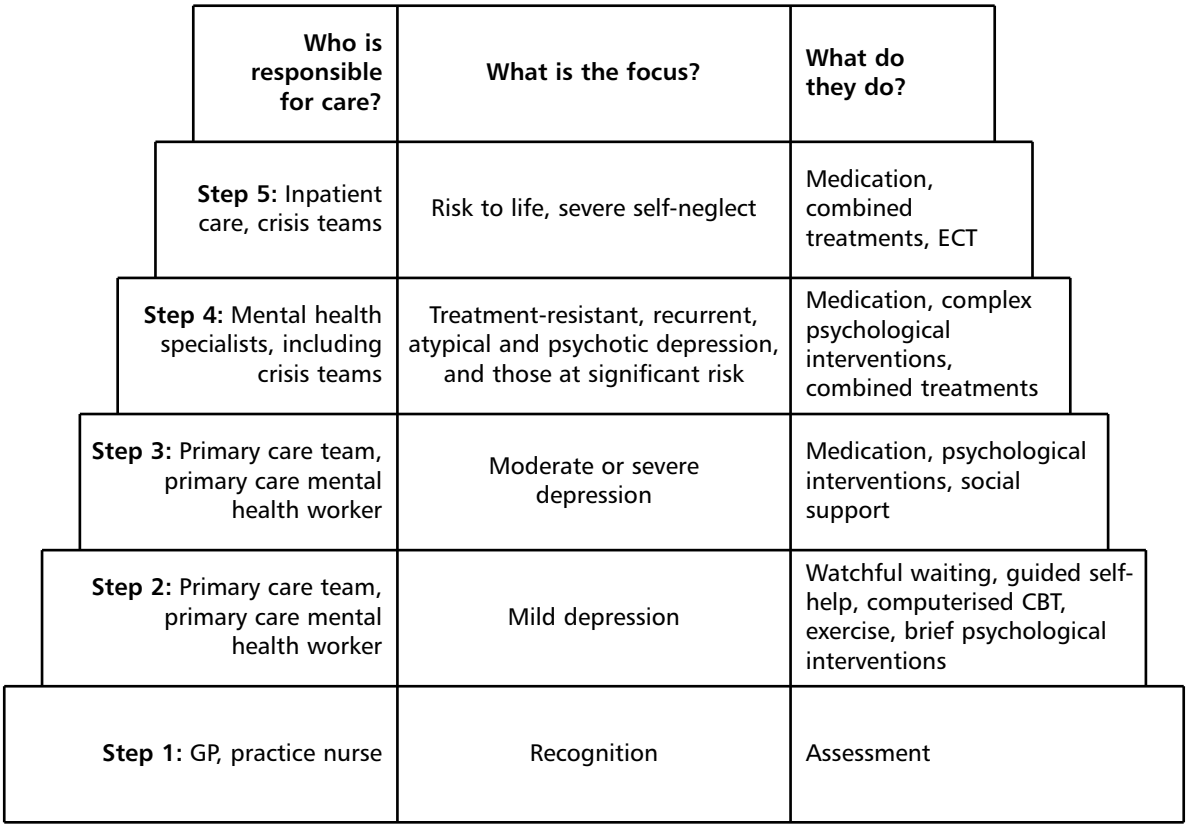
4.1.6.8 All health care professionals involved in diagnosis and management should have a demonstrably high standard of consultation skills, so that a structured approach can be taken to the diagnosis and subsequent management of depression. (GPP)

4.1.6.9 Healthcare professionals should ensure they maintain their competence in risk assessment and management. (GPP)

4.2 Stepped care

The stepped-care model of depression draws attention to the different needs that depressed people have – depending on the characteristics of their depression and their personal and social circumstances – and the responses that are required from services. It provides a framework in which to organise the provision of services supporting both patients and carers, and healthcare professionals in identifying and accessing the most effective interventions (see Figure 1).

Figure 1: The stepped care model.



The guidance follows these five steps:

- recognition of depression in primary care and general hospital settings
- managing recognised depression in primary care – mild depression
- managing recognised depression in primary care – moderate to severe depression
- involvement of specialist mental health services – treatment-resistant, recurrent, atypical and psychotic depression, and those at significant risk
- depression needing inpatient care.

Each step introduces additional interventions; the higher steps assume interventions in the previous step.

4.3 Step 1: Recognition of depression in primary care and general hospital settings

Around half of all people with depression in the community do not present to their GP. In addition, at least two-thirds of depressed people who see their GP present with physical or somatic symptoms rather than psychological symptoms, making recognition harder. Moreover, many patients with established physical diseases become depressed during the course of their illness, and recognition of depression for this population is important and can lead to improved outcomes. The following recommendations are for healthcare professionals working in primary care and general hospital settings.

4.3.1.1 Screening should be undertaken in primary care and general hospital settings for depression in high-risk groups – for example, those with a past history of depression, significant physical illnesses causing disability, or other mental health problems, such as dementia. (C)

4.3.1.2 Healthcare professionals should bear in mind the potential physical causes of depression and the possibility that depression may be caused by medication, and consider screening if appropriate. (C)

4.3.1.3 Screening for depression should include the use of at least two questions concerning mood and interest, such as: 'During the last month, have you often been bothered by feeling down, depressed or hopeless?' and 'During the last month, have you often been bothered by having little interest or pleasure in doing things?' (B)

4.4 Step 2: Recognised depression in primary care – mild depression

The large majority of patients with depression (more than 80%) are cared for solely in primary care. Of those who use secondary care services, most, if not all, continue to receive much of their care from the primary care team.

For a significant number of people with mild to moderate depression, brief interventions delivered by the primary care team are effective; for others – particularly if they have not responded to the initial brief intervention – more complex interventions, which could be provided in primary or secondary care, are required.

Many patients with milder depression respond to interventions such as exercise or guided self-help, although many improve while being monitored without additional help. More structured therapies, such as problem-solving, brief CBT or counselling can be helpful. Antidepressant drugs and psychological therapies, such as longer-term CBT or interpersonal psychotherapy (IPT), are not recommended as an initial treatment; these may be offered when simpler methods (for example, guided self-help or exercise) have failed to produce an adequate response.

4.4.1 General measures

Sleep and anxiety management

4.4.1.1 Patients with mild depression may benefit from advice on sleep hygiene and anxiety management. (C)

Watchful waiting

4.4.1.2 For patients with mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, a further assessment should be arranged, normally within two weeks ('watchful waiting'). (C)

4.4.1.3 Healthcare professionals should make contact with patients with depression who do not attend follow-up appointments. (C)

Exercise

4.4.1.4 Patients of all ages with mild depression should be advised of the benefits of following a structured and supervised exercise programme of typically up to three sessions per week of moderate duration (45 minutes to one hour) for between 10 and 12 weeks. (C)

Guided self-help

4.4.1.5 For patients with mild depression, healthcare professionals should consider recommending a guided self-help programme based on cognitive behavioural therapy (CBT). (B)

4.4.1.6 Guided self-help should consist of the provision of appropriate written materials and limited support from a healthcare professional, who typically introduces the self-help programme and reviews progress and outcome. This intervention should normally take place over six to nine weeks, including follow-up. (B)

4.4.2 Psychological interventions

For mild depression, a number of brief psychological interventions are effective. The choice of treatment should reflect the patient's preference based on informed discussion, past experience of treatment and the fact that the patient may not have benefited from other brief interventions. For all treatments the strength of the therapeutic alliance is important in ensuring a good outcome. Problem-solving is a brief treatment that can readily be learned by practice nurses and by GPs themselves.

4.4.2.1 In both mild and moderate depression, psychological treatment specifically focused on depression (such as problem-solving therapy, brief CBT and counselling) of six to eight sessions over 10 to 12 weeks should be considered. (B)

4.4.2.2 In patients with depression who have significant comorbidity, consideration should be given to extending the duration of treatment for depression, making use, where appropriate, of treatments that focus specifically on the comorbid problems. (C)

4.4.2.3 The full range of psychological interventions should be made available to older adults with depression, because they may have the same response to psychological interventions as younger people. (C)

4.4.2.4 Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE 2002)

4.4.2.5 Since the publication of NICE guidance on CCBT (NICE 2002), new evidence reporting positive results for CCBT with mild and moderate depression has emerged. Clinicians considering the use of CCBT should consider this evidence in making decisions about the use of CCBT, pending the publication of the updated NICE guidance, which is scheduled for June 2005. (GPP)

4.4.2.6 Healthcare professionals providing psychological treatment should be experienced in the treatment of the disorder and competent in the delivery of the treatment provided. (GPP)

4.4.2.7 In all psychological interventions, healthcare professionals should develop and maintain an appropriate therapeutic alliance, because this is associated with a positive outcome independent of the type of therapy provided. (C)

4.4.3 Antidepressant drugs

Randomised controlled trial (RCT) evidence indicates that for many patients there is little clinically important difference between antidepressants and placebo, and the placebo response is greatest in mild depression. For guidance on the use of antidepressant drugs, see Section 4.5.2.

4.4.3.1 Antidepressants are not recommended for the initial treatment of mild depression, because the risk–benefit ratio is poor. (C)

4.4.3.2 The use of antidepressants should be considered for patients with mild depression that is persisting after other interventions, and those whose depression is associated with psychosocial and medical problems. (C)

4.4.3.3 The use of antidepressants should be considered when patients with a past history of moderate or severe depression present with mild depression. (C)

4.5 Step 3: Recognised depression in primary care – moderate or severe

Moderate or severe depression can be treated in both primary and secondary care and, as with mild depression, the choice of treatment will reflect patient preference, past experience of treatment and the fact that the patient may not have benefited from other interventions. With more severe depression, the risk of suicide should always be considered. Referral to secondary services should be based on this assessment, the degree of functional impairment and the presence of significant comorbidities or specific symptoms. Where trained mental health professionals are working in primary care, specialised treatments may be available in this setting.

4.5.1 Risk to self or others

4.5.1.1 Where a patient presents considerable immediate risk to self or others, urgent referral to a specialist mental health service should be arranged. (GPP)

4.5.2 Antidepressant drugs

There is more evidence for the effectiveness of antidepressant medication in moderate to severe depression than in milder depression. Antidepressants are as effective as psychological interventions, widely available and cost less. Careful monitoring of symptoms, side effects and suicide risk (particularly in those aged under 30) should be routinely undertaken, especially when initiating antidepressant medication. Patient preference and past experience of treatment, and particular patient characteristics should inform the choice of drug. It is also important to monitor patients for relapse and discontinuation/withdrawal symptoms when reducing or stopping medication. Patients should be warned about the risks of reducing or stopping medication.

Starting treatment

4.5.2.1 In moderate depression, antidepressant medication should be routinely offered to all patients before psychological interventions. (B)

4.5.2.2 Common concerns about taking medication should be addressed. For example, patients should be advised that craving and tolerance do not occur, and that taking medication should not be seen as a sign of weakness. (GPP)

4.5.2.3 All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects and of the risk of discontinuation/withdrawal symptoms. (C)

4.5.2.4 Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed and the possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (GPP)

Monitoring risk

4.5.2.5 Patients started on antidepressants who are considered to present an increased suicide risk or are younger than 30 years (because of the potential increased risk of suicidal thoughts associated with the early stages of antidepressant treatment for this group) should normally be seen after one week and frequently thereafter as appropriate until the risk is no longer considered significant. (C)

4.5.2.6 For patients at high risk of suicide, a limited quantity of antidepressants should be prescribed. (C)

4.5.2.7 When a patient with depression is assessed to be at a high risk of suicide, the use of additional support such as more frequent direct contacts with primary care staff or telephone contacts should be considered. (C)

4.5.2.8 Particularly in the initial stages of SSRI treatment, healthcare professionals should actively seek out signs of akathisia, suicidal ideation, and increased anxiety and agitation. They should also advise patients of the risk of these symptoms in the early stages of treatment and advise them to seek help promptly if these are at all distressing. (C)

4.5.2.9 In the event that a patient develops marked and/or prolonged akathisia or agitation while taking an antidepressant, the use of the drug should be reviewed. (C)

Continuing treatment

4.5.2.10 Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after two weeks. Thereafter they should be seen on an appropriate and regular basis, for example, at intervals of two to four weeks in the first three months and at longer intervals thereafter, if response is good. (C)

4.5.2.11 Antidepressants should be continued for at least six months after remission of an episode of depression, because this greatly reduces the risk of relapse. (A)

4.5.2.12 When a patient has taken antidepressants for six months after remission, healthcare professionals should review with the patient the need for continued antidepressant treatment. This review should include consideration of the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties. (C)

The choice of antidepressants

4.5.2.13 When an antidepressant is to be prescribed in routine care, it should be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects. (A)

4.5.2.14 When prescribing an SSRI, consideration should be given to using a product in a generic form. Fluoxetine and citalopram, for example, would be reasonable choices because they are generally associated with fewer discontinuation/withdrawal symptoms. However, fluoxetine is associated with a higher propensity for drug interactions. (C)

4.5.2.15 Dosulepin, phenelzine, combined antidepressants and lithium augmentation of antidepressants should only be routinely initiated by specialist mental health professionals, including General Practitioners with a Special Interest in Mental Health. (C)

4.5.2.16 Venlafaxine treatment should only be initiated by specialist mental health medical practitioners, including General Practitioners with a Special Interest in Mental Health. (C)

4.5.2.17 Venlafaxine treatment should only be managed under the supervision of specialist mental health medical practitioners, including General Practitioners with a Special Interest in Mental Health. (C)

4.5.2.18 Toxicity in overdose should be considered when choosing an antidepressant for patients at significant risk of suicide. Healthcare professionals should be aware that the tricyclic antidepressants (with the exception of lofepramine) are more dangerous in overdose than other equally effective drugs recommended for routine use in primary care. (C)

4.5.2.19 If a depressed patient being treated with an SSRI develops increased agitation early in treatment, the prescriber should provide appropriate information, and if the patient prefers the drug should be changed to a different antidepressant. Alternatively, a brief period of concomitant treatment with a benzodiazepine should be considered, followed by a clinical review within two weeks. (C)

4.5.2.20 When a patient's depression fails to respond to the first antidepressant prescribed, the prescriber should check that the drug has been taken regularly and in the prescribed dose. (GPP)

4.5.2.21 If the response to a standard dose of an antidepressant is inadequate, and there are no significant side effects, a gradual increase in dose should be considered in line with the schedule suggested by the Summary of Product Charateristics. (C)

4.5.2.22 Prescribers should consider switching to another antidepressant if there has been no response at all after one month, but if there has been a partial response, a decision to switch can be postponed until six weeks. (C)

4.5.2.23 If an antidepressant has not been effective or is poorly tolerated and – after consideration of a range of other treatment options – the decision is made to offer a further course of antidepressants, then another single antidepressant should be prescribed. (C)

4.5.2.24 Reasonable choices for a second antidepressant include a different SSRI or mirtazapine, but consideration may also be given to other alternatives, including moclobemide, reboxetine, and tricyclic antidepressants (except dosulepin). (B)

4.5.2.25 When switching from one antidepressant to another, prescribers should be aware of the need for gradual and modest incremental increases of dose, of interactions between antidepressants and the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed. Features include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus. (C)

4.5.2.26 Before prescribing mirtazapine, practitioners should take into account its propensity to cause sedation and weight gain. (A)

4.5.2.27 Before prescribing moclobemide, practitioners should take into account the need to wash out previously prescribed antidepressants. (A)

4.5.2.28 Before prescribing reboxetine, practitioners should take into account the relative lack of data on side effects. Patients taking reboxetine should be monitored carefully. (B)

4.5.2.29 Before prescribing tricyclic antidepressants, practitioners should take into account their poorer tolerability compared with other equally effective antidepressants, the increased risk of cardiotoxicity and their toxicity in overdose. (B)

4.5.2.30 Where a tricyclic is chosen as an antidepressant, lofepramine is a reasonable choice because of its relative lack of cardiotoxicity. (C)

4.5.2.31 Patients who start on low-dose tricyclic antidepressants and who have a clear clinical response may be maintained on that dose with careful monitoring. (C)

4.5.2.32 Patients started on low-dose tricyclic antidepressants should be carefully monitored for side effects and efficacy, and the dose gradually increased if there is lack of efficacy and no major side effects. (GPP)

4.5.2.33 Although there is evidence that St John's wort may be of benefit in mild or moderate depression, healthcare professionals should not prescribe or advise its use by patients because of uncertainty about appropriate doses, variation in the nature of preparations and potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anticonvulsants). (C)

4.5.2.34 Patients who are taking St John's wort should be informed of the different potencies of the preparations available and the uncertainty that arises from this. They should also be informed of the potential serious interactions of St John's wort with other drugs (including oral contraceptives, anti-coagulants and anti-convulsants). (C)

Patient characteristics

Gender

4.5.2.35 When considering which antidepressants to prescribe for female patients, the fact that they have poorer tolerance of imipramine should be taken into account. (B)

Age

4.5.2.36 For older adults with depression, antidepressant treatment should be given at an age-appropriate dose for a minimum of six weeks before treatment is considered to be ineffective. If there has been a partial response within this period, treatment should be continued for a further six weeks. (C)

4.5.2.37 When prescribing antidepressants – in particular tricyclics – for older adults with depression, careful monitoring for side effects should be undertaken. (C)

4.5.2.38 Healthcare professionals should be aware of the increased frequency of drug interactions when prescribing an antidepressant to older adults who are taking other medications. (GPP)

Patients with dementia

4.5.2.39 Depression in patients with dementia should be treated in the same way as depression in other older adults. (C)

4.5.2.40 Healthcare professionals should be aware that depression responds to antidepressants even in the presence of dementia. (C)

Patients with cardiovascular disease

4.5.2.41 When initiating treatment in a patient with a recent myocardial infarction or unstable angina, sertraline is the treatment of choice as it has the most evidence for safe use in this situation.(B)

4.5.2.42 Healthcare professionals should take account of the increased risks associated with tricyclic antidepressants in patients with cardiovascular disease. (GPP)

4.5.2.43 An ECG should be carried out and blood pressure measurement taken before prescribing a tricyclic antidepressant for a depressed patient at significant risk of cardiovascular disease. (GPP)

4.5.2.44 For patients with pre-existing heart disease venlafaxine should not be prescribed. (C)

Stopping or reducing antidepressants

Although antidepressants are not associated with tolerance and craving, as experienced when withdrawing from addictive substances such as opiates or alcohol, some patients experience symptoms when stopping antidepressants or reducing the dose. These can include dizziness, nausea, paraesthesia, anxiety and headaches and, in this guideline, are referred to as discontinuation/withdrawal symptoms.

4.5.2.45 All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly. (C)

4.5.2.46 Patients should be advised to take the drugs as prescribed. This may be particularly important for drugs with a shorter half-life, such as paroxetine, in order to avoid discontinuation/withdrawal symptoms. (C)

4.5.2.47 Healthcare professionals should normally gradually reduce the doses of the drug over a four-week period, although some people may require longer periods. Fluoxetine can usually be stopped over a shorter period. (C)

4.5.2.48 If discontinuation/withdrawal symptoms are mild, practitioners should reassure the patient and monitor symptoms. If symptoms are severe, the practitioner should consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) and reduce gradually while monitoring symptoms. (C)

4.5.2.49 Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (GPP)

4.5.3 Psychological treatments

For moderate to severe depression, a number of structured psychological interventions of longer duration (usually of 16 to 20 sessions) from an appropriately trained member of the mental health team are effective. In addition to the evidence for their effectiveness, the choice of treatment will reflect patient preference and past experience of treatment. Most patients receiving these interventions will not have benefited from other interventions. The same principles underpinning the use of psychological therapies outlined for the treatment of mild depression (Step 2) also apply here.

Where depression is comorbid with another significant disorder, such as personality disorder, then treatment may need to be extended or varied.

Cognitive behavioural therapies and interpersonal therapy

The following recommendations focus on the provision of CBT. However, IPT can also be an effective treatment for depression. Where patient preference or clinician opinion favours the use of IPT, it may be appropriate to draw the patient's attention to the more limited evidence base for this therapy.

4.5.3.1 When considering individual psychological treatments for moderate, severe and treatment-resistant depression, the treatment of choice is CBT. IPT should be considered if the patient expresses a preference for it or if, in the view of the healthcare professional, the patient may benefit from it. (B)

4.5.3.2 For moderate and severe depression, the duration of all psychological treatments should typically be in the range of 16 to 20 sessions over six to nine months. (B)

4.5.3.3 CBT should be offered to patients with moderate or severe depression who do not take or who refuse antidepressant treatment. (B)

4.5.3.4 CBT should be considered for patients who have not had an adequate response to a range of other treatments for depression (for example, antidepressants and brief psychological interventions). (C)

4.5.3.5 CBT should be considered for patients with severe depression in whom the avoidance of side effects often associated with antidepressants is a clinical priority or personal preference. (B)

4.5.3.6 For patients with severe depression who are starting a course of CBT, consideration should be given to providing two sessions per week for the first month of treatment. (C)

4.5.3.7 Where patients have responded to a course of individual CBT, consideration should be given to follow-up sessions, which typically consist of two to four sessions over 12 months. (C)

Initial presentation of severe depression

4.5.3.8 When patients present initially with severe depression, a combination of antidepressants and individual CBT should be considered as the combination is more cost-effective than either treatment on its own. (B)

Couple-focused therapy

4.5.3.9 Couple-focused therapy should be considered for patients with depression who have a regular partner and who have not benefited from a brief individual intervention. An adequate course of couple-focused therapy should be 15 to 20 sessions over five to six months. (B)

Psychodynamic psychotherapy

4.5.3.10 Psychodynamic psychotherapy may be considered for the treatment of the complex comorbidities that may be present along with depression. (C)

4.5.4 Atypical depression

Depression can present with atypical features, commonly over-eating and over-sleeping. The syndrome is also associated with mood reactivity and a longstanding pattern of interpersonal rejection and over-sensitivity. In comparison with major depressive disorder without atypical features, patients with depression with atypical features are more often female, have a younger age of onset and a more severe degree of psychomotor slowing. Coexisting diagnoses of panic disorder, substance abuse and somatisation disorder are also common.

4.5.4.1 Patients whose depression has atypical features should be treated with an SSRI. (C)

4.5.4.2 Referral to mental health specialists should be considered for patients with atypical depression and significant functional impairment who have not responded to an SSRI. (GPP)

4.5.5 Chronic depression

Chronic depression is diagnosed when a person meets the diagnostic criteria for depression for at least two years. Such patients may require combination treatments and attention to social and support factors that may maintain or ameliorate their difficulties. Patients who have had chronic depression may require rehabilitation to help them regain confidence to return to more independent living. People who have had severe or chronic depression may require special help in returning to work. Work provides a number of protective factors for depression including structure to a day, social contacts and self-esteem.

4.5.5.1 Patients with chronic depression should be offered a combination of CBT and antidepressant medication. (A)

4.5.5.2 For male patients with chronic depression who have not responded to an SSRI, consideration should be given to a tricyclic antidepressant because men tolerate the side effects of tricyclic antidepressants reasonably well. (C)

4.5.5.3 For people with chronic depression who would benefit from additional social support, befriending should be considered as an adjunct to pharmacological or psychological treatments. Befriending should be by trained volunteers providing, typically, at least weekly contact for between two and six months. (C)

4.5.5.4 Where a patient's depression has resulted in loss of work or disengagement from other social activities over a longer term, a rehabilitation programme addressing these difficulties should be considered. (C)

4.5.6 Enhanced care in primary care

In primary care, the following strategies can improve the effectiveness of treatments offered.

4.5.6.1 The provision of telephone support by appropriately trained members of the primary care team, informed by clear treatment protocols, should be considered for all patients, in particular for the monitoring of antidepressant medication regimes. (B)

4.5.6.2 Primary care organisations should consider establishing multifaceted care programmes that integrate – through clearly specified protocols – the delivery and monitoring of appropriate psychological and pharmacological interventions for the care of people with depression. (C)

4.6 Step 4: Specialist mental health services – treatment-resistant, recurrent, atypical and psychotic depression, and those at significant risk

Specialist mental health professionals, including GPs with a Special Interest in Mental Health, provide assessment, treatment and consultancy services for this group of patients. They may do this in secondary care services or through attachment to primary care mental health teams. Patients may enter care directly at this step if they are assessed as requiring specialist services.

4.6.1.1 The assessment of patients with depression referred to specialist mental health services should include a full assessment of their symptom profile and suicide risk and, where appropriate, previous treatment history. Assessment of psychosocial stressors, personality factors and significant relationship difficulties should also be undertaken, particularly where the depression is chronic or recurrent. (GPP)

4.6.1.2 In specialist mental health services, after a thorough review of previous treatments for depression has been undertaken, consideration should be given to re-introducing previous treatments that have been inadequately delivered or adhered to. (GPP)

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

4.6.1.4 Medication in secondary-care mental health services should be initiated under the supervision of a consultant psychiatrist. (GPP)

4.6.2 Treatment-resistant depression

Some people with depression do not respond well to initial treatment. This guideline defines treatment-resistant depression as that which fails to respond to two or more antidepressants given sequentially at an adequate dose for an adequate time. Patients whose depression is treatment-resistant may benefit from psychological interventions. For chronically depressed patients, the combination of pharmacological and psychological treatment may be particularly effective. Patient preference, the level of risk, social and personal circumstances, and the drawbacks of all interventions will influence the choice of treatment.

Combined psychological and drug treatment

4.6.2.1 For patients whose depression is treatment-resistant, the combination of antidepressant medication with CBT should be considered. (B)

4.6.2.2 For patients with treatment-resistant moderate depression who have relapsed while taking, or after finishing, a course of antidepressants, the combination of antidepressant medication with CBT should be considered. (B)

Drug treatments

4.6.2.3 A trial of lithium augmentation should be considered for patients whose depression has failed to respond to several antidepressants and who are prepared to tolerate the burdens associated with its use. (B)

4.6.2.4 Before initiating lithium augmentation, an ECG should be carried out. (C)

4.6.2.5 Venlafaxine should be considered for patients whose depression has failed to respond to two adequate trials of other antidepressants. Consideration should be given to increasing the dose up to BNF limits if required, provided patients can tolerate the side effects. (C)

4.6.2.6 Before prescribing venlafaxine, practitioners should take into account the increased likelihood of patients stopping treatment because of side effects, compared with equally effective SSRIs. (A)

4.6.2.7 Before prescribing venlafaxine, practitioners should take into account its higher propensity for discontinuation/withdrawal symptoms if stopped abruptly, its toxicity in overdose and its higher cost. (C)

4.6.2.8 Before prescribing venlafaxine, an ECG and blood pressure measurement should be undertaken. (C)

4.6.2.9 For patients prescribed venlafaxine, consideration should be given to monitoring of cardiac function. Regular monitoring of blood pressure should be undertaken, particularly for those on higher doses. (C)

4.6.2.10 Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate the side effects. There is evidence for benefits from the addition of mianserin or mirtazapine to SSRIs. (C)

4.6.2.11 Where patients are treated with one antidepressant augmented by another, careful monitoring of progress and side effects is advised and the importance of this should be explained to the patient. Particular care should be taken to monitor for serotonin syndrome. (GPP)

4.6.2.12 When used to augment another antidepressant, mianserin should be used with caution, particularly in older adults, because of the risk of agranulocytosis. (C)

4.6.2.13 Where combinations of antidepressants other than mianserin with SSRIs and mirtazapine with SSRIs are considered, healthcare professionals should re-evaluate the adequacy of previous treatments carefully before proceeding, and consider seeking a second opinion. Any discussion should be documented in the notes. (C)

4.6.2.14 Phenelzine should be considered for patients whose depression has failed to respond to alternative antidepressants and who are prepared to tolerate the side effects and dietary restrictions associated with its use. However, its toxicity in overdose should be considered when prescribing for patients at high-risk of suicide. (C)

4.6.2.15 Augmentation of an antidepressant with carbamazepine, lamotrigine, buspirone, pindolol, valproate or thyroid supplementation is not recommended in the routine management of treatment-resistant depression. (B)

4.6.2.16 Dosulepin should not be initiated routinely because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose. (C)

4.6.2.17 There is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants. (C)

Referral

4.6.2.18 When a patient's depression has failed to respond to various strategies for augmentation and combination treatments, referral to a clinician with a specialist interest in treating depression should be considered. (GPP)

4.6.3 Recurrent depression and relapse prevention

Antidepressants can contribute significantly to reducing the frequency of recurrence when prescribed as maintenance medication. Structured psychological treatments can also make a significant contribution.

Drug advice

4.6.3.1 Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for two years. (B)

4.6.3.2 Patients on maintenance treatment should be re-evaluated, taking into account age, comorbid conditions and other risk factors in the decision to continue maintenance treatment beyond two years. (GPP)

4.6.3.3 The antidepressant dose used for the prevention of recurrence should be maintained at the level at which acute treatment was effective. (C)

4.6.3.4 Patients who have had multiple episodes of depression, and who have had a good response to treatment with an antidepressant and lithium augmentation, should remain on this combination for at least six months. (B)

4.6.3.5 When one drug is to be discontinued in a patient taking an antidepressant with lithium augmentation, this should be lithium in preference to the antidepressant. (C)

4.6.3.6 The use of lithium as a sole agent to prevent recurrence of depression in patients with previous recurrences is not recommended. (C)

Psychological treatments

4.6.3.7 CBT should be considered for patients with recurrent depression who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions. (C)

4.6.3.8 Where a patient with depression has a previous history of relapse and poor or limited response to other interventions, consideration should be given to CBT. (B)

4.6.3.9 When patients with moderate or severe depression have responded to another intervention but are unable or unwilling to continue with that intervention, and are assessed as being at significant risk of relapse, a maintenance course of CBT should be considered. (B)

4.6.3.10 Mindfulness-based CBT, usually delivered in a group format, should be considered for people who are currently well but have experienced three or more previous episodes of depression, because this may significantly reduce the likelihood of future relapse. (B)

4.6.4 Atypical depression

4.6.4.1 Phenelzine should be considered for women whose depression is atypical, and who have not responded to, or who cannot tolerate, an SSRI. However, its toxicity in overdose should be considered when prescribing for patients at high-risk of suicide. (C)

4.6.4.2 All patients receiving phenelzine require careful monitoring (including taking blood pressure) and advice on interactions with other medicines and foodstuffs, and should have their attention drawn to the product information leaflet. (C)

4.6.5 Recommendations for the pharmacological management of psychotic depression

4.6.5.1 For patients with psychotic depression, augmenting the current treatment plan with antipsychotic medication should be considered, although the optimum dose and duration of treatment are unknown. (C)

4.7 Step 5: Depression needing inpatient care

Certain specialist services – inpatient services and specialist treatments such as electroconvulsive therapy – will be provided by secondary care services. These services are for patients who are severely depressed and who may be assessed as being at high risk of self-harm or suicide.

4.7.1 Inpatient care

Depressed people are admitted to inpatient care for a number of reasons related to severity of the disorder, concerns with self-care and neglect, and suicide risk. It is important that acute psychiatric wards make every effort to provide a place of sanctuary that is non-threatening and enables healthcare professionals to provide appropriate care. Activities conducive to recovery for depression should be provided. Boredom and rumination can affect recovery.

4.7.1.1 Inpatient treatment should be considered for people with depression who are at significant risk of suicide or self-harm. (C)

4.7.1.2 Crisis resolution and home treatment teams should be considered for patients with depression who might benefit from an early discharge from hospital after a period of inpatient care. (C)

4.7.2 Electroconvulsive therapy

4.7.2.1 It is recommended that electroconvulsive therapy (ECT) is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective, and/or when the condition is considered to be potentially life-threatening, in individuals with a severe depressive illness. (NICE 2003)

4.7.2.2 The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current comorbidities; anticipated adverse events – particularly cognitive impairment – and the risks of not having treatment. (NICE 2003)

4.7.2.3 The risks associated with ECT may be enhanced during pregnancy, in older people, and in children and young people, and therefore clinicians should exercise particular caution when considering ECT treatment in these groups. (NICE 2003)

4.7.2.4 Valid consent should be obtained in all cases where the individual has the ability to grant or refuse consent. The decision to use ECT should be made jointly by the individual and the clinician(s) responsible for treatment, on the basis of an informed discussion. This discussion should be enabled by the provision of full and appropriate information about the general risks associated with ECT and about the risks and potential benefits specific to that individual. Consent should be obtained without pressure or coercion, which may occur as a result of the circumstances and clinical setting, and the individual should be reminded of their right to withdraw consent at any point. There should be strict adherence to recognised guidelines about consent and the involvement of patient advocates and/or carers to facilitate informed discussion is strongly encouraged. (NICE 2003)

4.7.2.5 In all situations where informed discussion and consent is not possible, advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted. (NICE 2003)

4.7.2.6 Clinical status should be assessed after each ECT session and treatment should be stopped when a response has been achieved, or sooner if there is evidence of adverse effects. Cognitive function should be monitored on an ongoing basis, and at a minimum at the end of each course of treatment. (NICE 2003)

4.7.2.7 It is recommended that a repeat course of ECT should be considered under the circumstances indicated in 4.7.2.1 only for individuals who have severe depressive illness, and who have previously responded well to ECT. In patients who are experiencing an acute episode but have not previously responded, a repeat trial of ECT should be undertaken only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate. (NICE 2003)

4.7.2.8 Because the longer-term benefits and risks of ECT have not been clearly established, it is not recommended as a maintenance therapy in depressive illness. (NICE 2003)

4.8 Research recommendations

4.8.1 Clinical research recommendations

- Research is needed into the cost-effectiveness of routine screening of populations known to be at high risk of depression.
- Efficacy studies of the role of guided self-help in a stepped-care programme are needed. The focus of such studies should be on the role of guided self-help in both early intervention and maintenance.
- Efficacy trials of the long-term effectiveness of exercise in improving outcomes in depression, including maintenance interventions and intensity of exercise should be undertaken.

- The efficacy of organisational interventions, such as chronic disease management programmes or other programmes of enhanced care for depression should be tested in large-scale multicentre trials in the NHS.

- Trials should be undertaken of the efficacy of a range of social support interventions for socially isolated and vulnerable groups of people with depression.

- Adequately powered RCTs reporting all relevant outcomes, including relapse rates, comparing the efficacy of different models of CBT, IPT and behaviour therapy should be undertaken to identify differential individual response to treatment and how this is related to the severity of baseline depression symptoms.

- An adequately powered RCT reporting all relevant outcomes to assess the efficacy of problem-solving therapy for moderate depression in primary care should be undertaken.

- An adequately powered RCT reporting all relevant outcomes to assess the efficacy of short-term psychodynamic therapy for depression should be undertaken.

- Further research is needed on all aspects of the pharmacological treatment of depression in the elderly, in particular in those older than 80 years of age. There is a special need for research evidence on optimum treatment and maintenance doses for elderly people.

- An adequately powered RCT reporting all relevant outcomes should be undertaken to assess the efficacy of antipsychotics (both singly and in combination with antidepressants) in the treatment of psychotic depression.

- Long-term trials of maintenance treatment with antidepressants are needed to determine the optimum dose and duration of treatment.

- Adequately powered RCTs reporting all relevant outcomes, including relapse rates and adverse events, comparing the effectiveness of different antidepressants should be undertaken in order to identify differential individual response to treatment, including how this relates to gender and ethnicity.

- Suicidal ideas, self-harming behaviour and completed suicide should be carefully and prospectively measured in large, independent multicentre trials using a variety of methods. Particular attention should be paid to the first four weeks of treatment.

- Trials of antidepressants in other disorders (e.g. chronic pain) should similarly monitor for the above negative outcomes.

- Adequately powered RCTs reporting all relevant outcomes should be undertaken to assess the efficacy of valproate and lamotrigine in the management of treatment-resistant depression.

4.8.2 Health economics research recommendations

For future research, it is recommended that studies should:

- Explore the cost-effectiveness of the different newer antidepressants used as first-line treatments in the UK.
- Determine the optimal length of maintenance antidepressant therapy.
- Investigate the comparative cost-effectiveness of IPT versus CBT for the secondary care treatment of depression with regard to the non-disease specific nature and the lower training needs of IPT.
- Measure the health-related quality-of-life of patients with depression in future studies.
- Analyse the efficiency of improving the early detection of depression.
- Estimate the overall cost impact of the implementation of the guideline.

5 Service-level and other interventions in the treatment and management of depression

5.1 Introduction

The large majority of people with depression are managed in primary care, but many cases go unrecognised (Del Piccolo *et al.*, 1998; Raine *et al.*, 2000). Where depression is recognised, care often falls short of optimal recommended practice (Donoghue & Tylee, 1996; Katon *et al.*, 1992) and outcomes are correspondingly below what is possible (Rost *et al.*, 1994). A number of responses have been developed over the past 20 or so years to address the problems of under-recognition and sub-optimal treatment, along with the considerable cost of care presented by depression in primary and secondary care. These responses have drawn from developments in the treatment of depression in primary and secondary care, the organisational and professional structures of primary and secondary care mental health services, and the development and adaptation of models for the management of chronic medical conditions, for example diabetes (Von Korff *et al.*, 1997; Von Korff & Goldberg, 2001). The focus of this section is primarily on those responses that have been developed at a primary care level, although some reference will be made to other approaches in secondary care.

The broad range of interventions that have emerged in recent years fall under a number of distinct headings that include:

- The development of staff roles in primary care and the development of new roles
- The introduction of secondary care mental health staff into primary care
- The use of computer-based technologies
- The development of patient-focused self-help and educational initiatives
- The use of the voluntary sector or informal support structures
- The introduction of interventions outside of those normally provided in mental health.

The framework of stepped care has often been proposed as the method by which these can be integrated. Stepped care seeks to identify the least restrictive and least costly intervention that will be effective for the problems with which an individual presents (Davison, 2000). In establishing a stepped care approach, consideration should not only be given to the degree of restrictiveness associated with a treatment and its costs and effectiveness, but the likelihood of its uptake by a patient and the likely impact that an unsuccessful intervention will have on the probability of other interventions being taken up.

For many staff-based interventions, the focus has been the enhancement of the care provided. For example, improved outcomes have been found where the additional staff facilitate antidepressant uptake and adherence (Katon *et al.*, 1995; Simon *et al.*, 2000), provide or facilitate referral to psychological therapies (Schulberg *et al.*, 1996; Ward *et al.*, 2000), or both (Katon *et al.*, 1996; Wells *et al.*, 2000). More recently, the additional staff member has often taken the role of a care co-ordinator, liaising with the GP, providing educational materials to the patient, and providing informal support, as well as encouraging the patient to take up and adhere to treatment (Katon *et al.*, 1995; Katon *et al.*, 1996; Simon *et al.*, 2000; Wells *et al.*, 2000).

In many of the earlier studies, mental health professionals have provided the enhanced staff input and undertaken the care co-ordinator role (Katon *et al.*, 1995; Katon *et al.*, 1996; Unutzer *et al.*, 2002). However, more recently, others including primary care nurses (Hunkeler *et al.*, 2000; Mann *et al.*, 1998; Rost *et al.*, 2000) or graduates without a core mental health professional training (Katzelnick *et al.*, 2000; Simon *et al.*, 2000) have taken this role. Most studies have been from the US. In the UK, one published study has used practice nurses in the care co-ordinator role, and this did not improve either patient antidepressant uptake or outcomes compared with usual GP care (Mann *et al.*, 1998).

In the UK, there are not sufficient mental health professionals to provide enhanced input and care co-ordination for all primary care patients with depression. Primary care nurses have multiple and increasing demands on their time and many are also uninterested in working with patients with psychological problems (Nolan *et al.*, 1999). Therefore, it is unlikely that practice nurses will take on a significant role in the routine care of patients with depression. A major NHS staffing initiative for primary care mental health is the appointment of new graduate primary care mental health workers (Department of Health, 2000; Department of Health, 2003) who may potentially and significantly affect this situation. The advent of these posts may also require further clarification of the role of all professionals working in primary care mental health.

There is an increasing focus in the NHS on the use of information technology to improve patient care; much of this work has centred on the use of such technology to support patient records. However, there has been a small but potentially valuable development in the use of information technology to impact directly on patient care. The most notable example of this is the use of computer technology to deliver direct patient care. This was recently the subject of a NICE Technology Appraisal (NICE, 2002), which looked at computerised cognitive behavioural therapy (CCBT) for anxiety and depression and made no specific recommendations.

There has been a long tradition of self-help in mental services and a considerable publication industry rests on the production of such guidance. Recently the use of such approaches has been subjected to formal evaluation which looks at both the simple use of self-help guides by patients themselves and their use with limited but targeted support from professionals or others working in mental health services. A related area focuses on the provision of educational materials to patients, a tradition that is probably better developed in the area of schizophrenia than depression.

Depression, as seen in the introduction, has a strong social aspect to its development and maintenance, and it is therefore not surprising that there have been a number of attempts to examine the role of interventions based on this. Many such interventions,

however, have not been subject to rigorous formal elevation (e.g. Cox *et al.*, 1991); where they have been, they have been evaluated on much broader diagnostic groups than the current focus of this guideline.

A novel intervention, which has attracted considerable recent interest, is the provision of exercise; this is an intervention that has broad applications beyond depression alone (Donaghy & Durwood, 2000).

The GDG focused on studies that included educational strategies for patients but not studies where the main focus was on educational strategies for primary care professionals. Although there have been several such studies concerning depression within a huge literature in this educational arena, this decision was taken because the guideline scope does not include educational strategies. It is still noteworthy that most educational studies have obtained a negative result (e.g. Thompson *et al.*, 2000) in Europe except for the small Gotland study (Rutz *et al.*, 1989), despite the success of studies in North America (e.g. Wells *et al.*, 2000).

Although the large majority of people with depression are treated in primary care settings, a significant number do require the provision of specialist services. Inpatient services are used regularly by people with depression, although little is known about their effectiveness and considerable disquiet with their provision exists. In contrast, day hospitals have an uncertain role in the treatment of depression and may potentially be an underused resource. The role of crisis teams in the treatment of depression has also been a particular concern for people who present at considerable risk.

The GDG discussed the priorities for review and settled on the following: screening, guided self-help, computerised CBT, exercise, organisational developments in the treatment of depression (and their various components), non-statutory support and key elements of the secondary care services including crisis resolution and home treatment teams, day hospitals and electroconvulsive therapy. In reaching this decision the GDG were assisted by access to the systematic reviews conducted by John Cape and Andrew Brown (unpublished).

5.2 Screening

5.2.1 Introduction

Screening has been advocated as a means of ensuring that depressed patients are identified and receive appropriate treatment. This, in part, stems from the fact that up to 50% of depressed patients are not recognised in primary care (Williams *et al.*, 1995). Yet, recommendations for routine screening are frequently made without reference to empirical data demonstrating that it will have its intended effect. As a consequence, screening remains controversial and considerable disagreement on its value remains (Gilbody *et al.*, 2001; Pignone *et al.*, 2002; Palmer & Coyne, 2003).

The arguments in favour of routine screening for depression among general medical patients seem straightforward and may appear compelling, given the large number of people with undetected depression and the associated personal and social costs

(Palmer & Coyne, 2003). However, relatively little is known of the impact of screening, particularly in primary care, on outcomes for those identified.

Many questionnaires for depression have been developed which have been used as screening instruments, such as the Beck Depression Inventory (BDI; Beck & Steer, 1987), the General Health Questionnaire (Goldberg & Williams, 1988), and the Zung Depression Scale (Zung, 1965), some of which have been validated for use in primary care. However, in most clinical situations these are not routinely used because they are time-consuming to administer, and may require training in their interpretation. In practice, primary care professionals tend to ask a couple of questions when they see a patient who they suspect may be depressed. There is also empirical support for this approach, with Whooley *et al.* (1997) suggesting that two simple questions may be as effective as a longer questionnaire. Another important issue in the identification of depression is distinguishing current state from more enduring attitudes and feelings. This means effective screening is essentially a two-stage process with the initial brief assessment to be followed by a more detailed assessment of the individual's mental state, and related psychosocial circumstances.

Critics of routine screening have advanced a number of arguments against it. These include the low positive predictive value of the instruments, the lack of empirical evidence for benefit to patients, the expenditure of resources on patients who may gain little benefit (many patients who are detected by such an approach may be mildly depressed and recover with no formal intervention), and the diversion of resource away from more seriously depressed and known patients who may be inadequately treated as a result. These issues are well covered by Palmer and Coyne (2003) in their review of screening for depression. Palmer and Coyne also go on to make a number of suggestions for improving screening, including ensuring effective interventions for those identified, focusing on patients with previous histories of depression and people known to have a high risk of developing depression such as those with a family history of the condition or significant physical health problems, such as chronic pain.

The ability to interpret the findings of screening studies has been hindered by a number of factors (in addition to the standard issues of poor reporting). These include variation in the definition of screening and its implementation, variation in the population and setting in which the screening took place, and very considerable variation in the outcomes reported. For the purpose of this review the definition of screening used in the National Screening Committee (NSC, 1998) first report was adopted and then further refined by the GDG. This is set out below.

NSC Definition

The systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder.

5.2.2 Studies considered for review

In reviewing the effectiveness of screening, the GDG took as its starting point the review by Pignone *et al.* (2002), supplementing this with further searches for other relevant

studies and descriptive reviews, in particular those published subsequent to the studies covered by Pignone *et al.* A review of the available studies indicated that it would not be possible to perform a quantitative review using primarily meta-analytic techniques and, therefore, a predominately narrative review was undertaken.

The review by Pignone *et al.* (2002), which summarises the work of a US Preventive Services Task Force working group on screening for depression, seemed an important starting point as it had recently led to a significant change in policy in the United States health care system with the recommendation that routine screening be adopted for the detection of depression. Specifically they recommended 'screening adults for depression in clinical practices that have systems in place to assure diagnosis, effective treatment and follow-up'. In recommending screening they were careful to emphasise the need for effective support following initial screening. This represented a significant change from the position in 1996, when a previous US Preventive Services Task Force found insufficient evidence to recommend for or against routine screening for depression with standardised questionnaires (US Preventive Services Task Force, 1996).

The Pignone *et al.* (2002) review identified 14 RCTs (which included trials where patients or services were the unit of randomisation) conducted in primary care settings evaluating the effect of routine screening of adult patients for depression. In eight of the studies reviewed, the only intervention was feedback of screening results to clinicians; the remaining studies combined feedback with other interventions for patients or clinicians. Outcomes varied across the trials, including recognition of depression, rates of treatment, and clinical improvement among patients with depression. In 50% of studies, screening with feedback of results resulted in an increased recognition of depression, especially major depression, but this did not generally result in increased uptake of treatment compared with usual care unless feedback was combined with treatment advice or other system supports. The majority of trials reported significant improvements in the clinical outcomes of depressed patients; in five cases this was significant but the period of follow-up varied considerably from one month to two years.

Screening was most effective where it was combined with an integrated approach to the subsequent management of depression, often involving complex systemic interventions in primary care (see Section 5.6, Organisational developments).

Pignone *et al.* (2002) also provide helpful indications of the likely benefits in primary care. For example, 11 patients identified as depressed as a result of screening would need to be treated to produce one additional remission, and assuming depression (which includes here not only major depression, but also dysthymia, and minor depression) is present in 10% of primary care patients, then 110 patients would need to be screened to produce one additional remission after six to 12 months of treatment.

Gilbody *et al.* (2001) report a less positive picture and, after reviewing a similar but not identical group of studies, conclude that routine administration and feedback of scores for all patients did not increase the overall rate of recognition of mental disorders. Although two studies found that selective feedback for high scorers only did increase recognition rates, this did not translate into an increased rate of intervention.

The studies reviewed by Pignone *et al.* (2002) and Gilbody *et al.* (2001) were re-assessed and no additional screening studies were identified by further electronic or hand searches. The re-assessment revealed considerable differences in the populations, setting

and design of the trials, which led to a number being excluded from consideration by the GDG. The criteria on which trials were excluded were firstly population characteristics (specifically those that included significant proportions of non-depressed patients) and secondly those that did not report any usable data on outcomes in relation to depression.

Five studies (CALLAHAN1994[3], KATZELNICK2000, WELLS2000, WHOOLEY2000, ZUNG1983) met the GDG's inclusion criteria providing data on 2318 participants. Of these, four were cluster randomised (CALLAHAN1994, KATZELNICK2000, WELLS2000, WHOOLEY2000) and one patient randomised (ZUNG1983), and as a result were analysed separately. The primary outcome was not identification of depression but the number of identified patients with persisting depression.

CALLAHAN1994, KATZELNICK2000 and WELLS2000 involved complex organisational interventions. For example, KATZELNICK2000 provided not only screening but also patient and professional educational programmes and co-ordination of treatment programmes by telephone contact. WHOOLEY2000 offered a more limited intervention and ZUNG1983 essentially offered only feedback.

5.2.2.1 Screening versus usual care

Limited analysis of the data obtained from the studies produced the following results for the cluster randomised trials.

There is evidence that there is a significant difference between screening and associated interventions and usual care on reducing the likelihood of persistent depression but the difference is unlikely to be of clinical significance (N = 3[4]; *n* = 1862; RR = 0.93; 95% CI, 0.87 to 0.99)

For patient randomised trials, the following statement was produced.

There is some evidence of a clinically significant difference favouring screening and associated interventions over usual care on reducing the likelihood of persistent depression (N = 1; *n* = 49; RR = 0.54; 95% CI, 0.31 to 0.94).

5.2.3 Clinical Summary

Routine screening for depression may be effective in identifying an increased number of cases but there is only limited evidence that screening alone may have any beneficial effect on depressive symptomatology, even when integrated into an accessible treatment programme in which a range of appropriate interventions is available for the identified patient. Studies do indicate that two brief focused questions that address mood and interest are likely to be as effective as more elaborate methods and are more compatible with routine use in settings such as primary care (Whooley *et al.*, 1997). However, although none of the studies reviewed has directly addressed the question, there is

[3] Here and elsewhere in the guideline, each study considered for review is referred to by a 'study ID' made up of first author and publication date in capital letters (unless a study is in press or only submitted for publication, when first author only is used). References for these studies are in Appendix 18 on the CD.

[4] KATZELNICK2000 was removed from this analysis to remove heterogeneity from the data set.

considerable concern that particular populations known to be at high risk of developing depression, including individuals with chronic physical health problems (e.g. heart disease, cerebrovascular disease, arthritic conditions, chronic pain, cancer), women around the time of child birth, those with a family history of depression and those with chronic drug or alcohol abuse, may also benefit from a more targeted approach to screening.

5.2.4 Clinical practice recommendations

5.2.4.1 Screening should be undertaken in primary care and general hospital settings for depression in high-risk groups – for example, those with a past history of depression, significant physical illnesses causing disability or other mental health problems such as dementia. (C)

5.2.4.2 Healthcare professionals should bear in mind the potential physical causes of depression and the possibility that depression may be caused by medication, and consider screening if appropriate. (C)

5.2.4.3 Screening for depression should include the use of at least two questions concerning mood and interest, such as: 'During the last month, have you often been bothered by feeling down, depressed or hopeless?' and 'During the last month, have you often been bothered by having little interest or pleasure in doing things?' (B)

5.2.5 Research recommendations

5.2.5.1 Research is needed into the cost-effectiveness of routine screening of populations known to be at high risk of depression.

5.3 Guided self-help

5.3.1 Introduction

Guided self-help is generally accepted as being more than simply giving patients literature to read (this simpler alternative is usually referred to as pure self-help), and often is based on a cognitive or behavioural psychological approach. Contact with professionals is limited and only of a supportive or facilitative nature. It is potentially more cost-effective, and could lead to a wider and more effective use of professional resources.

Most of the literature on guided self-help emanates from the US. In the US, there are over 2000 self-help manuals of different sorts published each year, and it is not within the scope of this guideline to make recommendations on specific self-help manuals, but the principle and practice of directed guided self-help for motivated patients appears to be one that can easily transpose to the UK.

Guided self-help has obvious limitations such as a requirement of a certain reading ability, and understanding of the language used; for example, 22% of the US population is functionally illiterate, and 44% will not read a book in any year. (NCES,1997).

Many patients are not keen on using medication, because of antidepressant intolerance, drug interactions, pregnancy, breast feeding or personal preference, and many patients are understandably worried about having a formal diagnosis of depression recorded in their medical records. For those people, guided self-help can be a more accessible and acceptable form of therapy. Carers and family members can also be involved in understanding the nature and course of depression through the material made available.

In a meta-analysis of seven studies of guided self-help in unipolar depression (Cuijpers, 1997), guided self-help was found to be no less effective than individual or group therapy, although the numbers involved in the studies were small. Benefit appears to be sustained at six-months' follow-up. In a review of guided self-help across a number of disorders including depression, commissioned by the Department of Health, Lewis *et al.* (2003) concluded that there was evidence to recommend guided self-help, provided this was CBT-based and that its use was monitored by a healthcare professional.

There is also some evidence (Munoz, 1993) that guided self-help can have preventative implications, helping to forestall an episode of major depression in individuals with sub-syndromal depression.

The majority of guided self-help programmes are in book form and this review is limited to these studies. However, a number of approaches have combined computer-based and other technologies with book forms. For example, Osgood-Hynes *et al.* (1998) describe a system comprising a computer-aided telephone system and a series of booklets that was used successfully by people with mild to moderate depression. An interactive voice response system was used, with free phone calls. Because it was often accessed out of hours, it potentially enhances patient flexibility and choice.

5.3.2 Definition

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

5.3.3 Studies considered for review

The review team conducted a new systematic search for RCTs of different types of guided self-help interventions used in the treatment and management of depression. Nine RCTs (BEUTLER1991, BOWMAN1995, BROWN1984, JAMISON1995, LANDREVILLE1997, SCHMIDT1983, SCOGIN1987, SCOGIN1989, WOLLERSHEIM1991) were included, providing data on 453 participants. Seven studies (BLENKIRON2001, DONNAN1990, HANNAY1999, HOLDSWORTH1996, KIELY1986, ROBINSON1997, SORBY1991) were excluded.

Data were available to compare guided self-help with wait list control, individual and group CBT, group guided self-help, telephone contact and individual or group psychotherapy. Guided self-help materials used were based on either CBT or behaviour principles.

5.3.4 Clinical evidence statements

5.3.4.1 Guided self-help versus wait list control

Effect of treatment on remission

There is strong evidence suggesting that there is a clinically significant difference favouring guided self-help over wait list control on increasing the likelihood of patients achieving remission (defined as BDI ≤ 11) at the end of treatment (N = 2; *n* = 96; RR = 0.60; 95% CI, 0.44 to 0.80).

Effect of treatment on symptom levels

There is strong evidence suggesting that there is a clinically significant difference favouring guided self-help over wait list control on reducing depression symptoms by the end of treatment as measured by the BDI (N = 7; *n* = 194; WMD = –7.70; 95% CI, –9.84 to –5.56).

There is strong evidence suggesting that there is a clinically significant difference favouring guided self-help over wait list control on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 4; *n* = 151; WMD = –8.91; 95% CI, –10.62 to –7.20).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and wait list control on reducing the likelihood of patients leaving the study early (N = 5; *n* = 189; RR = 2.01; 95% CI, 0.80 to 5.03).

5.3.4.2 Guided self-help versus group CBT

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group CBT on increasing the likelihood of achieving remission (defined as BDI ≤ 11) by the end of treatment (N = 1; *n* = 16; RR = 0.80; 95% CI, 0.33 to 1.92).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group CBT on reducing depression symptoms by the end of treatment as measured by the BDI (N = 2; *n* = 57; WMD = 3.24; 95% CI, –3.14 to 9.62).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group CBT on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 41; WMD = –1.02; 95% CI, –4.83 to 2.79).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group CBT on reducing depression symptoms as measured by the BDI:

- at three-months' follow-up (N = 1; *n* = 41; WMD = 0.03; 95% CI, –6.8 to 6.86)
- at six-months' follow-up (N = 1; *n* = 11; WMD = 0.07; 95% CI, –12.64 to 12.78).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group CBT on reducing depression symptoms at three-months' follow-up as measured by the HRSD (N = 1; *n* = 41; WMD = –0.59; 95% CI, –4.01 to 2.83).

5.3.4.3 Individual guided self-help versus group guided self-help versus telephone contact

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between individual guided self-help and group guided self-help on increasing the likelihood of achieving remission as defined by the Schedule for Affective Disorders and Schizophrenia – Research Diagnostic Criteria at six months' follow-up (N = 1; *n* = 38; RR = 0.96; 95% CI, 0.36 to 2.6).

There is insufficient evidence to determine if there is a clinically significant difference between individual guided self-help and telephone contact on increasing the likelihood of achieving remission as defined by the Schedule for Affective Disorders and Schizophrenia – Research Diagnotics Criteria at six months' follow-up (N = 1; *n* = 39; RR = 4.48; 95% CI, 0.62 to 32.23).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between individual guided self-help and group guided self-help on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 38; WMD = –0.40; 95% CI, –7.84 to 7.04).

There is some evidence suggesting that there is a clinically significant difference favouring group guided self-help over individual guided self-help on reducing depression symptoms at one month follow-up as measured by the BDI (N = 1; n = 38; WMD = 5.84; 95% CI, 0.3 to 11.38).

There is insufficient evidence to determine if there is a clinically significant difference between individual guided self-help and group guided self-help on reducing depression

symptoms at six-months' follow-up as measured by the BDI (N = 1; *n* = 38; WMD = 2.34; 95% CI, –2.47 to 7.15)

There is insufficient evidence to determine if there is a clinically significant difference between individual guided self-help and telephone contact on reducing depression symptoms as measured by the BDI:

- at the end of treatment (N = 1; *n* = 27; WMD = 2.01; 95% CI, –6.03 to 10.05)
- at one month follow-up (N = 1; *n* = 27; WMD = 3.1; 95% CI, –3.77 to 9.97)
- at six months' follow-up (N = 1; *n* = 27; WMD = –0.33; 95% CI, –5.2 to 4.54).

There is insufficient evidence to determine if there is a clinically significant difference between group guided self-help and telephone contact on reducing depression symptoms as measured by the BDI:

- at the end of treatment (N = 1; *n* = 39; WMD = 2.41; 95% CI, –5.05 to 9.87)
- at one month follow-up (N = 1; *n* = 39; WMD = –2.74; 95% CI, –7.82 to 2.34)
- at six months' follow-up (N = 1; *n* = 39; WMD = –2.67; 95% CI, –6.34 to 1).

5.3.4.4 Guided self-help versus individual or group psychotherapies

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and individual psychological therapies on reducing depression symptoms as measured by the BDI:

- at the end of treatment (N = 2; *n* = 44; WMD = 1.45; 95% CI, –2.69 to 5.60)
- at 10 months' follow-up (N = 2; *n* = 39; WMD = –1.02; 95% CI, –5.07 to 3.03).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and group psychotherapy on reducing depression symptoms as measured by the BDI:

- at the end of treatment (N = 3[5]; *n* = 81; WMD = 0.92; 95% CI, –3.40 to 5.24)
- at follow-up (N = 2; *n* = 63; WMD = 0.64; 95% CI, –3.86 to 5.13).

[5] Data from the small group therapy arm of SCHMIDT1983 was used since using the large group therapy arm introduced heterogeneity to the data set. This did not affect the overall result.

There is some evidence suggesting that there is a clinically significant difference favouring guided self-help over large group psychotherapy on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 23; WMD = –7.5; 95% CI, –12.92 to –2.08).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and large group psychotherapy on reducing depression symptoms at 10 months' follow-up as measured by the BDI (N = 1; *n* = 21; WMD = –4.10; 95% CI, –10.56 to 2.36).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and individual psychological therapies on reducing the likelihood of patients leaving treatment early (N = 2; *n* = 44; RR = 1.50; 95% CI, 0.28 to 8.09).

There is insufficient evidence to determine if there is a clinically significant difference between guided self-help and large group psychotherapy on reducing the likelihood of patients leaving treatment early (N = 1; *n* = 23; RR = 2.77; 95% CI, 0.12 to 61.66).

5.3.5 Clinical summary

Guided self-help produces a clinically significant reduction in depressive symptoms when compared with no intervention and, in patients with mild to moderate depression, may be as effective as some forms of individual therapy and more effective than group psychotherapy on reducing depression symptoms, although there is insufficient evidence that this benefit is retained at follow-up. There is insufficient evidence of its efficacy and acceptability to patients compared with other treatments. It potentially provides a cost-effective and acceptable intervention with potential for widespread use in the treatment of mild to moderate depression, in particular as part of a stepped care programme.

5.3.6 Clinical practice recommendations

5.3.6.1 For patients with mild depression, health care professionals should consider recommending a guided self-help programme based on cognitive behavioural therapy (CBT). (B)

5.3.6.2 Guided self-help should consist of the provision of appropriate written materials and limited support from a health care professional, who typically introduces the self-help programme and reviews progress and outcome. This intervention should normally take place over six to nine weeks including follow-up. (B)

5.3.7 Research recommendations

5.3.7.1 Efficacy studies of the role of guided self-help in a stepped care programme are needed. The focus of such studies should be on the role of guided self-help in both early intervention and maintenance.

5.4 Computerised cognitive behavioural therapy

5.4.1 Introduction

Whilst many patients generally prefer psychological therapies over other interventions for depression (Angermeyer & Matschinger, 1996; Tylee, 2001), and the National Service Framework for Mental Health (Department of Health, 1999b) has called for increased availability of such treatments for common mental health problems, such treatments are often not available. This limited access arises from the shortage of trained therapists, expense, waiting lists (Goldberg & Gournay, 1997), and the reluctance of some patients to enter therapy. A number of authors have called for alternative methods for delivering psychological therapies (Lovell & Richards, 2000).

In addition to the self-help methods discussed elsewhere in this chapter, the use of information technology to deliver psychological treatments has also been explored, for example self-help delivered by telephone (Osgood-Hynes *et al.*, 1998), over the internet (Christensen *et al.*, 2002), or by computer (Selmi *et al.*, 1990). Cognitive behavioural therapy (CBT) may lend itself readily to computerisation and to date CBT is the main psychological treatment approach that has been developed in this manner. Previous studies have shown that patients find computer-based treatment acceptable and they manifest degrees of clinical recovery similar to those after face-to-face therapy (Selmi *et al.*, 1990). However, these studies were carried out with relatively small samples and the majority of programs consisted largely of text, multiple choice questions and cartoons, without the advantage provided by the full multimedia interactive capability of contemporary computers to address important non-specific aspects of therapy.

The technology more recently available has led to the development of a number of more sophisticated and interactive computer-based or internet-based CBT programmes, for example, *Beating the Blues* (Gray *et al.*, 2000) and *Fear Fighter* (Marks *et al.*, 2003). These have recently been the subject of a rigorous evaluation by NICE (NICE, 2002). Essentially these programmes engage the patient in a structured programme of care, which replicates the care provided by a therapist following a standard CBT programme. Direct staff input is usually limited to introducing the programme, brief monitoring and being available for consultation. It has been suggested that this can be done by para-professional or administrative staff. Most of the programmes have been developed to treat a range of depressive and anxiety disorders, often explicitly as part of a stepped care programme. The programmes vary considerably in style, degree of complexity and content, and these factors are likely to have a significant impact on their effectiveness.

The NICE technology appraisal made the following recommendation regarding CCBT.

5.4.1.1 Current research suggests that the delivery of cognitive behavioural therapy via a computer interface (CCBT) may be of value in the management of anxiety and depressive disorders. This evidence is, however, an insufficient basis on which to recommend the general introduction of this technology into the NHS. (NICE, 2002)

Since the completion of the NICE technology appraisal, further work, particularly in the area of depression and CCBT, emerged and so a separate review from the NICE HTA focusing solely on depression was conducted.

5.4.2 Definition

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

5.4.3 Studies considered for review

The review team conducted a new systematic search for RCTs evaluating the use of CCBT in the treatment and management of depression. Four RCTs (BOWERS1993, PROUDFOOT2003, PROUDFOOT2003A, SELMI1990) were included, providing data on 499 participants. One study was excluded (WRIGHT2002).

Data were available to compare CCBT with traditional CBT, wait list control and treatment as usual.

5.4.4 Clinical evidence statements

5.4.4.1 Computerised cognitive behavioural therapy versus treatment as usual

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and treatment as usual on increasing the likelihood of achieving remission by the end of treatment as measured by a BDI score of less than or equal to eight and a HRSD score of less than or equal to seven (N = 1; *n* = 14; RR = 1.14; 95% CI, 0.88 to 1.49).

Effect of treatment on symptom levels

There is strong evidence suggesting that there is a clinically significant difference favouring CCBT over treatment as usual on reducing depression symptoms by the end of treatment as measured by BDI (N = 2[6]; *n* = 273; WMD = –5.95; 95% CI, –8.50 to –3.40).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over treatment as usual on reducing depression symptoms at one month follow-up as measured by BDI (N = 2; *n* = 244; WMD = –3.74; 95% CI,–6.62 to –0.86).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over treatment as usual on reducing depression symptoms at three months' follow-up as measured by BDI (N = 1[7]; *n* = 147; WMD = –3.47; 95% CI, –6.55 to –0.39).

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[6] BOWERS1993 was removed from the analysis due to heterogeneity, >50% of patients in the CCBT group left treatment early.

[7] PROUDFOOT2003 was removed from the analysis since <50% of randomised patients contributed data for this outcome.

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over treatment as usual on reducing depression symptoms at six months' follow-up as measured by BDI (N = 1[8]; *n* = 166; WMD = –5.1; 95% CI, –8.22 to –1.98).

Effect of treatment on acceptability

There is some evidence suggesting that there is a clinically significant difference favouring treatment as usual over CCBT on reducing the likelihood of patients leaving the study early for any reason (N = 3; *n* = 455; RR = 1.38; 95% CI, 1.07 to 1.77).

5.4.4.2 Computerised cognitive behavioural therapy versus traditional cognitive behavioural therapy

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and traditional CBT on increasing the likelihood of achieving remission by the end of treatment as defined by the study (N = 2; *n* = 38; RR = 1.23; 95% CI, 0.74 to 2.05).

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and traditional CBT on increasing the likelihood of achieving remission at two months' follow-up as defined by the study (N = 1; *n* = 24; RR = 1.33; 95% CI, 0.38 to 4.72).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and traditional CBT on reducing depression symptoms by the end of treatment as measured by BDI (N = 2; *n* = 38; Random effects WMD = 3.29; 95% CI, –5.64 to 12.22).

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and traditional CBT on reducing depression symptoms at two months' follow-up as measured by BDI (N = 1; *n* = 24; WMD = –2.1; 95% CI, –8.01 to 3.81).

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and traditional CBT on reducing depression symptoms by the end of treatment as measured by HRSD (N = 2; *n* = 38; Random effects WMD = 3.09; 95% CI, –4.38 to 10.56).

There is evidence suggesting that there is no clinically significant difference between CCBT and traditional CBT on reducing depression symptoms at two months' follow-up as

[8] PROUDFOOT2003 was removed from the analysis since <50% of randomised patients contributed data for this outcome.

measured by HRSD (N = 1; *n* = 24; WMD = 0.38; 95% CI, –1.61 to 2.37).

5.4.4.3 Computerised cognitive behavioural therapy versus wait list control

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between CCBT and wait list control on increasing the likelihood of achieving remission by the end of treatment as defined by the study (N = 1; *n* = 24; RR = 0.60; 95% CI, 0.32 to 1.12).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over wait list control on increasing the likelihood of achieving remission at two months' follow-up as measured by a BDI score of less than or equal to nine (N = 1; *n* = 24; RR = 0.36; 95% CI, 0.16 to 0.82).

Effect of treatment on symptom levels

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over wait list control on reducing depression symptoms by the end of treatment as measured by BDI (N = 1; *n* = 24; WMD = –8.17; 95% CI, –14.2 to –2.14).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over wait list control on reducing depression symptoms at two months' follow-up as measured by BDI (N = 1; *n* = 24; WMD = –14.5; 95% CI, –20.92 to –8.08).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over wait list control on reducing depression symptoms by the end of treatment as measured by HRSD (N = 1; *n* = 24; WMD = –8; 95% CI, –11.06 to –4.94).

There is some evidence suggesting that there is a clinically significant difference favouring CCBT over wait list control on reducing depression symptoms at two months' follow-up as measured by HRSD (N = 1; *n* = 24; WMD = –9.58; 95% CI, –13.62 to –5.54).

5.4.5 Clinical summary

Computerised cognitive behavioural therapy (CCBT) can have a positive impact on depressive symptoms compared with treatment as usual and there is also evidence from a small study of similar benefits when compared with wait list controls, but no evidence of superiority or inferiority compared with standard CBT in two small studies. The more recent, larger studies, which focus primarily on depression or mixed anxiety and depression, show some encouraging results. CCBT may, therefore, have value with mild and moderate depression as part of a stepped care programme. Its potential as an augmenter of therapist delivered treatment is unknown. Other developments such as internet delivered treatments may further increase the accessibility of such treatments and further reduce the costs.

5.4.6 Clinical practice recommendation

5.4.6.1 Since the publication of NICE guidance on CCPT (NICE, 2002), new evidence reporting positive results for CCBT in mild and moderate depression has emerged. Clinicians considering the use of CCBT should consider this evidence in making decisions about the use of CCBT, pending the publication of the updated NICE guidance, which is scheduled for June 2005. (GPP)

5.5 Exercise

5.5.1 Introduction

The effect of exercise on mental health has been the subject of research for several decades. There is a growing body of literature primarily from the US examining the effects of exercise in the management of depression. In the past decade 'exercise on prescription' schemes have become popular in primary care in the UK (Biddle *et al.*, 1994), many of which include depression as a referral criterion. Guidelines for exercise referral schemes have been laid down by the Department of Health (2001b).

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

5.5.2 Definition

For the purposes of the guideline, exercise was defined as a structured, achievable physical activity characterised by frequency, intensity and duration and used as a treatment for depression. It can be undertaken individually or in a group.

Exercise may be divided into aerobic forms (training of cardio-respiratory capacity) and anaerobic forms (training of muscular strength/endurance and flexibility/co-ordination/ relaxation) (American College of Sports Medicine, 1980).

The aerobic forms of exercise, especially jogging or running, have been most frequently investigated. In addition to the type of exercise, the frequency, duration and intensity should be described.

5.5.3 Studies considered for review

The review team conducted a new systematic search for RCTs of different types of exercise interventions used in the treatment and management of depression. Nine RCTs (BOSSCHER1993, FREMONT1987, GREIST1979, HERMAN2002, KLEIN1985,

MCCANN1984, MCNEIL1991, SINGH1997, VEALE1992) were included, providing data on 523 participants. Seven studies (BLAIR1998, DOYNE1987, DUNN2002, KRITZ-SILVERSTEIN2001, LABBE1988, MARTINSEN1989, MARTINSEN1993) were excluded.

Data were available to compare exercise (general, mixed and running therapy) with no exercise, antidepressants, cognitive therapy, group psychotherapy, social contact, meditation and time-limited psychotherapy.

5.5.4 Clinical evidence statements

5.5.4.1 Exercise versus no exercise

Effect of treatment on remission

There is some evidence suggesting that there is a clinically significant difference favouring exercise over no exercise on increasing the likelihood of achieving remission by the end of treatment as measured by DSM-IV criteria for depression or dysthymia (N = 1; *n* = 32; RR = 0.29; 95% CI, 0.10 to 0.89).

There is insufficient evidence to determine if there is a clinically significant difference favouring exercise over no exercise on increasing the likelihood of achieving remission at 20 weeks' follow-up as measured by BDI<9 (N = 1; *n* = 32; RR = 0.53; 95% CI, 0.25 to 1.11).

Effect of treatment on symptom levels

There is strong evidence suggesting that there is a clinically significant difference favouring exercise over no exercise on reducing depression symptoms as measured by the BDI at the end of treatment (N = 4; *n* = 146; WMD = –4.16; 95% CI, –5.39 to –2.93).

There is evidence suggesting that there is no clinically significant difference between exercise and no exercise on reducing depression symptoms as measured by the BDI at 26 weeks' follow-up (N = 1; *n* = 29; WMD = –1.40; 95% CI, –3.00 to 0.20).

There is some evidence suggesting that there is a clinically significant difference favouring exercise over no exercise on reducing depression symptoms as measured by the HRSD at the end of treatment (N = 1; *n* = 32; WMD = –3.6; 95% CI, –4.50 to –2.70).

Response to treatment

There is some evidence suggesting that there is a clinically significant difference favouring exercise over no exercise on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 32; RR = 0.51; 95% CI, 0.28 to 0.96).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between exercise and no exercise on reducing the likelihood of patients leaving the study early for any reason (N = 2; *n* = 115; RR = 1.24; 95% CI, 0.56 to 2.79).

5.5.4.2 Running therapy versus time-limited psychotherapy

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between running therapy and time-limited psychotherapy on reducing the likelihood of patients leaving treatment early (N = 1; *n* = 16; RR = 1.2; 95% CI, 0.14 to 10.58).

5.5.4.3 Running therapy versus mixed exercise

Effect of treatment on symptom levels

There is some evidence suggesting there is a clinically significant difference favouring running therapy over mixed exercise on reducing depression symptoms as measured by the Self-rating depression scale at the end of treatment (N = 1; *n* = 18; WMD = –11.9; 95% CI, –20.48 to –3.32).

There is some evidence suggesting there is a clinically significant difference favouring running therapy over mixed exercise on reducing depression symptoms as measured by the Hopkins Symptom Checklist at the end of treatment (N = 1; *n* = 18; WMD = –32.7; 95% CI, –57.89 to –7.51).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between running therapy and mixed exercise on reducing the likelihood of patients leaving treatment early (N = 1; *n* = 24; RR = 1.00; 95% CI, 0.25 to 4.00).

5.5.4.4 Exercise versus cognitive therapy

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between exercise and cognitive therapy in individuals experiencing problems with negative moods on reducing depression symptoms as measured by the BDI:

- by the end of treatment (N = 1; *n* = 31; WMD = –1.90; 95% CI, –6.72 to 2.92)
- at two months' follow-up (N = 1; *n* = 31; WMD = –0.60; 95% CI, –5.40 to 4.20)
- at four months' follow-up (N = 1; *n* = 26; WMD = –3.10; 95% CI, –8.79 to 2.59).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between exercise and cognitive therapy in individuals experiencing problems with negative moods on reducing the likelihood of patients leaving the study early (N = 1; *n* = 40; RR = 1.81; 95% CI, 0.52 to 6.25).

5.5.4.5 Exercise versus social contact

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between exercise and social contact in community-dwelling depressed older individuals on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 20; WMD = –0.70; 95% CI, –3.80 to 2.40).

5.5.4.6 Exercise versus meditation

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between running and meditation on reducing depression symptoms by the end of treatment as measured by the Depression Symptom Checklist (N = 1; *n* = 22; WMD = 0.20; 95% CI, –0.41 to 0.81).

There is insufficient evidence to determine if there is a clinically significant difference between running and meditation on reducing depression symptoms at nine months' follow-up as measured by the Depression Symptom Checklist (N = 1; *n* = 16; WMD = 0.04; 95% CI, –0.72 to 0.80).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between running and meditation on reducing the likelihood of patients leaving the study early (N = 1; *n* = 50; RR = 0.85; 95% CI, 0.48 to 1.51).

5.5.4.7 Exercise versus group psychotherapy

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between running and group psychotherapy on reducing depression symptoms by the end of treatment as measured by the Depression Symptom Checklist (N = 1; *n* = 28; WMD = –0.20; 95% CI, –0.86 to 0.46).

There is insufficient evidence to determine if there is a clinically significant difference between running and group psychotherapy on reducing depression symptoms at nine months' follow-up as measured by the Depression Symptom Checklist (N = 1; *n* = 18; WMD = –0.45; 95% CI, –1.13 to 0.23).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between running and group psychotherapy on reducing the likelihood of patients leaving the study early (N = 1; *n* = 51; RR = 1.33; 95% CI, 0.66 to 2.70).

5.5.4.8 Exercise versus antidepressant drugs

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between exercise and antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by DSM-IV criteria for depression and a score of less than six on the HRSD (N = 1; *n* = 101; RR = 1.21; 95% CI, 0.80 to 1.82).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between exercise and antidepressants on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 101; WMD = 1.06; 95% CI, –1.55 to 3.67).

There is evidence suggesting that there is no clinically significant difference between exercise and antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 101; WMD = 0.40; 95% CI, –1.82 to 2.62).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between exercise and antidepressants on reducing the likelihood of patients leaving the study early (N = 1; *n* = 101; RR = 1.81; 95% CI, 0.80 to 4.11).

5.5.4.9 Exercise versus exercise plus antidepressant drugs

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between exercise and exercise + antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by DSM-IV criteria for depression and a score of less than six on the HRSD (N = 1; *n* = 108; RR = 1; 95% CI, 0.70 to 1.43).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between exercise and exercise + antidepressants on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 108; WMD = –1.4; 95% CI, –3.98 to 1.18).

There is insufficient evidence to determine if there is a clinically significant difference between exercise and exercise + antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 108; WMD = –1.15; 95% CI, –3.44 to 1.14).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between exercise and exercise + antidepressants on reducing the likelihood of patients leaving the study early (N = 1; *n* = 108; RR = 1.32; 95% CI, 0.66 to 2.64).

5.5.4.10 Exercise plus antidepressant drugs versus antidepressant drugs alone

Effect of treatment on remission

There is insufficient evidence to determine if there is a clinically significant difference between exercise + antidepressants and antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by DSM-IV criteria for depression and a score of less than six on the HRSD (N = 1; *n* = 103; RR = 1.21; 95% CI, 0.80 to 1.81).

Effect of treatment on symptom levels

There is insufficient evidence to determine if there is a clinically significant difference between exercise + antidepressants and antidepressants on reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 103; WMD = 2.40; 95% CI, –0.09 to 4.89).

There is insufficient evidence to determine if there is a clinically significant difference between exercise + antidepressants and antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 103; WMD = 1.60; 95% CI, –0.48 to 3.68).

Effect of treatment on acceptability

There is insufficient evidence to determine if there is a clinically significant difference between exercise + antidepressants and antidepressants on reducing the likelihood of patients leaving the study early (N = 1; *n* = 103; RR = 1.37; 95% CI, 0.58 to 3.26).

Effect of treatment on tolerability

There is insufficient evidence to determine if there is a clinically significant difference between exercise + antidepressants and antidepressants on reducing the likelihood of patients leaving the study early due to side effects (N = 1; *n* = 103; RR = 0.87; 95% CI, 0.27 to 2.83).

5.5.5 Clinical summary

For patients with depression, in particular those with mild or moderate depressive disorder, structured and supervised exercise can be an effective intervention that has a clinically significant impact on depressive symptoms. There is also evidence to suggest that individuals with low mood may also benefit from structured and supervised exercise. Other than some evidence from a single small trial showing the benefit of running over mixed exercise, there is no evidence to indicate any differential advantage

in the type of exercise. Generally, exercise programmes are of relatively high frequency (up to three times a week) and of moderate duration (45 minutes to one hour) and are typically provided for 10 to 12 weeks. Older individuals and those suffering from physical health problems may also benefit from such programmes. There is no evidence on the long-term benefits of such exercise in preventing relapse, nor is there any evidence on the provision of 'maintenance' exercise programmes.

5.5.6 Clinical practice recommendations

5.5.6.1 Patients of all ages with mild depression should be advised of the benefits of following a structured and supervised exercise programme of typically up to three sessions per week of moderate duration (45 minutes to one hour) for between 10 and 12 weeks. (C)

5.5.7 Research recommendations

5.5.7.1 Efficacy trials of the long-term effectiveness of exercise in improving outcomes in depression, including maintenance interventions and intensity of exercise, should be undertaken.

5.6 Organisational developments in the treatment of depression

5.6.1 Introduction

Over the past 15 years, there has been a growing interest primarily from North America in the development of systems of care for managing depression. This work has been influenced by organisational developments in healthcare in the US, such as managed care and Health Maintenance Organisations (Katon *et al.*, 1999), developments in the treatment of depression, the development of stepped care (Davison, 2000), and influences from physical healthcare, for example, chronic disease management. A significant factor in driving these developments has been the recognition that for many people depression is a chronic and disabling disorder.

A similar process is now taking place in the UK, fuelled in part by the advent of Primary Care Organisations in the NHS. A key challenge in reviewing this literature is the translation of findings from non-UK settings to the NHS in England and Wales.

Other international developments, for example the development of Crisis intervention teams, have also been led by non-UK base services for example in the US (Stein & Test, 1980) and Australia (Hoult *et al.*, 1983), although their place in the UK healthcare system is more developed (see the role of crisis services in the National Service Framework, Department of Health, 1999b) than managed care systems for the treatment of depression.

5.6.2 Definitions

There are many terms used to describe the interventions covered in this section and they are often used interchangeably in this area. For the purposes of the guideline, we identified a series of interventions that we consider to be of most relevance to the NHS. They included telephone support, guideline implementation, development in the roles of mental health specialists and primary care staff, and multifaceted care (where a number of different models are delivered concurrently).

These approaches may or may not be provided within the context of a fixed budget (e.g. the Health Maintenance Organisation (HMO) in the US). Primary Care Trusts are required to develop protocols for the treatment of depression in primary care within the National Service Framework for Mental Health.

Other terms subsumed within the definition are: collaborative care, stepped care, enhanced care and integrated care.

5.6.3 Interventions included

The following interventions were considered:

- Organisational developments – this is used as an 'umbrella' term to cover all interventions considered in this section.

- Multifaceted care – this was defined as any systematic approach to the treatment of depression that combined any standard treatment approach with any of the following approaches to the management of depression: telephone contact, specialist assessment or consultation, professional or para-professional role development and guideline implementation.

- Telephone support (protocol and non-protocol driven) – this was defined as an augmentation of a therapeutic intervention designed to improve the effectiveness of the intervention; it usually consisted of a limited number of telephone contacts that had a facilitative and monitoring function.

- Guideline implementation – this was defined as any intervention designed to support the implementation of guideline recommendations.

- Nurse-led care (either primary care or specialist nurses) – this was defined as any intervention which placed a specific role or responsibility on a nurse (either a practice or specialist nurse) for the implementation of whole or part of an intervention.

Psychoeducation was considered for inclusion in this section, but the searches revealed no separate and appropriate trials in this area specifically for depression.

5.6.4 Studies considered for review

The review team conducted a new systematic search for RCTs of different types of organisational development used in the treatment and management of depression. Twenty-one RCTS were considered, with 15 meeting the inclusion criteria set by the GDG (ARAYA2003, BAKER2001, BLANCHARD1995, HUNKELER2000, KATON1995, KATON1996, KATON1999, KATON2001, KATZELNICK2000, MANN1998STUDY2, ROLLMAN2002, ROST2002, SIMON2000, UNUTZER2002, WELLS2000). Five of these were cluster randomised (BAKER2001, KATZELNICK2000, ROLLMAN2002, ROST2002, WELLS2002) so were not included in the main analyses. However, BAKER2001 and ROLLMAN2002 were included in the analysis of guideline implementation since they were the only studies in this comparison (see below). Overall there were data from 5163 participants (4234 in 'organisational developments' plus 929 in 'guideline approach'). Six studies were excluded (ARTHUR2002, COLEMAN1999, LIN2001, LLEWELYN-JONES1999, MANN1998STUDY1, PEVELER1999).

Apart from ARAYA2003, which was undertaken in Chile with low-income women, and BAKER2001, BLANCHARD1995 and MANN1998STUDY1 which were UK-based, all studies were carried out in the US. Since all interventions were compared with usual care, it should be noted that the usual care received by those in the ARAYA2003 study was of poorer quality than that in studies based in more developed countries because of deficiencies in primary healthcare.

All participants in BLANCHARD1995 and UNUTZER2002 were older adults (aged at least 60). At least 65% of those in UNUTZER2002 are described as having significant chronic pain, and 35% had cognitive impairment.

Apart from those, which were cluster randomised, all studies were included in more than one comparison as follows:

Organisational development: ARAYA2003, BLANCHARD1995, HUNKELER2000, KATON1995, KATON1996, KATON1999, KATON2001, MANN1998STUDY2, SIMON2000, UNUTZER2002.

Multifaceted care: ARAYA2003, HUNKELER2000, KATON1995, KATON1996, KATON1999, KATON2001, SIMON2000, UNUTZER2002.

Nurse-led care: (primary care nurse) HUNKELER2000, MANN1998STUDY2; (specialist nurse) BLANCHARD1995

Guideline approach: BAKER2001, ROLLMAN2002

Telephone support: (protocol-driven telephone support) KATON2001, KATZELNICK2000, SIMON2000; (non-protocol-driven telephone support) HUNKELER2000

Comparisons are all with usual care.

5.6.5 Clinical evidence statements

5.6.5.1 Organisational developments versus usual care

Effect of treatment on remission

There is evidence suggesting that there is a statistically significant difference favouring organisational developments over usual care on increasing the likelihood of patients achieving remission (as defined by the study) three or four months after the start of treatment but the size of this difference is unlikely to be of clinical significance (N = 5[9]; *n* = 2925; RR = 0.88; 95% CI, 0.84 to 0.91).

There is some evidence suggesting that there is a clinically significant difference favouring organisational developments over usual care on increasing the likelihood of patients achieving remission (as defined by the study):

- six months after the start of treatment (N = 3[10]; *n* = 2398; RR = 0.83; 95% CI, 0.79 to 0.87)
- 12 months after the start of treatment (N = 1; *n* = 1759; RR = 0.82; 95% CI, 0.78 to 0.85).

Effect of treatment on achieving a response

There is evidence to suggest that there is no clinically significant difference between organisational developments and usual care on increasing the likelihood of patients achieving a response six weeks after the start of treatment (N = 1; *n* = 302; RR = 1; 95% CI, 0.85 to 1.17).

There is strong evidence suggesting that there is a clinically significant difference favouring organisational developments over usual care on increasing the likelihood of patients achieving a response:

- three or four months after the start of treatment (N = 4[11]; *n* = 2552; RR = 0.8; 95% CI, 0.76 to 0.84)
- six months after the start of treatment (N = 3[12]; *n* = 2472; RR = 0.74; 95% CI, 0.69 to 0.79)
- 12 months after the start of treatment (N = 1; n = 1759; RR = 0.68; 95% CI, 0.64 to 0.73).

Effect of treatment on relapse

There is insufficient evidence to determine if there is a clinically significant difference between organisational developments and usual care on reducing the likelihood of patients experiencing a relapse (N = 1; *n* = 386; RR = 0.95; 95% CI, 0.55 to 1.64).

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[9] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[10] ARAYA2003 was removed from the analysis to reduce heterogeneity.

Effect of treatment on reducing depression symptoms

There is evidence to suggest that there is no clinically significant difference between organisational developments and usual care on reducing depression symptoms one month after the start of treatment as measured by the HRSD and the SCL-20 (N = 3; *n* = 381; SMD = –0.08; 95% CI, –0.29 to 0.12).

There is some evidence suggesting that there is a clinically significant difference favouring organisational developments over usual care on reducing depression symptoms three or four months after the start of treatment as measured by the HRSD and the SCL-20 (N = 4[13]; *n* = 2171; SMD = –0.44; 95% CI, –0.53 to –0.36).

There is evidence suggesting that there is a statistically significant difference favouring organisational developments over usual care on reducing depression symptoms six or seven months after the start of treatment as measured by the HRSD and the SCL-20 but the size of this difference is unlikely to be of clinical significance (N = 4[14]; *n* = 2159; SMD = –0.39; 95% CI, –0.48 to –0.31).

There is strong evidence suggesting that there is a clinically significant difference favouring organisational developments over usual care on reducing depression symptoms 12 months after the start of treatment as measured by the HRSD and the SCL-20 (N = 1; *n* = 1759; SMD = –0.6; 95% CI, –0.69 to –0.5).

There is evidence to suggest that there is no clinically significant difference between organisational developments and usual care on reducing symptoms 19 months after the start of treatment as measured by the SCL-90 (N = 1; *n* = 116; SMD = 0.01; 95% CI, –0.36 to 0.37).

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between organisational developments and usual care on reducing the likelihood of patients leaving treatment early (N = 5[15]; n = 2906; RR = 1.15; 95% CI, 0.90 to 1.46).

5.6.5.2 Multifaceted care versus usual care

Effect of treatment on remission (as defined by the study)

There is strong evidence suggesting that there is a clinically significant difference favouring multifaceted care over usual care on increasing the likelihood of patients achieving remission (as defined by the study) three or four months after the start of treatment (N = 3[16]; *n* = 860; RR = 0.71; 95% CI, 0.63 to 0.81).

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[11] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[12] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[13] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[14] ARAYA2003 was removed from the analysis to reduce heterogeneity.

There is some evidence suggesting that there is a clinically significant difference favouring multifaceted care over usual care on increasing the likelihood of patients achieving remission (as defined by the study) six months after the start of treatment (N = 3[17]; *n* = 2398; RR = 0.83; 95% CI, 0.79 to 0.87).

There is some evidence suggesting that there is a clinically significant difference favouring multifaceted care over usual care on increasing the likelihood of patients achieving remission (as defined by the study) 12 months after the start of treatment (N = 1; *n* = 1759; RR = 0.82; 95% CI, 0.78 to 0.85).

Effect of treatment on achieving a response

There is evidence to suggest that there is no clinically significant difference between multifaceted care and usual care on increasing the likelihood of patients achieving a response six weeks after the start of treatment (N = 1; *n* = 302; RR = 1; 95% CI, 0.85 to 1.17).

There is strong evidence suggesting that there is a clinically significant difference favouring multifaceted care over usual care on increasing the likelihood of patients achieving a response:

- three or four months after the start of treatment (N = 4[18]; *n* = 2552; RR = 0.8; 95% CI, 0.76 to 0.84)
- six months after the start of treatment (N = 3[19]; n = 2472; RR = 0.74; 95% CI, 0.69 to 0.79)
- 12 months after the start of treatment (N = 1; *n* = 1759; RR = 0.68; 95% CI, 0.64 to 0.74).

Effect of treatment on relapse

There is insufficient evidence to determine if there is a clinically significant difference between multifaceted care and usual care on reducing the likelihood of patients experiencing a relapse (N = 1; *n* = 386; RR = 0.95; 95% CI, 0.55 to 1.64).

Effect of treatment on depression symptoms

There is evidence to suggest that there is no clinically significant difference between multifaceted care and usual care on reducing depression symptoms one month after the start of treatment as measured by the SCL-20 (N = 3; *n* = 381; SMD = –0.08; 95% CI, –0.29 to 0.12).

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[15] KATON2001 was removed from the analysis to reduce heterogeneity. This study does not contribute data to any efficacy outcome. However, some heterogeneity remains which could not be removed systematically.

[16] UNUTZER2002 was removed from the analysis to reduce heterogeneity.

[17] ARAYA2003 was removed from the analysis to reduce heterogeneity.

There is evidence suggesting that there is a statistically significant difference favouring multifaceted care over usual care on reducing depression symptoms three or four months after the start of treatment as measured by the HRSD and the SCL-20 but the size of this difference is unlikely to be of clinical significance (N = 4[20]; *n* = 2171; SMD = –0.44; 95% CI, –0.53 to –0.36).

There is evidence suggesting that there is a statistically significant difference favouring multifaceted care over usual care on reducing depression symptoms six or seven months after the start of treatment as measured by the HRSD and the SCL-20 but the size of this difference is unlikely to be of clinical significance (N = 4[21]; *n* = 2159; SMD = –0.39; 95% CI, –0.48 to –0.31).

There is strong evidence suggesting that there is a clinically significant difference favouring multifaceted care over usual care on reducing depression symptoms 12 months after the start of treatment as measured by the SCL-20 (N = 1; n = 1759; SMD = –0.6; 95% CI, –0.69 to –0.5).

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between multifaceted care and usual care on reducing the likelihood of patients leaving treatment early (N = 3[22]; *n* = 2433; RR = 1.17; 95% CI, 0.92 to 1.49).

5.6.5.3 Nurse-led care versus usual care

Effect of treatment on remission (as defined by the study)

There is insufficient evidence to determine if there is a clinically significant difference between nurse-led care and usual care on increasing the likelihood of patients achieving remission (as defined by the study) three or four months after the start of treatment (N = 2; *n* = 515; Random effects RR = 0.94; 95% CI, 0.63 to 1.4).

Effect of treatment on response

There is evidence to suggest that there is no clinically significant difference between nurse-led care and usual care on increasing the likelihood of patients achieving a response six weeks after the start of treatment (N = 1; *n* = 302; RR = 1; 95% CI, 0.85 to 1.17).

There is some evidence suggesting that there is a clinically significant difference favouring nurse-led care over usual care on increasing the likelihood of patients achieving a response six months after the start of treatment (N = 1; *n* = 302; RR = 0.76; 95% CI, 0.63 to 0.92).

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[18] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[19] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[20] ARAYA2003 was removed from the analysis to reduce heterogeneity.

[21] ARAYA2003 was removed from the analysis to reduce heterogeneity.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between nurse-led care and usual care on reducing the likelihood of patients leaving treatment early (N = 2; *n* = 515; RR = 0.65; 95% CI, 0.37 to 1.14).

Results are similar when the data set is divided by type of nurse (primary care or specialist nurse).

5.6.5.4 Telephone versus usual care

Effect of treatment on remission (as defined by the study)

There is some evidence suggesting that there is a clinically significant difference favouring telephone support over usual care on increasing the likelihood of patients achieving remission (as defined by the study) three or four months after the start of treatment (N = 1; *n* = 392; RR = 0.65; 95% CI, 0.42 to 1).

There is insufficient evidence to determine if there is a clinically significant difference between telephone support and usual care on increasing the likelihood of patients achieving remission (as defined by the study) six months after the start of treatment (N = 1; *n* = 392; RR = 0.57; 95% CI, 0.32 to 1.02).

Effect of treatment on response

There is evidence to suggest that there is no clinically significant difference between telephone support and usual care on increasing the likelihood of patients achieving a response six weeks after the start of treatment (N = 1; *n* = 302; RR = 1; 95% CI, 0.85 to 1.17).

There is some evidence suggesting that there is a clinically significant difference favouring telephone support over usual care on increasing the likelihood of patients achieving a response:

- three or four months after the start of treatment (N = 1; *n* = 392; RR = 0.83; 95% CI, 0.72 to 0.95)
- six months after the start of treatment (N = 2; *n* = 694; RR = 0.74; 95% CI, 0.65 to 0.85).

Effect of treatment on relapse

There is insufficient evidence to determine if there is a clinically significant difference between telephone support and usual care on reducing the likelihood of patients experiencing a relapse (N = 1; *n* = 386; RR = 0.95; 95% CI, 0.55 to 1.64).

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[22] KATON2001 was removed from the analysis to reduce heterogeneity. This study does not contribute data to any efficacy outcome. However, some heterogeneity remains which could not be removed systematically.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between telephone support and usual care on reducing the likelihood of patients leaving treatment early (N = 2; *n* = 778; Random effects RR = 0.96; 95% CI, 0.24 to 3.76).

Results are similar when the data set is divided by protocol- and non-protocol-driven interventions.

5.6.5.5 Guideline approach versus usual care

Effect of treatment on remission (as defined by the study)

There is evidence to suggest that there is no clinically significant difference between guideline approach and usual care on increasing the likelihood of patients achieving remission (as defined by the study) three or four months after the start of treatment (N = 2; *n* = 929; RR = 1.07; 95% CI, 0.93 to 1.23).

Acceptability of treatment

There is evidence to suggest that there is no clinically significant difference between guideline approach and usual care on reducing the likelihood of patients leaving treatment early (N = 2; *n* = 929; RR = 1.01; 95% CI, 0.85 to 1.19).

5.6.6 Clinical summary

The complex nature of many of the interventions covered in this section makes for difficult interpretation; this is exacerbated by the fact that the majority of the large well-conducted studies have been undertaken almost exclusively in the US and this leads inevitably to considerable caution in their extrapolation to the UK.

Three key findings emerge from the review. First, that multifaceted care has a number of significant benefits for the treatment and care of depression. Although there was considerable variation in both the nature of the populations covered and the complexity of the interventions these programmes have a number of shared characteristics that are common to most if not all of the studies. These include a system-based approach to the delivery of care focusing on all levels of the primary care organisation; the use of clear protocols to guide professional practice (for example, medication protocols) and facilitate inter-professional communication; a stepped approach to care; and the development of specific staff roles (for example, depression care managers). There has also been an increasing trend in these studies towards the use of para-professional or non-specialist mental health staff.

Secondly, and in contrast to the work on multifaceted care, there appears to be no support for guideline implementation programmes as single interventions for improving outcomes for people with depression. This finding is consistent with another review (Von Korff & Goldberg, 2001), which recommends a multi-modal (or multifaceted) approach to guideline implementation.

Thirdly, the evidence for an enhanced role for nurses working in primary care in the care of depression in interventions is equivocal. It is possible that this reflects differences among healthcare systems; the results in the US looked better, but this could reflect some other difference than just the characteristics of the healthcare system. One such possibility is that the enhanced nurse interventions in the US appeared to have a more system-based approach and were supported by the protocols that may well play an important part in the success of multifaceted care. Clearly this area needs further research.

5.6.7 Clinical practice recommendations

5.6.7.1 The provision of telephone support by appropriately trained members of the primary care team, informed by clear treatment protocols, should be considered for all patients, in particular for the monitoring of antidepressant medication regimes. (B)

5.6.7.2 Primary Care Organisations should consider establishing multifaceted care programmes that integrate – through clearly specified protocols – the delivery and monitoring of appropriate psychological and pharmacological interventions for the care of people with depression. (C)

5.6.8 Research recommendations

5.6.8.1 The efficacy of organisational interventions, such as chronic disease management programmes or other programmes of enhanced care for depression, should be tested in large-scale multicentre trials in the NHS.

5.7 Non-statutory support

5.7.1 Introduction

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

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

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

5.7.2 Definition

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

5.7.3 Studies considered for review

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

5.7.4 Clinical evidence statements

5.7.4.1 Befriending versus wait list control

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

There is some evidence suggesting that there is a clinically significant difference favouring befriending over wait list control on increasing the likelihood of patients achieving remission (defined as patients not meeting 'caseness' for depression[23]) (N = 1, *n* = 86, RR = 0.58; 95% CI, 0.36 to 0.93).

Other treatments monitored naturalistically did not relate to remission nor did initial duration of chronic episode or comorbidity. Although remission tended to be higher among those completing the full 12 months of befriending, as opposed to two to six months, this did not reach statistical significance. This suggests that the benefits of befriending may be obtained by a shorter intervention.

Additional trials with less restricted intake conditions and in more naturalistic general practice settings might confirm volunteer befriending as a useful adjunct to current treatments.

5.7.5 Clinical summary

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

5.7.6 Clinical practice recommendations

5.7.6.1 For people with chronic depression who would benefit from additional social support, befriending should be considered as an adjunct to pharmacological or psychological treatments. Befriending should be by trained volunteers providing, typically, at least weekly contact for between two and six months. (C)

5.7.6.2 Primary Care Trusts and mental health communities should collate information on local self-help groups for practitioners. (GPP)

5.7.7 Research recommendations

5.7.7.1 Trials should be undertaken of the efficacy of a range of social support interventions for socially isolated and vulnerable groups of people with depression.

5.8 Crisis resolution and home treatment teams

5.8.1 Introduction

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

5.8.2 Definition

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

[23] Depressed mood at four out of 10 symptoms on the Present State Examination (PSE-10).

- Crisis resolution is any type of crisis-oriented treatment of an acute psychiatric episode by staff with a specific remit to deal with such situations, in and beyond 'office hours'.

- 'Standard care' is the normal care given to those suffering from acute psychiatric episodes in the area concerned; this involved hospital-based treatment for all studies included.

For the purposes of the guideline, the focus of this section is to examine the effects of CRHTT care for people with serious mental illness (where the majority of the sample was diagnosed with non-psychotic disorders) experiencing an acute episode compared with the standard care they would normally receive. Studies were excluded if they were largely restricted to people who were under 18 years or over 65 years old, or to those with a primary diagnosis of substance misuse or organic brain disorder.

5.8.3 Studies considered for review

The GDG chose to use the Cochrane review of CRHTTs (Joy *et al.*, 2003), which included five RCTs (FENTON1979, HOULT1981, MUIJEN21992, PASAMANICK1964, STEIN1975), as the starting point for this section. A further search identified no new RCTs suitable for inclusion. Of the five RCTs included in the Cochrane review, only STEIN1975 met the inclusion criteria set by the GDG (all the other studies had a very significant or exclusive focus on schizophrenia), providing data for 130 participants.

5.8.4 Clinical evidence statements

5.8.4.1 Crisis resolution and home treatment teams versus standard care

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

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

Effect of treatment on acceptability

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

Effect of treatment on burden to family life

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

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

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

There is some evidence suggesting a clinically significant difference favouring CRHTTs over 'standard care' on reducing the likelihood of a patient's family reporting physical illness due to the patient's illness by six months (N = 1; *n* = 130; RR = 0.79; 95% CI, 0.66 to 0.95).

Effect of treatment on burden to community

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

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

5.8.5 Clinical summary

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

5.8.6 Clinical practice recommendations

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

5.8.6.2 Crisis resolution and home treatment teams should be considered for patients with depression who might benefit from an early discharge from hospital after a period of inpatient care. (C)

5.9 Day hospitals

5.9.1 Acute day hospital care

5.9.1.1 Introduction

Given the substantial costs and high level of use of inpatient care, the possibility of day hospital treatment programmes acting as an alternative to acute admission gained credence in the early 1960s, initially in the US (Kris, 1965; Herz *et al.*, 1971) and later in Europe (Wiersma *et al.*, 1989) and the UK (Dick *et al.*, 1985; Creed *et al.*, 1990).

5.9.1.2 Definition

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

5.9.1.3 Studies considered for review

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

5.9.1.4 Clinical evidence statements

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

Effect of treatment on efficacy

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

Effect of treatment on inpatient days per month

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

Effect of treatment on acceptability

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

5.9.2 Non-acute day hospital care

5.9.2.1 Introduction

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

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

5.9.2.2 Definition

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

- Psychiatric day hospitals offering continuing care to people with severe mental disorders.

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

5.9.2.3 Studies considered for review

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

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

5.9.2.4 Clinical evidence statements

Effect of treatment on death (all causes)

There is insufficient evidence to determine whether there is a clinically significant difference between non-acute day hospitals and outpatient care on reducing the likeihood of death during the study (N = 1; *n* = 106; RR = 2.42; 95% CI, 0.23 to 25.85).

Effect of treatment on efficacy

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

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

Effect of treatment on social functioning

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

Effect of treatment on acceptability

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

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

5.9.3 Clinical summary

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

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

5.10 Electroconvulsive therapy

5.10.1 Introduction

Electroconvulsive therapy (ECT) has been used as a treatment for depression since the 1930s. In its modern form ECT is perceived by many healthcare professionals to be a safe and effective treatment for severe depression that has not responded to other standard treatments (Geddes *et al.*, 2003b). But many others, including many patient groups, consider it to be an outdated and potentially damaging treatment (Rose *et al.*, 2003). During ECT, an electric current is passed briefly through the brain, via electrodes applied to the scalp, to induce generalised seizure activity. The individual receiving treatment is placed under general anaesthetic and muscle relaxants are given to prevent body spasms. The ECT electrodes can be placed on both sides of the head (bilateral placement) or on one side of the head (unilateral placement). Unilateral placement is usually to the non-dominant side of the brain, with the aim of reducing cognitive side effects. The number of sessions undertaken during a course of ECT usually ranges from six to 12, although a substantial minority of patients responds to fewer than six sessions. ECT is usually given twice a week; less commonly it is given once a fortnight or once a month as continuation or maintenance therapy to prevent the relapse of symptoms. It can be given on either an inpatient or day patient basis.

ECT may cause short- or long-term memory impairment for past events (retrograde amnesia) and current events (anterograde amnesia) and appears to be dose related. These cognitive impairments have been highlighted as a particular concern by many patients (Rose *et al.*, 2003).

In line with NICE policy regarding the relationship of Technology Appraisals to clinical practice guidelines, the clinical practice recommendations in this guideline are taken directly from the Technology Appraisal (NICE, 2003), which itself drew on other recent

reviews of ECT. The Technology Appraisal covered the use of ECT in the treatment of mania and schizophrenia as well as depression in children and adolescents. Only the recommendations on the use of ECT for adults with depression are reproduced here.

Key points to emerge from the review, which conclude that ECT is an effective treatment, include:

- Real ECT had greater short-term benefit than sham ECT
- ECT had greater benefit than the use of certain antidepressants
- Bilateral ECT was reported to be more effective than unilateral ECT
- The combination of ECT with pharmacotherapy was not shown to have greater short-term benefit than ECT alone
- Cognitive impairment does occur but may only be short-term
- Compared with placebo, continuation pharmacotherapy with tricyclic antidepressants and/or lithium reduced the rate of relapses in people who had responded to ECT
- Preliminary studies indicate that ECT is more effective than repetitive trans-cranial magnetic stimulation.

5.10.2 Clinical practice recommendations

5.10.2.1 It is recommended that electroconvulsive therapy (ECT) is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective, and/or when the condition is considered to be potentially life-threatening, in individuals with a severe depressive illness. (NICE 2003)

5.10.2.2 The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current comorbidities; anticipated adverse events – particularly cognitive impairment – and the risks of not having treatment. (NICE 2003)

5.10.2.3 The risks associated with ECT may be enhanced during pregnancy, in older people, and in children and young people, and therefore clinicians should exercise particular caution when considering ECT treatment in these groups. (NICE 2003)

5.10.2.4 Valid consent should be obtained in all cases where the individual has the ability to grant or refuse consent. The decision to use ECT should be made jointly by the individual and the clinician(s) responsible for treatment, on the basis of an informed discussion. This discussion should be enabled by the provision of full and appropriate information about the general risks

associated with ECT and about the risks and potential benefits specific to that individual. Consent should be obtained without pressure or coercion, which may occur as a result of the circumstances and clinical setting, and the individual should be reminded of their right to withdraw consent at any point. There should be strict adherence to recognised guidelines about consent and the involvement of patient advocates and/or carers to facilitate informed discussion is strongly encouraged. (NICE 2003)

5.10.2.5 In all situations where informed discussion and consent is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted. (NICE 2003)

5.10.2.6 Clinical status should be assessed after each ECT session and treatment should be stopped when a response has been achieved, or sooner if there is evidence of adverse effects. Cognitive function should be monitored on an ongoing basis, and at a minimum at the end of each course of treatment. (NICE 2003)

5.10.2.7 It is recommended that a repeat course of ECT should be considered under the circumstances indicated in 5.10.2.1 only for individuals who have severe depressive illness, and who have previously responded well to ECT. In patients who are experiencing an acute episode but have not previously responded, a repeat trial of ECT should be undertaken only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate. (NICE 2003)

5.10.2.8 Because the longer-term benefits and risks of ECT have not been clearly established, it is not recommended as a maintenance therapy in depressive illness. (NICE 2003)

6 Review of psychological therapies for depression

6.1 Introduction

It has long been recognised that focusing on their psychology can help people with depression. For example, the early Greek physicians recognised the value of helping depressed people come to terms with grief and increase their levels of activity, and the use of persuasion (Jackson, 1986). In the east a variety of old traditions have emphasised the importance of 'mind training' as an antidote to depression and other difficulties (Sheikh & Sheikh, 1996), techniques now being explored for relapse prevention (Teasdale *et al.*, 2002). However, it has only been in the last century that different formal 'psychotherapies' have been developed (Ellenberger, 1970; Ehrenwald, 1976). These have proliferated rapidly (Roth & Fonagy, 1996). In addition there has been a vast expansion of different *theories* about the causes, vulnerabilities and maintenance factors for depression (Gilbert, 1992). More recent has been the development of psychological therapies designed *specifically for depression*, linked to specific theories, and the use of randomised control trials for assessing efficacy (Wampold *et al.*, 2002). The focus of this guideline is on those approaches for which there is some evidence of efficacy and which are routinely used in the NHS.

6.1.1 What was known before

In their systematic review of a large number of studies, Roth and Fonagy (1996) concluded that there was good evidence for some psychological interventions for a range of psychological disorders, including depression. Many reviews have found that psychological treatments specifically designed for depression (e.g. cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT)) are equivalent to drugs in terms of efficacy (DeRubeis *et al.*, 1999; Hollon *et al.*, 2002). Recently, the Health Technology Assessment Group published a 'Systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression' (Churchill *et al.*, 2001). Their general finding was that psychological therapies were effective, with 50% or more of those taking part having recovered by the end of treatment. However, they caution that a sizeable proportion of this may be due to non-specific factors, such as the therapeutic relationship and natural time course of depression. No significant differences were found between treatments that were specifically designed for depression, such as cognitive therapy, behavioural therapy and interpersonal therapy (a finding similar to Wampold *et al.*, 2002) although they included non-RCTs and did not compare psychotherapies with pharmacological treatments. However, they note that many studies that obtain this result often use participants recruited via media advertising and this affects outcome.

Although non-specific therapies tend to perform less well than specific therapies Leichsenring's (2001) meta-analytic study on the comparative effects of short-term cognitive behavioural therapy and psychodynamic therapy found little evidence of difference. This may be a result of large numbers of patients who respond in trials independent of the nature of the intervention as a result of non-specific therapeutic factors.

In many of these reviews studies other than randomised controlled trials were included in analyses so caution should be exercised when interpreting the findings.

6.1.2 Current recommendations

In 1999 the Clinical Standards Advisory Group acknowledged the effectiveness of some psychological interventions for depression and advised on the need for localities to develop resources for providing such interventions. The Department of Health's *Treatment Choice in Psychological Therapies and Counselling Evidence-Based Clinical Practice Guideline* (2001a) made similar recommendations. Indeed, in other countries such as the USA (Beutler *et al.*, 2000) and Canada (Segal *et al.*, 2001a; Segal *et al.*, 2001b), guideline development groups are consistent in noting the effectiveness of psychological therapies, especially those that have been designed for depression such as cognitive behavioural therapy and interpersonal psychotherapy and recommending them as effective treatments.

6.1.3 Challenges to the assessment of evidence of what works for whom

It is now recognised that specifying the active ingredients in effective outcomes of a therapy is difficult. These difficulties are compounded by many issues relating to both the therapies themselves and other factors, including the nature of the disorder being treated. They require careful consideration when judging the evidence.

Commonalities and developments in psychological treatment

Although separate approaches can be operationalised into 'pure forms', in practice most psychological treatments for depression share common features. Indeed, there has long been a debate about the 'specificity versus the non-specificity' of treatment (Karasu, 1986). Many of these common features relate to the therapeutic relationship such as providing an accepting, open and active listening relationship that helps to de-shame and remoralise people. In addition, however, there have been many suggestions for psychotherapy integration (Norcross & Goldfried, 1992). Even without a deliberate attempt to integrate therapies many approaches have evolved overlapping features in focus and intervention. For example, cognitive behavioural therapy, as the term implies, involves both cognitive and behavioural interventions and aids people's problem-solving abilities. Other developments in cognitive behavioural treatments seek to integrate cognitive and interpersonal approaches (Keller *et al.*, 2000). Others seek to integrate different conceptual approaches (the cognitive and the psychodynamic), such as cognitive analytic therapy (Ryle, 1989). Within any broad approach to therapy there can be variations that differ subtly in conceptualisation, focus and technique. Nonetheless, work is proceeding to clarify specific elements of therapies and how these may or may not contribute to the processes of change that lead to improvement of mood (e.g. Goldfried *et al.*, 1997). Ultimately, however, all therapists should be cognisant of the scientific research and findings on the psychological regulators of mood states. Treatments may work for reasons other than those for which their proponents think they do.

Therapies are also constantly evolving. For example, while the early trials of cognitive therapy focused primarily on automatic thoughts and assumptions, more recently some cognitive therapists have advocated additional elements of schema focus (e.g, Young *et al.*, 2001). Salkovskis (2002) has argued that, 'In most incidences, CBT for any particular psychological problem is quite different now to CBT as practised ten or even five years ago. This process is evolutionary and interactive, and pragmatic outcome trials play a relatively minor part in this development'. Of course, the same will apply to other forms of psychological treatment. This means that treatment manuals are necessary to clarify exactly what was done in a trial. It will also direct people to specific skills needed to engage that therapy as was conducted in the trial. However, treatment manuals also have a number of disadvantages in routine practice. First, they may restrict innovation because therapies are often in a constant process of development and change in line with new findings (Elliott, 1998). Secondly, as therapies become more complex and combine different elements in new packages, this can lead to a proliferation and an increasingly large number of different treatment manuals requiring validation. Although RCTs using manualised treatments can be one of a number of research endeavours that lead to the evolution of therapeutic understanding and techniques, it is unclear how an uncritical use of this approach will avoid stifling innovative practice.

Therapist variables

Therapists differ in their personality, values and beliefs about the causes of depression, and these may affect the outcome of treatment (Blatt *et al.*, 1996b). Therapists who take part in research studies vary in their level of training and experience, and in whether they have received basic counselling training or not. For example, cognitive behavioural training often assumes basic counselling skills (Beck *et al.*, 1979), whereas many psychodynamic approaches may not and thus these issues are addressed as part of psychodynamic training. Some studies of psychological interventions have used comparatively untrained therapists (e.g. GPs or primary care workers) who are taught specific interventions. Graduate clinical or internship students are also often used in clinical trials. Their therapeutic practice may be untypical of routine clinical practice and their approach highly structured adhering closely to a treatment manual.

Good practice point

6.1.3.1 Healthcare professionals providing psychological treatment should be experienced in the treatment of the disorder and competent in the delivery of the treatment provided. (GPP)

Relationship factors

Many approaches advocate a therapeutic stance of genuineness, empathy and positive regard as derived from early counselling models of change (Rogers, 1957). Indeed, there have been important developments in understanding the role of the therapeutic relationship and alliance (Safran & Muran, 2000) and therapeutic 'universals' such as remoralisation, social support and reassurance are also regarded as important factors for treatments (Norcross, 2002; Schaap *et al.*, 1993). The quality of the alliance/relationship may account for a significant percentage of variance in outcome (Norcross, 2002; Roth & Fonagy, 1996). Despite this, few research trials offer data on therapist characteristics or capacity to create a good therapeutic relationship.

Recommendation

6.1.3.2 In all psychological interventions healthcare professionals should develop and maintain an appropriate therapeutic alliance, because this is associated with a positive outcome independent of the type of therapy provided. (C)

Variation in the delivery of psychological treatment

Treatments can vary considerably in the mode by which they are delivered, including individual, marital, family and group. When evaluating the effectiveness of a particular intervention the effect of setting needs consideration independently of the therapeutic approach. Hence, for example, individual cognitive therapy should be tested against group cognitive therapy.

Disorder variations

Typically, the symptom-focused diagnostic approach distinguishes between types of depression (e.g. psychotic versus non-psychotic), severity (mild, moderate and severe), chronicity, and treatment resistance. As this is the approach adopted in much contemporary research, and underpins the evidence base, it is adopted for this guideline. However, as proposed by Akiskal and McKinney (1975) nearly 30 years ago, depression is best considered a final common pathway that can have many routes into it. It is primarily a disorder of the positive affect system. There are therefore growing concerns as to adequacy of the current diagnostic system for efficacy research and the relationship between different diagnoses and different psychological and physiological processes (and indeed pharmacological interventions). For example, it is common for depressed patients to have different comorbid diagnoses, such as social phobia, panic and various personality disorders (Brown *et al.*, 2001), which can affect outcome. Pre-existing disorders such as social anxiety disorders may, for example, increase vulnerability to depression, influence treatment seeking, the therapeutic relationship, and staying in treatment.

Variations in length of therapy

A key issue in the provision of therapy is deciding on the number of sessions to be undertaken. There are at least three factors to take into account. Barkham *et al.* (1996) found that eight sessions of either cognitive behavioural or psychodynamic interpersonal therapy appeared to generate faster change than 16 sessions. These authors suggest that time constraints may have speeded up engagement and work on therapy. However, different symptoms, e.g. those of distress versus those of self-criticism, appear to have a different time course. Key issues relating to the ability to form a therapeutic relationship will have an impact on time course and responses to time limited therapies (Hardy *et al.*, 2001). Third, historical factors such as sexual abuse may significantly impact upon speed of engagement and recovery. With this in mind the GDG undertook a separate analysis of short-term psychotherapies in Section 6.10.

Patient variations

There is evidence that the effectiveness of psychotherapy designed for depression can vary extensively across individuals, with some patients making rapid gains and others changing more slowly (Roth & Fonagy, 1996; Hardy *et al.*, 2001). Part of the reason for

this is that depressed patients vary greatly in their personalities, premorbid difficulties and histories (e.g. sexual abuse), cultural backgrounds, psychological mindedness, psychological competencies and current relational and social problems – all of which may significantly affect outcomes (Sotsky *et al.*, 1991). As noted in our introduction, socio-economic factors (e.g. poverty and unemployment) account for large variations in population rates of depression. There is some evidence that patients who are perfectionistic (Blatt *et al.*, 1996a) and highly self-critical (Rector *et al.*, 2000) may do less well with standardised therapies. However, few studies of the psychological treatment for depression (or indeed any other type of intervention) control for patient variations.

Taken together these variations raise concern that depression may be far too heterogeneous a diagnosis in biological, psychological and social terms to enable clarity on which to develop specific and effective interventions. The data reported below are from trials that treat depression as a single disorder. However, depression is a highly heterogeneous disorder with many variables affecting outcome, including history (e.g. of child abuse) personality (e.g. perfectionism and self-criticalness) and life events. We would hope that future research might seek to be more specific on sub-typing in relation to therapy success and failure.

Recommendation

6.1.3.3 In patients with depression who have significant comorbidity consideration should be given to extending the duration of treatment for depression, making use of treatments where appropriate, that focus specifically on the comorbid problems. (C)

Recruitment

The populations studied in a clinical trial can be influenced by the method of recruitment to the trial. For example, in some studies patients are recruited through media advertisements, while in others they are recruited via routine service referral. Hence, although all patients will have met diagnostic criteria for 'depression' the settings in which recruitment takes place may exert an important influence on the type of depression treated, and patient variation. These factors can influence outcome (Churchill *et al.*, 2001).

6.1.4 Use of RCTs in psychotherapy

RCTs for psychotherapy have been adopted from the methods of drug studies and this can raise a number of difficulties (Elliott, 1998; Roth & Fonagy, 1996). They have some disadvantages: for example, they may have unrepresentative patient populations, limited outcome measures, and significant problems with truly blinding assessors to the intervention. Nevertheless RCTs have a key role in developing evidence-based practice but are best seen as only one element of a complex chain, which moves from initial case series through controlled trials (development studies) on to randomised control trials (efficacy studies) and beyond to their application to routine care in 'ordinary' clinical settings (effectiveness studies). These issues were borne in mind by the GDG when assessing the evidence.

Despite the proliferation of psychological treatments, the number of high quality trials of adequate statistical power is low. In addition, trial results can be hard to interpret because of poor description of the trial participants, poor control for adherence to the therapy, uncertainty about therapist training and experience and, in some cases, participants having adjunct therapy, including antidepressants, during a trial. These concerns are amongst those that have led us to be conservative in our selection of studies considered for review.

6.1.5 Therapies considered for review

The following therapies are considered as they were seen as available in the NHS and there was initial evidence of a sufficient evidence base to warrant further investigation:

- Cognitive behavioural therapies (CBT) (for individuals and groups)
- Behaviour therapy (BT)
- Interpersonal psychotherapy (IPT)
- Problem-solving therapy
- Non-directive counselling
- Short-term psychodynamic psychotherapy
- Couple-focused therapies.

In addition, two sub-analyses on the whole data set were performed. One pulled together all studies undertaken exclusively on older adults with depression (mean age 65 years) and the other looked at studies of short-term psychotherapy.

6.2 Cognitive behavioural therapies (CBT)

6.2.1 Introduction

Cognitive behavioural therapy for depression was developed by Beck during the 1950s and was formalised into a treatment in the late 1970s (Beck *et al.*, 1979). Its original focus was on the styles of conscious thinking and reasoning of depressed people. For example, when depressed, people focus on negative views of themselves, the world and the future. A key aspect of the therapy is to take an educative approach where, through collaboration and guided discovery, the depressed person learns to recognise his or her negative thinking patterns and how to re-evaluate his or her thinking. This approach also requires people to practise re-evaluating their thoughts and new behaviours (called homework). The approach does not focus on unconscious conflicts, transference or offer interpretation as in psychodynamic therapy. As with any psychological treatment, cognitive behavioural therapy is not static and has been evolving and changing. For example, as noted, some cognitive therapies for depression may now focus on a schema-based approach (Young *et al.*, 2001)

or help depressed people evaluate the effects of their behaviour on relationships (e.g. McCullough, 2000). However, studies that have explored different 'ingredients' of CBT (e.g. behavioural activation, skills to modify automatic thoughts and schema focus) suggest that behavioural activation and thought-focused treatments may be as effective at altering negative thinking as full schema-focused cognitive behavioural therapy (Jacobson *et al.*, 1996). The guideline refers to 'cognitive behavioural therapies' to indicate the range of approaches included in this term.

6.2.2 Definition

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

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

6.2.3 Studies considered for review[1]

6.2.3.1 Source of studies

The review team used the existing systematic review by Gloaguen *et al.* (1998) as the starting point for this section. Gloaguen *et al.* included 48 trials, of which 34 failed to meet the criteria set by the GDG and so were not included in this section:

- Two trials were of adolescents and, therefore, outside the scope of this guideline (LEWINSOHN1990[2], REYNOLDS1986)
- Three were unpublished and the review team were unable to obtain full trial reports (NEIMEYER1984, ROTZER1985, ZIMMER1987)

[1] Full details of the search strategy for this and other reviews in the guideline are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17 on the CD, which also contains a list of excluded studies with reasons for exclusions.

[2] Here and elsewhere in the guideline, each study considered for review is referred to by a 'study ID' made up of first author and publication date in capital letters (unless a study is in press or only submitted for publication, when first author only is used). References for these studies are in Appendix 18 on the CD.

- Twenty-five failed to meet the inclusion criteria (see table of excluded references in Appendix 17; BECK1985, BEUTLER1987, BOWERS1990, COMAZ-DIAZ1981, DUNN1979, HOGG1988, HOLLON1992, LAPOINTE1980, MACASKILL1996, MCNAMARA1986, MAYNARD1993, PACE1993, ROSS1985, RUSH1977, SHAPIRO1982, SHAW1977, STEUER1984, TAYLOR1977, TEASDEALE1984, THOMPSON1987, WARREN1988, WIERZBICKI1987, WILSON1983, WILSON1990, ZETTLE1989)

- Two were considered in the section examining couple-focused therapies (EMANUELS-ZUURVEEN1996, JACOBSON1991)

- Two used an intervention that did not meet the GDG's criteria for CBT (MCLEAN1979 used behaviour therapy with a small cognitive element, and SCOGIN1987 used a form of guided self-help).

New searches[3] conducted by the review team found a further 40 trials either published too recently to be included in the Gloaguen *et al.* (1998) review, or not identified in that review, with two more being found through checking reference lists. Twenty-nine of these failed to meet the inclusion criteria set by the GDG.

In addition, two unpublished studies were identified by contacting researchers known to the GDG (Appendix 5): Freeman *et al.* (unpublished), which was used in the analysis, and one by Steve Hollon, which was not used because a full trial report was unavailable.

Thus, 30 trials (14 from Gloaguen *et al.*, 1998, 15 from new searches, one unpublished study) were included in this section: 17 from the US, 10 from the UK and three from Europe. In all, data from 2940 participants were used.

6.2.3.2 Study characteristics

There were 18 studies of individual CBT for patients with a primary diagnosis of depression at baseline, six of which included follow-up data (BLACKBURN1981, BLACKBURN1997, GALLAGHER-THOMPSON1994, HAUTZINGER1994, MURPHY1984, SHAPIRO1996). A further study included a range of diagnoses at baseline with 62% having a primary diagnosis of depression (WARD2000). Since this is an important primary care-based study comparing CBT with counselling and GP care, it is included in the review of counselling and short-term psychological therapies in Section 6.10 where there is little other RCT-level evidence. Two additional studies looked at CBT for patients with residual symptoms after initial treatment (FAVA1994 and PAYKEL1999); both included follow-up. A further two studies looked at continuation treatment in treatment responders (JARRETT2001 and TEASDALE2000).

Four studies compared group CBT to other group therapies (BEUTLER1991, BRIGHT1999, COVI1987, KLEIN1984), one of which, BEUTLER1991, included follow-up.

[3] Full details of the search strategy and information about each study along with an assessment of methodological quality are included in the guideline as appendices.

In most studies participants had a primary diagnosis of depression. The exception is JARRETT1999 where participants are described as having 'atypical depression' defined as 'a sub-type of MDD during which patients have reactive mood and at least two of the following four symptoms: hyperphagia, hypersomnia, leaden paralysis, or a lifetime history of interpersonal sensitivity to rejection, resulting in functional impairment' (p.431). In the opinion of the GDG the definition of this did not comply with accepted criteria and was, in fact, major depressive disorder. Apart from the 'placebo plus clinical management' treatment group, where more than 50% of study participants left treatment early, data from this study were retained in the analysis.

Studies also varied as followed:

- Baseline severity – moderate to very severe
- Therapist experience and training – from PhD students trained specifically for the study to experienced therapists
- Setting and source of patients, including inpatient, outpatient, primary care and volunteer studies
- Study length – six to 21 weeks
- Number of sessions – six to 25.

6.2.3.3 Special note: the clinical management of trial participants on study medication

In many studies with an antidepressant treatment arm, medication was administered within the context of a clinical management protocol, often following the NIMH treatment manual (Fawcett *et al.*, 1987). This involves 20-minute weekly sessions with a study psychiatrist to assess clinical status and to provide a supportive atmosphere, plus access to 24-hour emergency care. This could be considered a psychosocial intervention in its own right. For example in Malt *et al.* (1999) a 'counselling' intervention was based on this protocol. This kind of clinical management is not analogous to routine NHS psychiatric or GP care, and this should be borne in mind when assessing the following results.

6.2.3.4 Comparisons

Since so many comparisons were possible from the available data, some were combined in an attempt to increase statistical power (for example, behaviour therapy and IPT were combined as 'therapies designed for depression').

6.2.4 Evidence statements[4]

6.2.4.1 Individual CBT compared with wait list control

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring CBT over wait list control on reducing depression symptoms at the end of

treatment as measured by the BDI (N = 2; *n* = 54; WMD = –8.30; 95% CI, –13.14 to –3.47).

There is some evidence suggesting that there is a clinically significant difference favouring CBT over wait list control on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 24; RR = 0.45; 95% CI, 0.23 to 0.91).

There is insufficient evidence to determine if there is a clinically significant difference between CBT and wait list control on increasing the likelihood of achieving remission as measured by the BDI (N = 1; *n* = 24; RR = 0.70; 95% CI, 0.41 to 1.20).

Tolerability and acceptability of treatment

There is no data on which to assess the acceptability of CBT versus wait list control.

6.2.4.2 Individual CBT compared with pill placebo (plus clinical management)

Data from only one study (ELKIN1989) were available for this comparison. Efficacy data from the other study (JARRETT1999) comparing CBT with placebo plus clinical management were not extracted because more than 50% of the placebo plus clinical management group left the study early.

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and placebo plus clinical management either on increasing the likelihood of achieving remission or on reducing depression symptoms by the end of treatment as measured by either the HRSD or the BDI.

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and placebo plus clinical management on reducing the likelihood of leaving treatment early for any reason.

6.2.4.3 Individual CBT compared with other psychotherapies

The available data were sub-divided to make two comparisons of individual CBT with other psychotherapies. The first combined therapies specifically designed for the treatment of depression (i.e. IPT and behaviour therapy), and the second combined non-directive psychotherapies (i.e. brief psychodynamic therapy, gestalt therapy, Hobson's conversational model of psychodynamic interpersonal psychotherapy, and Rogerian counselling).

Effect of treatment on efficacy outcomes

For both sub-comparisons, there is insufficient evidence to determine whether there is a clinically significant difference between CBT and other psychotherapies on either

[4] All statements are from Level I evidence. The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on the CD.

increasing the likelihood of achieving remission or on reducing depression symptoms.

Tolerability and acceptability of treatment

For both sub-comparisons, there is insufficient evidence to determine whether there is a clinically significant difference between CBT and other psychotherapies on reducing the likelihood of leaving treatment early for any reason.

6.2.4.4 Individual CBT compared with GP care

From the studies of individual CBT, three compared CBT undertaken in primary care with GP care (SCOTT1992, SCOTT1997[5], FREEMAN). (The HRSD data were not extracted from FREEMAN because more than 50% of the participants in the CBT group were missing from this outcome.)

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between CBT provided in primary care and GP care (with antidepressant treatment) on reducing depression symptoms as measured by the BDI or the HRSD at the end of treatment or at five months' follow-up.

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT provided in primary care and GP care on reducing the likelihood of leaving treatment early for any reason.

6.2.4.5 Group CBT compared with other group therapies

There were few RCTs of sufficient quality to assess group CBT fully. It was not possible to make comparisons with either individual CBT, antidepressants or no active treatment. However, a comparison was possible with other group therapies, including gestalt therapy (BEUTLER1991), mutual support group therapy (BRIGHT1999), 'traditional' psychotherapy (COVI1987), and meditation-relaxation therapy (KLEIN1984).

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring group CBT over other group therapies on increasing the likelihood of achieving remission as measured by the BDI (N = 2; *n* =111; RR = 0.60; 95% CI, 0.46 to 0.79).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between group CBT and other treatments on reducing the likelihood of leaving treatment early.

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[5] SCOTT1997 also appears in the comparison of CBT versus antidepressants because all but one of the GP care group took antidepressants.

6.2.4.6 CBT compared with antidepressants

As described above, antidepressant drugs in some trials in this comparison were administered within the framework of 'clinical management' (ELKIN1989, HAUTZINGER1996, JARRETT1999, KELLER2000, THOMPSON2001). In MIRANDA2003 participants received weekly telephone calls to assess adverse effects, adherence and treatment effects. In the remaining trials, either this is not mentioned (BLACKBURN1981, SCOTT1992) or participants received non-manualised general support (BLACKBURN1997, MURPHY1984). A sub-analysis of the presence or absence of manualised clinical management was not possible because there were insufficient data in the non-clinical management group to calculate an effect size. Therefore, the complete data set was retained. A sub-analysis by mean baseline severity was also undertaken. Participants in one trial (KELLER2000) had chronic depression.

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT and antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 8[6]; *n* = 480; SMD = –0.06; 95% CI, –0.24 to 1.12) or HRSD (N = 10[7]; *n* = 1096; SMD = 0.01; 95% CI, –0.11 to 0.13)

- increasing the likelihood of achieving remission as measured by the HRSD (N = 5; *n* = 839; RR = 1; 95% CI, 0.91 to 1.10).

A sub-analysis by severity did not indicate any particular advantage for antidepressants over CBT based on severity of depression at baseline.

When analysed by severity, there is evidence suggesting that there is no clinically significant difference between CBT and antidepressants on reducing depression symptoms by the end of treatment:

- In moderate or moderate/severe depression assessed with either the HRSD (N = 5; *n* = 798; Random effects: SMD = 0; 95% CI, –0.22 to 0.22) or the BDI (N = 3; *n* = 184; SMD = –0.06; 95% CI, –0.35 to 0.23)

- In severe depression assessed with either the HRSD (N = 3; *n* = 197; SMD = –0.04; 95% CI, –0.32 to 0.24) or the BDI (N = 3; *n* = 197; SMD = 0; 95% CI, –0.28 to 0.28)

- In severe to very severe depression (HRSD: N = 2; *n* = 101; SMD = –0.10; 95% CI, –0.49 to 0.30; BDI: N = 2; *n* = 99; WMD= –1.93; 95% CI, –6.02 to 2.16)

- In chronic depression (but with a moderate level of symptoms) (HRSD: N = 1; *n* = 436; WMD = 0.20; 95% CI, –1.56 to 1.96).

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[6] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

[7] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

However, one year after treatment, CBT appears to maintain a reduction in symptoms compared with antidepressants:

There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing depression symptoms 12 months after treatment as measured by the HRSD (N = 3[8]; *n* = 137; WMD = –4.00; 95% CI, –6.60 to –1.40) and the BDI (N = 3[9]; *n* = 134; WMD = –5.21; 95% CI, –9.37 to –1.04).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of relapse.

Tolerability and acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing the likelihood of leaving treatment early (N = 10[10]; *n* = 1042; RR = 0.82; 95% CI, 0.67 to 1).

A sub-analysis showed that this result was mainly due to those with severe to very severe depression:

There is some evidence suggesting that there is a clinically significant difference favouring CBT over antidepressants on reducing the likelihood of leaving treatment early for any reason in people with severe to very severe depression (N = 2; n = 129; RR = 0.55; 95% CI, 0.32 to 0.94).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of leaving treatment early for any reason in people with moderate, moderate/severe depression or severe depression.

6.2.4.7 CBT combined with antidepressants compared with antidepressants alone

Effect of treatment on efficacy outcomes

CBT improves the effect of antidepressants compared with antidepressants alone, although it is not clear if this effect is maintained after treatment:

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone (with/without clinical management) on reducing depression symptoms at the end of treatment as measured by the HRSD (N = 6; *n* = 724; SMD= –0.46; 95% CI, –0.61 to –0.31).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants over antidepressants alone (with/without

[8] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

[9] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

[10] One study (HAUTZINGER1996) is counted as two because data from two groups of patients are input separately.

clinical management) on increasing the likelihood of achieving remission as measured by the HRSD (N = 4; *n* = 646; Random effects: RR = 0.76; 95% CI, 0.55 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants compared with antidepressants alone (without clinical management) on reducing depression symptoms:

- After six months' maintenance treatment as measured by the HRSD and the BDI (HRSD: N = 1; *n* = 16; WMD = 1.70; 95% CI, –1.43 to 4.83; BDI: N = 1; *n* =15; WMD = 2.10; 95% CI, –3.94 to 8.14)

- One year after treatment as measured by the BDI (N = 2; *n* = 92; WMD = –3.78; 95% CI, –8.89 to 1.33).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT combined with antidepressants and antidepressants alone on reducing relapse rates.

The effectiveness of CBT plus antidepressants over antidepressants alone was particularly marked for those with moderate and moderate/severe depression or severe/very severe depression:

There is strong evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on increasing the likelihood of achieving remission in people with moderate and moderate/severe depression by the end of treatment as measured by the HRSD (N = 2; *n* = 499; RR = 0.71; 95% CI, 0.62 to 0.82).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD:

- In people with chronic depression (but a moderate level of symptoms) (N = 1; *n* = 454; RR = 0.73; 95% CI, 0.62 to 0.84)

- In people with severe to very severe depression by the end of treatment (N = 1; *n* = 31; RR = 0.47; 95% CI, 0.22 to 0.99).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants alone on reducing depression symptoms by the end of treatment:

- In those with moderate or moderate/severe depression as measured by the HRSD (N = 3; *n* = 561; SMD = –0.50; 95% CI, –0.67 to –0.33)

- In those with severe or very severe depression as measured by the BDI (N = 3; *n* = 128; WMD = –4.54; 95% CI, –8.35 to –0.72).

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants and antidepressants alone on reducing

depression symptoms in those with severe depression as measured by the BDI one year after treatment (N = 2; *n* = 92; WMD = –3.78; 95% CI, –8.89 to 1.33).

Tolerability and acceptability of treatment

Although it was not possible to detect a statistically significant difference between CBT plus antidepressants and antidepressants alone on reducing the likelihood of patients leaving treatment early for any reason, there was a trend favouring combination treatment:

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants when compared with antidepressants (with/without CM) on reducing the likelihood of leaving treatment early for any reason (N = 8; *n* = 831; RR = 0.81; 95% CI, 0.65 to 1.01).

6.2.4.8 CBT combined with antidepressants compared with CBT alone

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT plus antidepressants and CBT alone on reducing depression symptoms at the end of treatment as measured by the HRSD (N = 4; *n* = 220; WMD = –0.33; 95% CI, –2.07 to 1.40).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT plus antidepressants and CBT alone on reducing the likelihood of leaving treatment early for any reason (N = 5; *n* = 710; RR = 1; 95% CI, 0.77 to 1.30).

6.2.4.9 CBT in residual depression

Two studies looked at the effect of CBT on people with residual symptoms (FAVA1994, PAYKEL1999). The former compared CBT with clinical management and reported relapse data only, and the latter combined CBT with antidepressants and compared this to antidepressants (with clinical management).

The effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between CBT plus antidepressants and antidepressants (with clinical management) in people with residual depression on reducing depression symptoms at the end of treatment as measured by the HRSD (HRSD: N = 1; *n* = 158; WMD = –0.70; 95% CI, –2.34 to 0.94).

There is evidence suggesting that there is no clinically significant difference between CBT plus antidepressants and antidepressants (with clinical management) in people with residual depression on reducing depression symptoms 17 months after the end of treatment, as measured by the HRSD (*n* = 158; WMD = 0.00; 95% CI, –1.56 to 1.56).

There is some evidence suggesting that there is a clinically significant difference favouring CBT plus antidepressants over antidepressants (with clinical management) in people with residual depression on reducing relapse rates 12 months (n = 158; RR = 0.60; 95% CI, 0.37 to 0.96) and 18 months (n = 158; RR = 0.61; 95% CI, 0.40 to 0.92) after treatment (with continuation treatment).

One study (FAVA1994) followed up participants for six years. However, there is insufficient evidence to determine if there is a clinically significant difference between CBT and clinical management in people with residual depression on reducing relapse rates two and six years after treatment.

There is some evidence suggesting that there is a clinically significant difference favouring CBT over clinical management in people with residual depression on reducing relapse rates four years after treatment (N = 1; n = 40; RR = 0.50; 95% CI, 0.26 to 0.97).

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between CBT and other treatments for patients with residual symptoms on reducing the likelihood of leaving treatment early for any reason.

6.2.4.10 Mindfulness-based group CBT as maintenance treatment in treatment responders

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring group mindfulness-based CBT plus usual GP care over usual GP care on reducing the likelihood of relapse 60 weeks after the start of treatment (N = 2; n = 220; RR = 0.74; 95% CI, 0.57 to 0.96).

In people who have had up to two episodes of depression, there is insufficient evidence to determine whether there is a clinically significant difference between mindfulness-based CBT plus usual GP care and usual GP care on reducing the likelihood of relapse 60 weeks after the start of treatment (N = 2; n = 94; RR = 1.42; 95% CI, 0.87 to 2.32).

In people who have had more than two episodes of depression, there is strong evidence suggesting that there is a clinically significant difference favouring group mindfulness-based CBT plus usual GP care over usual GP care on reducing the likelihood of relapse 60 weeks after the start of treatment (N = 2; n = 124; RR = 0.46; 95% CI, 0.29 to 0.72).

6.2.5 Overall clinical summary for CBT

In the only comparison available from a single trial there was insufficient evidence to determine the efficacy of individual CBT for depression compared with either pill placebo (plus clinical management) or other psychotherapies. However, stronger data do exist when CBT is compared with antidepressants (a number of which include clinical

management); here individual CBT is as effective as antidepressants in reducing depression symptoms by the end of treatment. These effects are maintained a year after treatment in those treated with CBT whereas this may not be the case in those treated with antidepressants. CBT appears to be better tolerated than antidepressants, particularly in patients with severe to very severe depression. There is a trend suggesting that CBT is more effective than antidepressants on achieving remission in moderate depression, but not for severe depression. There was also evidence of greater maintenance of a benefit of treatment for CBT compared with antidepressants. We recognise that this is a different finding to that of Elkin *et al.* (1989).

Adding CBT to antidepressants is more effective than treatment with antidepressants alone, particularly in those with severe symptoms. (This is the subject of a cost-effectiveness analysis in Chapter 9.) There is no evidence that adding an antidepressant to CBT is generally helpful, although we have not explored effects on specific symptoms (e.g. sleep). There is insufficient evidence to assess the effect of CBT plus antidepressants on relapse rates.

There is evidence from one large trial (Keller *et al.*, 2000) for chronic depression that a combination of CBT and antidepressants is more beneficial in terms of remission than either CBT or antidepressants alone. In residual depression the addition of CBT may also improve outcomes.

It appears to be worthwhile adding CBT to antidepressants compared with antidepressants alone for patients with residual depression as this reduces relapse rates at follow-up, although the advantage is not apparent post-treatment.

In regard to modes of delivery there is evidence that group CBT is more effective than other group therapies, but little data on how group CBT fares in comparison with individual CBT. Much may depend on patient preferences for different modes of therapy. However, group mindfulness-based CBT appears to be effective in maintaining response in people who have recovered from depression, particularly in those who have had more than two previous episodes.

6.3 Behaviour therapy (BT)

6.3.1 Introduction

Behaviour therapy for depression evolved from learning theory that posits two types of learning: operant or instrumental learning and classical conditioning. Although classical conditioning theories for depression have been put forward (e.g. Wolpe, 1971; Ferster, 1973) with treatment recommendations (Wolpe, 1979) there have been no treatment trials of this approach. Operant or instrumental learning posits that people acquire depressive behaviours due to the punishment and reinforcers contingent on behaviour. In this approach depression is seen as the result of a low rate of positive rewarded and rewardable behaviour. Hence the therapy focuses on behavioural activation aimed at encouraging the patient to develop more rewarding and task-focused behaviours. The approach was developed by Lewinsohn (1975). In recent years there has been renewed interest in

behavioural activation as a therapy in its own right. These therapies include many of the key features of earlier behavioural models, such as teaching relaxation skills, problem-solving and engaging in pleasant activities, but also include elements of learning to tolerate and accept certain feelings and situations. Early indications are that behavioural activation has some promise as a treatment for some types of depression (Hopko *et al.*, 2003).

6.3.2 Definition

Behaviour therapy was defined as a discrete, time limited, structured psychological intervention, derived from the behavioural model of affective disorders and where the therapist and patient:

- Work collaboratively to identify the effects of behaviours on current symptoms, feelings states and/or problem areas.

- Seek to reduce symptoms and problematic behaviours through behavioural tasks related to: reducing avoidance, graded exposure, activity scheduling, behavioural activation and increasing positive behaviours.

6.3.3 Studies considered for review

No suitable existing systematic review was available. Of the seven references downloaded from searches of electronic databases that appeared to be relevant RCTs, two eventually satisfied the inclusion criteria set by the GDG (GALLAGHER1983 and MCLEAN1979), with five being excluded. No additional trials were found from other sources, including searches of reference lists.

6.3.4 Study characteristics

GALLAGHER1983: 12-week RCT (16 sessions) using outpatients referred from regional health centres or private physicians, or self-referred. Mean age of participants 66 to 69 years.

MCLEAN1979: 10-week RCT (eight to 12 sessions) with outpatients meeting Feighner *et al.* (1972) criteria for depression and a BDI of at least 23, with a mean age 39.2 years (±10.9).

6.3.5 Evidence statements[11]

There is insufficient evidence to determine whether there is a clinically significant difference between behaviour therapy and other psychotherapies on reducing the likelihood of leaving treatment early for any reason.

There is no evidence to determine whether there is a clinically significant difference between behaviour therapy and other psychotherapies on any efficacy outcome.

6.4 Interpersonal psychotherapy (IPT)

6.4.1 Introduction

Interpersonal psychotherapy (IPT) was developed by Klerman and Weissman (Klerman *et al.*, 1984) initially for depression although it has now been extended to other areas (Weissman *et al.*, 2000). IPT focuses on current relationships, not past ones, and on interpersonal processes rather than intrapsychic ones (such as negative core beliefs or automatic thoughts as in CBT, or unconscious conflicts as in psychodynamic therapy). It is time limited and focused on difficulties arising in the daily experience of maintaining relationships and resolving difficulties whilst suffering an episode of major depression. The main clinical tasks are to help patients to learn to link their mood with their interpersonal contacts and to recognise that, by appropriately addressing interpersonal situations, they may simultaneously improve both their relationships and their depressive state. Early in the treatment, patient and therapist agree to work on a particular focal area that would include: interpersonal role transitions, interpersonal roles/conflicts, grief and/or interpersonal deficits. IPT is appropriate when a person has a key area of difficulty that is specified by the treatment (e.g. grief, interpersonal conflicts). It can be delivered as an individual focused therapy but has also been developed as a group therapy (Wilfley *et al.*, 2000).

The character of the therapy sessions is, largely, facilitating understanding of recent events in interpersonal terms and exploring alternative ways of handling interpersonal situations. Although there is not an explicit emphasis on 'homework', tasks may be undertaken between sessions.

6.4.2 Definition

Interpersonal therapy was defined as a discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where the therapist and patient:

- Work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems.

- Seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

[11] The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on the CD.

6.4.3 Studies considered for review

No suitable existing systematic review was available. Of the 107 references downloaded from searches of electronic databases, 15 appeared to be relevant RCTs, with seven eventually satisfying the inclusion criteria set by the GDG (DEMELLO2001, ELKIN1989, FRANK1990, REYNOLDS1999, REYNOLDS1999b, SCHULBERG1996, WEISSMAN1992), and eight being excluded (DIMASCIO1979, FRANK1989, JACOBSON1977, KLERMAN1974, MARTIN2001, MOSSEY1996, SZAPOCZNIC1982, ZEISS1979). In addition, one unpublished trial, FREEMAN, was sourced from the authors. No additional trials were found from other sources, including searches of reference lists.

6.4.4 Study characteristics

The eight included studies looked at IPT in a variety of settings, including outpatient and primary care. Most were undertaken in the US, although one (DEMELLO2001) was Brazilian and another (FREEMAN) British. Two studies looked at older adults, and in one, most participants were diagnosed with double depression (i.e. dysthymia superimposed on major depressive disorder) (DEMELLO2001) rather than major depression alone. Two studies looked at IPT during a continuation phase after successful acute phase treatment (REYNOLDS1999, SCHULBERG1996), and two examined IPT during a three-year maintenance treatment in treatment responders (FRANK1990, REYNOLDS1999B).

6.4.5 Evidence statements

6.4.5.1 IPT compared with placebo (plus clinical management) or usual GP care

Effect of treatment on efficacy outcomes

IPT is more effective than either placebo plus clinical management or usual GP care. In both studies comparing IPT with usual GP care, patients receiving GP care were prescribed antidepressants: in SCHULBERG1996 45%, and in FREEMAN all patients.

There is some evidence suggesting that there is a clinically significant difference favouring IPT over placebo plus clinical management on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 123; WMD = –3.4; 95% CI, –6.17 to –0.63)
- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 123; RR = 0.73; 95% CI, 0.56 to 0.93).

There is some evidence suggesting that there is a clinically significant difference favouring IPT over usual GP care on reducing depression symptoms by the end of treatment as measured by the BDI and HRSD (BDI: N = 1; *n* = 72; WMD = –9.23; 95% CI, –15.45 to –3.01; HRSD: N = 1; *n* = 185; WMD = –3.09; 95% CI, –5.59 to –0.59).

Tolerability and acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring usual GP care over IPT on reducing the likelihood of leaving treatment early (N = 1; *n* = 185; RR = 4.14; 95% CI, 2.29 to 7.47).

There is some evidence suggesting that there is a clinically significant difference favouring IPT over placebo plus clinical management on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 123; RR = 0.57; 95% CI, 0.33 to 0.99).

6.4.5.2 IPT combined with antidepressants

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT alone (with/without placebo) on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 33; RR = 2.26; 95% CI, 1.03 to 4.97).

However, there was insufficient evidence to assess IPT in combination with antidepressants compared with antidepressants alone.

Tolerability and acceptability of treatment

There was insufficient evidence to determine whether IPT was more acceptable than any comparator treatment for which data were available.

6.4.5.3 IPT compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between IPT and antidepressants on reducing depression symptoms as measured by the HRSD at the end of treatment (N = 2; *n* = 302; WMD = 0.64; 95% CI, –1.32 to 2.59).

6.4.5.4 IPT as a continuation treatment

Effect of treatment on efficacy outcomes

When used as continuation treatment after response and in comparison with treatment as usual (TAU), IPT was effective in the treatment of depression:

There is some evidence suggesting that, after four months' continuation treatment, there is a clinically significant difference favouring IPT over TAU on:

- increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 185; RR = 0.66; 95% CI, 0.53 to 0.82)
- reducing depression symptoms as measured by the HRSD (N = 1; *n* = 185; WMD = –3.8; 95% CI, –6.29 to –1.31).

There is evidence suggesting that, after four months' continuation treatment, there is no clinically significant difference between IPT and antidepressants on reducing depression symptoms as measured by the HRSD (N = 1; *n* = 184; WMD = 0.30; 95% CI, –2.34 to 2.94).

However, there is insufficient evidence to determine the efficacy of IPT in combination with antidepressants, in continuation treatment, against antidepressants alone or IPT alone.

There is strong evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favouring IPT plus antidepressants over:

- IPT plus placebo on reducing relapse rates (N = 2; *n* = 101; RR = 0.42; 95% CI, 0.27 to 0.65)

- medication clinic plus placebo on reducing relapse rates (N = 1; *n* = 54; RR = 0.22; 95% CI, 0.1 to 0.49).

There is some evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favouring IPT plus antidepressants over IPT alone on reducing relapse rates (N = 1, *n* = 51; RR = 1.73; 95% CI, 1 to 2.98).

There is some evidence suggesting that, after three years' maintenance treatment, there is a clinically significant difference favouring IPT plus placebo over medication clinic plus placebo on reducing relapse rates (N = 2; *n* = 103; RR = 0.8; 95% CI, 0.66 to 0.97).

There was insufficient evidence to determine the efficacy of IPT against other comparator treatments for which data were available.

Tolerability and acceptability of treatment

There are no data on which to assess the tolerability and acceptability of IPT as a continuation treatment.

There is insufficient evidence to determine the tolerability and acceptability of IPT as a maintenance treatment.

6.4.6 Clinical summary

IPT has been the subject of a small number of well-designed RCTs. There is some evidence to suggest that IPT is more effective than placebo and usual GP care and that its effectiveness may be increased when combined with an antidepressant. There was insufficient evidence to compare IPT with other psychological interventions (see Section 6.2 on CBT). It can also be effective as a maintenance intervention where patients have remitted following previous treatment. Studies of long-term relapse prevention are yet to be conducted.

6.5 Problem-solving therapy

6.5.1 Introduction

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

6.5.2 Definition

Problem-solving therapy was defined as a discrete, time limited, structured psychological intervention, which focuses on learning to cope with specific problems areas and where:

- Therapist and patient work collaboratively to identify and prioritise key problem areas, to break problems down into specific, manageable tasks, problem solve, and develop appropriate coping behaviours for problems.

6.5.3 Studies considered for review

6.5.3.1 Source of studies

No suitable existing systematic review was available. Of the 188 references downloaded from searches of electronic databases, 12 appeared to be relevant RCTs, with three eventually satisfying the inclusion criteria set by the GDG (DOWRICK2000, MYNORS-WALLIS1995, MYNORS-WALLIS2000), and nine being excluded. No additional trials were found from other sources, including searches of reference lists.

6.5.3.2 Study characteristics

The three included studies were:

- DOWRICK2000 – patients responding to a survey, all met DMS-IV criteria for major depressive disorder (single episode or recurrent), dysthymia (16%), adjustment disorder (4%) or other (9%). Baseline BDI around 22 points. Nine-centre international trial comparing no treatment with either problem-solving therapy or group psychoeducation. Problem-solving therapy versus no treatment control is extracted for this section.

- MYNORS-WALLIS1995 – patients from primary care, all met RDC for major depression (Spitzer *et al.*, 1978), with an HRSD score over 13; problem-solving therapy is compared with pharmacotherapy (amitriptyline at 150 mg/day) and pill placebo.

- MYNORS-WALLIS2000 – patients from primary care, meeting RDC for probable or definite major depression, with an HRSD score over 13; problem-solving therapy (either by a GP or practice nurse) is compared with pharmacotherapy (fluvoxamine (100 to 150 mg) or paroxetine (10 to 40 mg)) and with a combination of psychotherapy and pharmacotherapy.

All gave participants six sessions over a period of three months.

6.5.4 Evidence statements

6.5.4.1 Problem-solving versus placebo or no treatment control

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring problem solving over placebo on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 55; WMD = –4.7; 95% CI, –8.42 to –0.98) and BDI (N = 1; *n* = 55; WMD = –7.8; 95% CI, –13.78 to –1.82)

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 60; RR = 0.55; 95% CI, 0.33 to 0.89) and BDI (N = 1; *n* = 60; RR = 0.62; 95% CI, 0.39 to 0.99).

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and no treatment on reducing the likelihood of being diagnosed with a depressive disorder:

- Six months after the start of treatment (N = 1; *n* = 245; RR = 0.83; 95% CI, 0.68 to 1.02)

- Twelve months after the start of treatment (N = 1; *n* = 245; RR = 0.98; 95% CI, 0.79 to 1.22).

Tolerability and acceptability of problem-solving therapy

There is strong evidence suggesting that there is a clinically significant difference favouring problem-solving over placebo on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 60; RR = 0.11; 95% CI, 0.03 to 0.44).

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and placebo on reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 60; RR = 0.2; 95% CI, 0.01 to 4).

6.5.4.2 Problem-solving versus antidepressants

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and antidepressants when compared with antidepressants alone on any efficacy measure:

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 116; RR = 1.43; 95% CI, 0.85 to 2.39) or BDI (N = 1; *n* = 61; RR = 0.67; 95% CI, 0.41 to 1.09)

- reducing depression symptoms by the end of treatment as measured by the HRSD or BDI (HRSD: N = 2; *n* = 124; WMD = 0.65; 95% CI, –1.9 to 3.21; BDI: N = 2; *n* = 124; WMD = –1.34; 95% CI, –5.23 to 2.55).

One year after the end of treatment there is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and antidepressants on:

- increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 116; RR = 0.93; 95% CI, 0.59 to 1.45)

- reducing depression symptoms one year after the end of treatment as measured by the HRSD (N = 1; *n* = 55; WMD = –1.4; 95% CI, –5 to 2.2) or BDI (N = 1; *n* = 55; WMD = –1.9; 95% CI, –8.83 to 5.03).

Tolerability and acceptability of problem-solving therapy

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving and antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 2; *n* = 177; Random effects RR = 0.88; 95% CI, 0.18 to 4.2).

There is some evidence suggesting that there is a clinically significant difference favouring problem-solving over antidepressants on reducing the likelihood of leaving treatment early due to side effects (N = 2; *n* = 177; RR = 0.12; 95% CI, 0.01 to 0.97).

6.5.4.3 Problem-solving plus antidepressants versus antidepressants alone

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving plus antidepressants and antidepressants alone on any efficacy measure:

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 71; RR = 1.2; 95% CI, 0.65 to 2.22)

- reducing depression symptoms by the end of treatment as measured by the HRSD or BDI (HRSD: N = 1; *n* = 65; WMD = 1.3; 95% CI, –2.09 to 4.69; BDI: N = 1; *n* = 65; WMD = –2.5; 95% CI, –7.33 to 2.33).

One year after the end of treatment there is insufficient evidence to determine whether there is a clinically significant difference between problem-solving plus antidepressants and antidepressants alone on:

- increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 71; RR = 0.77; 95% CI, 0.43 to 1.39)

- maintaining a reduction in depression symptoms as measured by the HRSD (N = 1; *n* = 60; WMD = –1.5; 95% CI, –4.47 to 1.47) or BDI (N = 1; *n* = 60; WMD = –2.9; 95% CI, –8.64 to 2.84).

Tolerability and acceptability of problem-solving therapy

There is insufficient evidence to determine whether there is a clinically significant difference:

- between problem-solving plus antidepressants and antidepressants alone on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 71; RR = 1.03; 95% CI, 0.37 to 2.89);

- between problem-solving plus antidepressants and antidepressants alone on reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 71; RR = 2.06; 95% CI, 0.4 to 10.52).

6.5.4.4 Problem-solving administered by a GP compared with problem-solving administered by a nurse

There is insufficient evidence to determine whether there is a clinically significant difference between problem-solving therapy administered by a GP and problem-solving therapy administered by a nurse on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 70; WMD = –0.2; 95% CI, –3.95 to 3.55) or the BDI (N = 1; *n* = 70; WMD = –0.8; 95% CI, –6.25 to 4.65).

6.5.5 Clinical summary

Problem-solving provides direct and practical support for patients with mild depression with their current life difficulties. The evidence is that this can be helpful for patients with mild depression and may be as useful to them as antidepressants. Both appropriately trained GPs and practice nurses can deliver this treatment effectively. However, all the studies of problem-solving therapy have been carried out in primary care; we do not know about its value in secondary care (for example, how it compares with active drugs or with CBT) and for depression other than in its mild form.

6.6 Counselling

6.6.1 Introduction

Counselling was developed by Carl Rogers (1957) who believed that people had the means for self-healing, problem resolution and growth if the right conditions could be created. These include the provision of positive regard, genuineness and empathy. Rogers's original model was developed into structured counselling approaches by Truax and Carkhuff (1967) and, independently, by Egan (e.g. 1990) who developed the three-stage model: exploration, personalising and action. Voluntary sector counselling training (e.g. Relate) tends to draw on these models. Counsellors are taught to listen and reflect patient feelings and meaning (Rogers, 1957). Although many other therapies now use these basic ingredients of client-centred counselling (Roth & Fonagy, 1996) there are differences in how they are used (Kahn, 1985; Rogers, 1986). Today, however, counselling is really a generic term used to describe a broad range of interventions delivered by counsellors usually working in primary care; the various approaches may include psychodynamic, systemic or cognitive behavioural (Bower *et al.*, 2003).

The British Association for Counselling and Psychotherapy (BACP) defines counselling as 'a systematic process which gives individuals an opportunity to explore, discover and clarify ways of living more resourcefully, with a greater sense of well-being. Counselling may be concerned with addressing and resolving specific problems, making decisions, coping with crises, working through conflict, or improving relationships with others' (BACP comments on second draft of this guideline).

6.6.2 Definition

For the guideline counselling was defined as a discrete, usually time limited, psychological intervention where:

- The intervention may have a facilitative approach often with a strong focus on the therapeutic relationship but may also be structured and at times directive

- An intervention was classified as counselling if the intervention(s) offered in the study did not fulfil all the criteria for any other psychological intervention. If a study using counsellors identified a single approach, such as cognitive behavioural or interpersonal, it has been analysed in that category.

6.6.3 Source of studies

No suitable existing systematic review was available. Of the 1027 references downloaded from searches of electronic databases, nine appeared to be relevant RCTs, with three eventually satisfying the inclusion criteria set by the GDG, and six being excluded. No additional trials were found from other sources, including searches of reference lists.

6.6.3.1 Study characteristics

The three included studies were BEDI2000, SIMPSON2003 and WARD2000, all of which were carried out in the UK.

- BEDI2000 studied outpatients recruited via GP practices with a diagnosis of major depression (RDC) and a mean baseline BDI score of around 27 (±8). The comparator treatment was antidepressant medication. GPs had a choice of three drugs which had to be given at an adequate dose for between four and six months after response. Counsellors used whatever approach they felt was most appropriate.

- SIMPSON2003 studied participants from primary care with a BDI score of at least 14 who had been depressed for at least six months – many patients were on concurrent medication during the trial. Counsellors followed a psychodynamic Freudian model.

- WARD2000 studied GP referrals with a BDI score of at least 14, although depression was the primary diagnosis in only 62% of the sample. The comparator treatments were CBT and 'usual GP care'. Due to the problem with diagnosis, this trial was excluded from the review of CBT. However, it is included here because of the lack of suitable trials. In addition, despite GPs being asked not to prescribe antidepressants for study, patients receiving psychotherapy, 30% of the counselling group and 27% of those receiving CBT took concomitant antidepressants. Counsellors used a non-directive approach.

6.6.4 Evidence statements

Effect of treatment on efficacy outcomes

When compared with GP care, counselling appears to be effective, although there is insufficient evidence at follow-up:

There is some evidence suggesting that there is a clinically significant difference favouring counselling over GP care on reducing depression symptoms at the end of treatment as measured by the BDI (N = 1; *n* = 134; WMD = –5.4; 95% CI, –9.11 to –1.69).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and GP care on reducing depression symptoms 12 months after treatment as measured by the BDI (N = 1; *n* = 134; WMD = –0.3; 95% CI, –3.67 to 3.07).

When compared with antidepressants, antidepressants are more effective at follow-up, although only one study made this comparison (BEDI2000):

There is some evidence suggesting that there is a clinically significant difference favouring antidepressants over counselling on increasing the likelihood of achieving remission 12 months after the end of treatment as measured by the RDC (N = 1; *n* = 103; RR = 1.41; 95% CI, 1.08 to 1.83).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and antidepressants on maintaining a reduction in depression symptoms 12 months after the end of treatment as measured by the BDI (N = 1; *n* = 65; WMD = 2.1; 95% CI, –3.88 to 8.08).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and CBT on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 130; WMD = –1.4; 95% CI, –4.87 to 2.07)

- reducing depression symptoms 12 months after the end of treatment as measured by the BDI (N = 1; *n* = 130; WMD = 0.4; 95% CI, –3.12 to 3.92).

When added to GP care and compared with GP care alone there is no advantage in patients who have been depressed for at least six months:

There is evidence suggesting that there is no clinically significant difference between counselling plus GP care and GP care alone on reducing depression symptoms six months after the start of treatment to below 14 points on the BDI (N = 1; *n* = 145; RR = 0.94; 95% CI, 0.73 to 1.22).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling plus GP care and GP care alone on any other outcome including at follow-up.

Tolerability and acceptability of treatment

There was no evidence for tolerability against antidepressants. However, when compared with GP care or CBT:

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and GP care on reducing the likelihood of patients leaving the study early four months after the start of treatment (N = 1; *n* = 134; RR = 1.00; 95% CI, 0.30 to 3.30) or 12 months after the start of treatment (N = 1; *n* = 134; RR = 0.90; 95% CI, 0.39 to 2.07).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling plus GP care and GP care alone on reducing the likelihood of patients leaving the study early (N = 1; *n* = 145; RR = 1.13; 95% CI, 0.43 to 2.95).

There is insufficient evidence to determine whether there is a clinically significant difference between counselling and CBT on reducing the likelihood of patients leaving the study early four months after the start of treatment (N = 1; *n* = 130; RR = 0.67; 95% CI, 0.22 to 2.01) or 12 months after the start of treatment (N = 1; *n* = 130; RR = 0.65; 95% CI, 0.3 to 1.42).

6.6.5 Clinical summary

Counselling as currently delivered in the NHS covers a wide range of different interventions; to some extent that variety in the nature of the intervention was reflected in the studies reported here. There is evidence for the efficacy of counselling for depression in primary care for patients with mild to moderate depression of recent onset when it is compared with antidepressants, GP care and other psychological interventions. There is no evidence of its effectiveness for chronic depression. Although counselling appears to be effective, there was little evidence about tolerability.

6.7 Short-term psychodynamic psychotherapy

6.7.1 Introduction

Psychodynamic psychotherapy is a derivative of psychoanalysis. As with other schools of therapy there are now many variations and hybrids of the original model with some approaches focusing on the dynamic of drives (e.g. aggression) while others focus on relationships (Greenberg & Mitchell, 1983). Other forms of this type of therapy have been influenced by attachment theory (Holmes, 2001). Clinical trials of psychodynamic psychotherapy have focused on short-term psychological therapy (10 to 20 weeks) usually in comparison with antidepressants, CBT or BT.

6.7.2 Definition

Psychodynamic interventions were defined as psychological interventions, derived from a psychodynamic/psychoanalytic model, and where:

- Therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference).
- This leads to patients being given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with a technical focus on interpreting and working though conflicts.
- Therapy is non-directive and recipients are not taught specific skills (e.g. thought monitoring, re-evaluating, or problem-solving).

6.7.3 Studies considered for review

6.7.3.1 Source of studies

No suitable existing systematic review was available. Of the 188 references downloaded from searches of electronic databases, 11 appeared to be relevant RCTs, with three eventually satisfying the inclusion criteria set by the GDG (GALLAGHER-THOMPSON1994, MCLEAN1979, SHAPIRO1994), and eight being excluded. An additional trial

(BURNAND2002) was sourced through an update search undertaken towards the end of the guideline development process. No further trials were found from other sources, including searches of reference lists.

6.7.3.2 Study characteristics

BURNAND2002 – participants were referred to acute outpatient treatment at a community mental health centre. All had major depressive disorder according to DSM-IV criteria and HRSD ≥ 20 at baseline. The trial compared psychodynamic psychotherapy plus clomipramine with clomipramine and supportive therapy (providing empathetic listening, guidance, support and facilitation of an alliance by one carefully designated caregiver). Trial length: 10 weeks; number of sessions not clear.

GALLAGHER-THOMPSON1994 – caregivers recruited through referrals from healthcare professionals. The majority of participants met RDC for major depression, with the remainder meeting criteria for minor depression. Brief psychodynamic therapy is compared with CBT. Trial length: 16 to 20 sessions, twice a week for first four weeks, then once a week for remainder of therapy.

MCLEAN1979 – participants were outpatients meeting Feighner *et al.* (1972) criteria for depression and a BDI score of at least 23. This was a three-arm trial comparing psychodynamic psychotherapy with behaviour therapy and antidepressants. Efficacy data were not extracted because dropouts were replaced. Trial length: 10 sessions over 10 weeks.

SHAPIRO1994 – participants were outpatients recruited from self-referrers responding to recommendations by occupational health personnel or responding to publicity materials distributed at the workplace or by GPs, or referred directly by GPs or mental health services. All had a diagnosis of major depressive disorder (DSM-III; APA, 1980). Psychodynamic-interpersonal psychotherapy based on Hobson's conversational model is compared with CBT. Trial length: 16 weeks.

6.7.4 Evidence statements

Effect of treatment on efficacy outcomes

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy and CBT on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 3; *n* = 57; Random effects: WMD = 2.07; 95% CI, –3.70 to 7.84)
- reducing depression symptoms by six months after treatment as measured by the BDI (N = 3; *n* = 56; WMD = 1.44; 95% CI, –2.7 to 5.58)
- reducing depression symptoms by one year after treatment as measured by the BDI (N = 3; *n* = 50; Random effects: WMD = –1.98; 95% CI, –9.83 to 5.88)
- reducing the likelihood of still being depressed at the end of treatment as measured by RDC (N = 1; *n* = 66; RR = 1.7; 95% CI, 0.97 to 2.97)

- reducing the likelihood of still being depressed three months after treatment as measured by RDC (N = 1; *n* = 66; RR = 1.34; 95% CI, 0.86 to 2.08).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy plus antidepressants and antidepressants plus supportive therapy on:

- increasing the likelihood of achieving remission by the end of treatment (N = 1; *n* = 95; RR = 1.09; 95% CI, 0.8 to 1.48)

- reducing depression symptoms by the end of treatment (N = 1; *n* = 74; WMD = –0.8; 95% CI, –4.06 to 2.46).

Effect of treatment on tolerability

There is some evidence suggesting that there is a clinically significant difference favouring behaviour therapy over psychodynamic therapy on reducing the likelihood of leaving treatment early (N = 1; *n* = 95; RR = 3.02; 95% CI, 1.07 to 8.5).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic treatment and antidepressants on reducing the likelihood of leaving treatment early (N = 1; *n* = 90; RR = 0.76; 95% CI, 0.41 to 1.41).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy and CBT on reducing the likelihood of leaving treatment early (N = 1; *n* = 66; RR = 2.16; 95% CI, 0.81 to 5.76).

There is insufficient evidence to determine whether there is a clinically significant difference between psychodynamic psychotherapy plus antidepressants and antidepressants plus supportive therapy on reducing the likelihood of leaving treatment early (N = 1; *n* = 95; RR = 1.43; 95% CI, 0.71 to 2.89).

6.7.5 Clinical summary

Despite the fact that psychodynamic psychotherapy is the longest established psychotherapy, good quality research studies are rare. Comparisons between short-term psychodynamic therapy and CBT or antidepressants demonstrate a clear but not definitive trend towards increasing effectiveness for drugs and CBT at end of treatment. The potential superior efficacy of antidepressants and CBT is not maintained at follow-up. However, psychodynamic psychotherapy may be of value in the treatment of the complex comorbidities that may be present along with depression.

6.8 Couple-focused therapies

6.8.1 Introduction

Therapists have noted that a partner's critical behaviour may trigger an episode, and/or maintain or exacerbate relapse in the long term (e.g. Hooley & Teasdale, 1989), although other researchers have questioned this (e.g. Hayhurst *et al.*, 1997). Couple-focused therapies focus on the way distressed couples differ from non-distressed couples and teach communication and interpersonal skills to increase relationship satisfaction (Wheeler *et al.*, 2001). There has also been some work looking at differences in the vulnerabilities between men and women within an intimate relationship, with physical aggression by a partner predicting depression in women. Difficulties in developing intimacy, and coping with conflict, also predict depression in both men and women (Christian *et al.*, 1994). In some forms of therapy depression is seen to constitute a challenge to the relationship and therapy is aimed at coping with the depression. In other forms of therapy the relationship interacts with the depression. Each may be true for different people. Like other therapies a couple-focused approach has evolved in recent years. For example, Wheeler *et al.* (2001) have outlined the development of integrative couple behaviour therapy, from traditional cognitive behavioural therapy, with an outline of the key therapeutic principals. Systemic couple therapy aims to give the couple new perspectives on the presenting problem (e.g. depressing behaviours), and explore new ways of relating (Jones & Asen, 1999). In our analysis of couple-focused therapies, where one partner is depressed, we have not focused on a specific approach but define couple-focused therapies more generally.

6.8.2 Definition

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

- Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems.

- The aim is to change the nature of the interactions so that they may develop more supportive and less conflictual relationships.

The style of the therapy can vary and reflect different approaches, e.g. cognitive behavioural or psychodynamic.

6.8.3 Studies considered for review

6.8.3.1 Source of studies

No suitable existing systematic review was available. Of the 42 references downloaded from searches of electronic databases, 15 appeared to be relevant RCTs, with five eventually satisfying the inclusion criteria set by the GDG and 10 being excluded. No additional trials were found from other sources, including searches of reference lists.

6.8.3.2 Study characteristics

Participants in the five included studies were couples in which at least one partner met criteria for depression and where marital difficulties had been identified. Three were undertaken in the US (BEACH1992, FOLEY1989, OLEARY1990), one in the UK (LEFF2000) and one in Holland (EMANUELS-ZUUVEEN1996). Most studies used CBT or IPT tailored to couples. LEFF2000, however, used systemic couples therapy.

6.8.4 Evidence statements

Effect of treatment on efficacy

There is strong evidence suggesting that there is a clinically significant difference favouring couple-focused therapies over wait list control on reducing depression symptoms by the end of treatment as measured by the BDI (N = 2; *n* = 54; WMD = –11.64; 95% CI, –16.12 to –7.16).

Unfortunately, there was no evidence to make a comparison with antidepressants, since more than 50% of participants in the antidepressant group in the only available study (LEFF2000) left treatment early.

There is insufficient evidence to determine whether there is a clinically significant difference between couple-focused therapies and individual therapy (CBT or IPT) on reducing depression symptoms at the end of treatment as measured by the BDI (N = 2; *n* = 57; WMD = –2.73; 95% CI, –7.06 to 1.6) or HRSD (N = 1; *n* = 18; WMD = 0.6; 95% CI, –11.04 to 12.24).

Tolerability and acceptability of couple-focused therapies

There is some evidence suggesting that there is a clinically significant difference favouring couple-focused therapies over antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 77; RR = 0.4; 95% CI, 0.21 to 0.75).

There is insufficient evidence to determine whether there is a clinically significant difference between couple-focused therapies and antidepressants on reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 77; RR = 0.31; 95% CI, 0.01 to 7.36).

There is insufficient evidence to determine whether there is a clinically significant difference between couple-focused therapies and individual therapy (CBT or IPT) on reducing the likelihood of leaving treatment early (N = 3; *n* = 84; RR = 1.22; 95% CI, 0.56 to 2.65).

6.8.5 Clinical summary

There is some evidence for couple-focused therapies as effective treatments for depression when compared with wait list control, and they appear to be more acceptable than antidepressants. They appear to be as acceptable as individual therapy

(CBT and IPT). Unfortunately, there was no evidence to determine their efficacy compared with antidepressants.

6.9 Psychological interventions in older adults

6.9.1 Introduction

It is well known that after the age of 65 there is an increasing risk of major life events associated with depression. These include loss of employment, loss of intimate (e.g. spouse), changing social environments (such as retirement or a move), increasing risk of social isolation and changes in health status (Tolliver, 1983). Indeed it is estimated that approximately 15% of older adults may be depressed at any one time (Beekman *et al.*, 1999). Depression is a major cause of suicide in older adults (Lebowitz *et al.*, 1997) and depression can significantly handicap people's ability to cope with physical ailments. Depression can often present as pseudo-dementia (Wells, 1979). As most older patients with symptoms of depression will be seen in primary care, it is important that clinicians consider depressive symptoms in the context of life events and ongoing difficulties. However, attention and one study of reminiscence therapy also showed promise (McCusker *et al.*, 1998).

6.9.2 Studies reviewed

From the studies reviewed elsewhere in this chapter, four were exclusively of older adults (mean age 65 years or over). Three of these were of IPT (REYNOLDS1999, REYNOLDS1999B, WEISSMAN1992) and one of CBT (THOMPSON2001).

6.9.3 Evidence statements

6.9.3.1 CBT versus antidepressants

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT and antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 64; WMD = –2.20; 95% CI, –6.41 to 2.01)
- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 64; WMD = –2.50; 95% CI, –5.75 to 0.75).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT and antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 64; RR = 0.62; 95% CI, 0.28 to 1.37).

6.9.3.2 Older patients: CBT plus antidepressants versus antidepressants

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants and antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the BDI (N = 1; *n* = 69; WMD = –2.90; 95% CI, –6.63 to 0.83)
- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 69; WMD = –3.00; 95% CI, –6.09 to 0.09).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between CBT plus antidepressants and antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 69; RR = 0.92; 95% CI, 0.48 to 1.75).

6.9.3.3 Older patients: IPT (with/without placebo) versus IPT + antidepressants

Effect of treatment on efficacy

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT (with/without placebo) on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 33; RR = 2.26; 95% CI, 1.03 to 4.97).

Tolerability and acceptability

In older patients there is insufficient evidence to determine whether there is a clinically significant difference between IPT (with/without placebo) and IPT plus antidepressants on:

- reducing the likelihood of patients leaving treatment early for any reason (N = 2; *n* = 58; RR = 1.44; 95% CI, 0.72 to 2.86)
- reducing the likelihood of patients leaving treatment early due to side effects (N = 2; *n* = 58; RR = 0.34; 95% CI, 0.06 to 2.08).

6.9.3.4 Older patients: IPT plus antidepressants versus antidepressants

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 41; RR = 0.71; 95% CI, 0.30 to 1.66).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 41; RR = 0.10; 95% CI, 0.01 to 1.67)
- reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 41; RR = 0.31; 95% CI, 0.02 to 5.99).

6.9.3.5 IPT (with/without placebo) versus antidepressants (with/without clinical management)

Effect of treatment on efficacy

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT and antidepressants on increasing the likelihood of achieving remission as measured by the HRSD (N = 1; *n* = 42; RR = 1.60; 95% CI, 0.94 to 2.75).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT and antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 42; RR = 0.63; 95% CI, 0.19 to 2.10)
- reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 42; RR = 0.29; 95% CI, 0.01 to 5.67).

6.9.3.6 IPT as maintenance treatment (three years)

Effect of treatment on efficacy

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over IPT plus placebo on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; *n* = 50; RR = 0.31; 95% CI, 0.14 to 0.72).

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus antidepressants over medication clinic plus placebo on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; *n* = 54; RR = 0.22; 95% CI, 0.10 to 0.49).

In older patients there is some evidence suggesting that there is a clinically significant difference favouring IPT plus placebo over medication clinic plus placebo on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; *n* = 54; RR = 0.71; 95% CI, 0.52 to 0.98).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and medication clinic plus antidepressants on reducing the likelihood of a relapse after three years' maintenance treatment (N = 1; *n* = 53; RR = 0.47; 95% CI, 0.19 to 1.14).

Tolerability and acceptability

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and IPT plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; *n* = 50; RR = 0.75; 95% CI, 0.19 to 3.01).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and medication clinic plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; *n* = 54; RR = 8.08; 95% CI, 0.44 to 149.20).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus placebo and medication clinic plus placebo on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; *n* = 54; RR = 10.38; 95% CI, 0.59 to 183.92).

In older patients there is insufficient evidence to determine if there is a clinically significant difference between IPT plus antidepressants and antidepressants on reducing the likelihood of leaving maintenance treatment early for any reason (N = 1; *n* = 53; RR = 0.84; 95% CI, 0.21 to 3.39).

6.9.4 Clinical summary

There are few RCTs of psychotherapies undertaken on exclusively older populations. Therefore, there is largely insufficient evidence for the efficacy of psychological therapies in this patient group. There is some evidence, however, for the addition of antidepressants to IPT compared with IPT alone on achieving remission by the end of treatment and on reducing the likelihood of relapse after three years' maintenance treatment.

6.10 Short-term psychological treatments

6.10.1 Introduction

In primary care, there is a clear desire to find effective and rapid treatments for depression, particularly milder disorders. This has led to the development of short-term cognitive behavioural and other structured psychological therapies with six to eight sessions. Most short-term interventions cover the same material as long-term therapies, but introduce it at a faster rate. In addition, therapists aim to establish a therapeutic relationship with clients much more quickly. Clients are expected to be able to articulate their problems clearly, not to have difficult interpersonal problems that would interfere

with the establishing of a good therapeutic alliance, to be able to understand and appreciate the rationale of the therapy, and to be able to engage in independent work outside the therapy sessions.

6.10.2 Studies considered for review

The following studies of short-term psychotherapy (six to 12 sessions) included in other sections of this chapter were used:

BEDI2000 (Counselling versus GP care (including antidepressants))

MIRANDA2003 (CBT versus antidepressants)

MYNORS-WALLIS1995 (Problem-solving therapy versus antidepressants versus placebo)

MYNORS-WALLIS2000 (Problem-solving therapy versus antidepressants (versus combination treatment – not used))

SCOTT1997 (CBT versus GP care (most participants on antidepressants))

SELMI1990 (CBT versus wait list control (versus CCBT – not used))

SHAPIRO1994 (CBT versus psychodynamic psychotherapy)

SIMPSON2003 (Counselling plus GP care versus GP care (some participants on antidepressants))

WARD2000 (Counselling versus GP care (some participants on antidepressants))

Short-term psychological therapy was compared with other treatments and with placebo and wait list control.

6.10.3 Evidence statements

6.10.3.1 Short-term psychotherapies versus other therapies

Tolerability and acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on reducing the likelihood of leaving treatment early for any reason (N = 5; *n* = 504; RR = 1.16; 95% CI, 0.75 to 1.79).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over other treatments on reducing the likelihood of leaving treatment early due to side effects (N = 2; *n* = 177; RR = 0.12; 95% CI, 0.01 to 0.97).

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is a statistically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms by the end of treatment as measured by the BDI, but there is insufficient evidence to determine its clinical significance (N = 8; *n* = 481; WMD = –1.89; 95% CI, –3.63 to -0.16).

There is evidence suggesting that there is no clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 4; *n* = 336; Random effects WMD = 0.35; 95% CI, –1.84 to 2.55).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission by the end of treatment as measured by the BDI (N = 1; *n* = 116; RR = 1.43; 95% CI, 0.85 to 2.39).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 116; RR = 1.43; 95% CI, 0.85 to 2.39).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on increasing the likelihood of achieving remission at one year follow-up as measured by the HRSD (N = 1; *n* = 116; RR = 0.93; 95% CI, 0.59 to 1.45).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms at one year follow-up as measured by the HRSD (N = 1; *n* = 55; WMD = –1.4; 95% CI, –5 to 2.2).

There is evidence suggesting that there is no clinically significant difference between short-term psychological therapies and other treatments on reducing depression symptoms at one year follow-up as measured by the BDI (N = 3; *n* = 264; WMD = –0.99; 95% CI, –3.16 to 1.17).

6.10.3.2 Short-term psychotherapies versus placebo or wait list control

Tolerability and acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on reducing the likelihood of leaving treatment early for any reason (N = 1; *n* = 60; RR = 0.11; 95% CI, 0.03 to 0.44).

There is insufficient evidence to determine whether there is a clinically significant difference between short-term psychological therapies and placebo or wait list control on reducing the likelihood of leaving treatment early due to side effects (N = 1; *n* = 60; RR = 0.2; 95% CI, 0.01 to 4).

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on reducing depression symptoms by the end of treatment as measured by the BDI (N = 2; *n* = 79; WMD = –7.41; 95% CI, –11.96 to –2.85).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 55; WMD = –4.7; 95% CI, –8.42 to –0.98).

There is some evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on increasing the likelihood of achieving remission by the end of treatment as measured by the BDI (N = 2; *n* = 84; RR = 0.65; 95% CI, 0.45 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring short-term psychological therapies over placebo or wait list control on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 2; *n* = 84; RR = 0.52; 95% CI, 0.35 to 0.77).

6.10.4 Clinical summary

Short-term psychological therapies (counselling, problem-solving therapy or CBT) are more effective and more acceptable to patients than either placebo or wait list control. There is evidence that there is no difference in efficacy between short-term psychological therapies and other treatments (mostly antidepressants and GP care), although psychological therapy appears to be more tolerable.

6.11 Clinical practice recommendations for psychological interventions

6.11.1.1 The full range of psychological interventions should be made available to older adults with depression, because they may have the same response to psychological interventions as younger people. (C)

6.11.1.2 In both mild and moderate depression, psychological treatment specifically focused on depression (such as problem-solving therapy, brief CBT and counselling) of six to eight sessions over 10 to 12 weeks should be considered. (B)

6.11.1.3 When considering individual psychological treatments for moderate, severe and treatment-resistant depression, the treatment of choice is CBT. IPT should be considered if the patient expresses a preference for it or if, in the view of the healthcare professional, the patient may benefit from it. (B)

6.11.1.4 For moderate and severe depression, the duration of all psychological treatments should typically be in the range of 16 to 20 sessions over six to nine months. (B)

6.11.1.5 In moderate depression, antidepressant medication should be routinely offered to all patients before psychological interventions. (B)

6.11.1.6 CBT should be offered to patients with moderate or severe depression who do not take or who refuse antidepressant treatment. (B)

6.11.1.7 Where patients have responded to a course of individual CBT, consideration should be given to follow-up sessions, which typically consist of two to four sessions over 12 months. (B)

6.11.1.8 Couple-focused therapy should be considered for patients with depression who have a regular partner and who have not benefited from a brief individual intervention. An adequate course of a couple-focused therapy should be 15 to 20 sessions over five to six months. (B)

6.11.1.9 CBT should be considered for patients who have not had an adequate response to a range of other treatments for depression (for example, antidepressants and brief psychological interventions). (C)

6.11.1.10 CBT should be considered for patients with recurrent depression who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions. (C)

6.11.1.11 For patients whose depression is treatment-resistant, the combination of antidepressant medication with CBT should be considered. (B)

6.11.1.12 When patients present initially with severe depression, a combination of antidepressants and individual CBT should be considered as the combination is more cost-effective than either treatment on its own. (B)

6.11.1.13 CBT should be considered for patients with severe depression in whom the avoidance of side effects often associated with antidepressants is a clinical priority or personal preference. (B)

6.11.1.14 For patients with severe depression who are starting a course of CBT, consideration should be given to providing two sessions per week for the first month of treatment. (C)

6.11.1.15 Patients with chronic depression should be offered a combination of CBT and antidepressant medication. (A)

6.11.1.16 For patients with treatment-resistant moderate depression who have relapsed while taking, or after finishing, a course of antidepressants, the combination of antidepressant medication with CBT should be considered. (B)

6.11.1.17 Where a patient with depression has a previous history of relapse and poor or limited response to other interventions, consideration should be given to CBT. (B)

6.11.1.18 Mindfulness-based CBT, usually delivered in a group format, should be considered for people who are currently well but have experienced three or more previous episodes of depression, because this may significantly reduce the likelihood of future relapse. (B)

6.11.1.19 When patients with moderate or severe depression have responded to another intervention but are unable or unwilling to continue with that intervention, and are assessed as being at significant risk of relapse, a maintenance course of CBT should be considered. (B)

6.11.1.20 Psychodynamic psychotherapy may be considered for the treatment of the complex comorbidities that may be present along with depression. (C)

6.12 Research recommendations for psychological interventions

6.12.1.1 Adequately powered RCTs reporting all relevant outcomes, including relapse rates, comparing the efficacy of different models of CBT, IPT and behaviour therapy should be undertaken to identify differential individual response to treatment and how this relates to the severity of baseline depression symptoms.

6.12.1.2 An adequately powered RCT reporting all relevant outcomes to assess the efficacy of problem-solving therapy for moderate depression in primary care should be undertaken.

6.12.1.3 An adequately powered RCT reporting all relevant outcomes to assess the efficacy of short-term psychodynamic therapy for depression should be undertaken.

7 Introduction to pharmacological interventions in the treatment and management of depression

This chapter introduces the pharmacological interventions in the management of depression covered by this guideline. It discusses some of the issues that the GDG addressed in assessing the evidence base in order to form recommendations, including that of placebo response. The reviews of pharmacological interventions themselves are presented in the following chapter.

7.1 Introduction

Since the introduction of the monoamine oxidase inhibitors (MAOIs) and the first tricyclic antidepressant (TCA), imipramine, in the late 1950s, many new antidepressants have been introduced and currently approximately 35 different antidepressants in a number of classes are available worldwide. Over the succeeding 45 years there has been intensive research on the effects of drug therapy on depression and how drugs might alter the natural history of the disorder. A large number of reviews and meta-analyses are available. It is beyond the scope of this document to provide a comprehensive literature review of every drug or discuss the plethora of guidelines that have been produced over the last 10 years. Excellent reviews of the topic are to be found in the British Association for Psychopharmacology *Evidence-Based Guidelines for Treatment of Depressive Disorder* (Anderson *et al.*, 2000) and in the World Federation of Societies of Biological Psychiatry (WFSBP) *Guidelines for the Biological Treatment of Unipolar Depressive Disorders Parts 1 and 2* (Bauer *et al.*, 2002a and 2002b).

Differences in outcome between antidepressant drug treated and untreated major depression are difficult to demonstrate in naturalistic studies (Ronalds *et al.*, 1997). A possible reason is that treatment is often inadequate with less than 50% of patients with major depression receiving the recommended intensity of antidepressant drug treatment. There is some evidence: an untreated depressive episode typically lasts about six months or longer (Angst & Preisig, 1995) but in a 10-year prospective study of 258 subjects with treated unipolar depression the duration of recurrent mood disorders averaged approximately 20 weeks (Solomon *et al.*, 1997). Short-term response rates in intention-to-treat samples are approximately 50 to 65% on antidepressants compared with 25 to 30% on placebo in randomised controlled trials (Schulberg *et al.*, 1999). In a naturalistic study without a placebo, recovery rates in moderately depressed patients randomised to treatment as usual were much lower at eight months (only 20%) than those randomised to psychotherapy or antidepressant drug treatment (approximately 50%) (Schulberg *et al.*, 1996).

There is strongest evidence for efficacy of medication when treating major depression of at least moderate severity. In primary care a greater adequacy of treatment has not been shown to improve clinical outcome significantly (Simon *et al.*, 1995), whereas there is some evidence that outcome may improve in more severely ill patients in psychiatric care

(Ramana *et al.*, 1999). A likely reason is that up to half of patients in primary care have mild major depression as defined by DSM-IV where efficacy of antidepressant treatment is unproven (Schwenk *et al.*, 1996). Scores on the Hamilton Rating Scale for Depression (HRSD) in these patients are generally between 12 and 16. Paykel *et al.* (1988) found that patients with HRSD scores of 13 or greater benefited from amitriptyline compared with placebo treatment, but in those with scores below 13 response was equally good on both treatments. Ottevanger (1991) found a higher threshold of HRSD scores (17 to 18) before antidepressants were of benefit over placebo.

Systematic reviews using meta-analysis suggest that the commonly available antidepressants have comparable efficacy in the majority of patients seen in primary care or outpatient settings (Anderson, 2000; Geddes *et al.*, 2002). There is little consensus on the relationship between clinical typology and outcome with antidepressants. Some evidence suggests that monoamine oxidase inhibitors (MAOIs) may be less effective than TCAs in hospitalised patients but more effective in non-hospitalised patients with atypical depression. It appears likely that this difference is due to the relative inefficacy of imipramine in atypical patients. The reviews cited above suggest that TCAs may be more effective than selective serotonin reuptake inhibitors (SSRIs) in patients hospitalised for major depression and that dual-action antidepressants (i.e. actions on both 5HT and noradrenaline) without some of the side effects of the older tricyclics may be more effective than SSRIs for major depression of at least moderate severity. There is some evidence that new antidepressants are better tolerated than older tricyclics and also that they are safer in overdose. SSRIs are more likely than older tricyclics to be prescribed at recommended doses for adequate periods (see *Current Practice of Antidepressant Prescribing in the UK* below). There are concerns over side effects following short- and long-term treatment, which limit adherence to treatment with antidepressants. There is general agreement that adherence to treatment with medication is poor and evidence that this is improved by drug counselling but not by information leaflets alone. The side effects from antidepressant medication are dose-related and, in general (see below), there is evidence that an adequate dose of a tricyclic is 100 mg or above.

There is evidence that earlier non-persistent improvement in depressive symptoms may be due to a placebo response (Quitkin *et al.*, 1987). An eventual response is unlikely if no improvement is evident after four weeks of treatment although older adults may take longer to respond (Anderson et al., 2000). At the present time there are a variety of strategies for improving efficacy following initial non-response which are supported by existing guidelines or systematic reviews using meta-analyses including lithium, the addition of thyroid hormones, adjunctive psychotherapy and dose escalation. Analysis of these modalities is a major feature of this current review.

In view of the high relapse or recurrence rate in depression it is currently recommended that antidepressant drug treatment is continued for a minimum of six months after remission of major depression (12 months in older adults). It is recommended that the same dose of antidepressant is used in this continuation phase. It is also recommended that patients with recurrent major depression should go on to receive maintenance antidepressant drug treatment (Geddes *et al.*, 2003a). There is good evidence that patients with residual symptoms are at increasing risk of relapse of major depression and the current practice is to continue treatment for longer in those patients. The recurrence rate is lower when treatment is maintained with the effective acute treatment dose compared with the reduction to half the dose. Lithium is an alternative for maintenance treatment and is recommended as an effective second-line alternative to antidepressants for maintenance treatment (Anderson *et al.*, 2000).

There is good evidence that discontinuation symptoms may occur on abruptly stopping all classes of antidepressants. They are usually mild and self-limiting, but can occasionally be severe and prolonged. Some symptoms are more likely with individual drugs (Lejoyeux *et al.*, 1996; Haddad, 2001). This effect appears more common with longer treatment. The syndrome generally resolves rapidly with reinstatement or within a few days to weeks without reinstatement. Discontinuation symptoms differ in pattern from those of a depressive relapse. It is generally recommended that patients should be warned that a discontinuation reaction might occur if treatment is stopped abruptly. It is recommended currently that all antidepressants are tapered in dose and frequency over a minimum of two weeks except in the situation where a patient switches into a hypomanic state. Some authorities recommend tapering the dose over six months in patients who have been on long-term maintenance treatment. If a discontinuation reaction does occur, explanation and reassurance are often all that is required. But if these are not sufficient, and/or the reaction is more severe, antidepressant treatment should be restarted and tapered more slowly.

7.2 Dose and duration of antidepressant treatment: Evidence from clinical practice

7.2.1 Prevalence of antidepressant prescribing

In 1992 the Royal College of Psychiatrists launched the 'Defeat Depression' campaign to raise public awareness of depression and improve treatment (Vize & Priest, 1993). During the launch year, 9.9 million prescriptions for antidepressants were dispensed by community pharmacists in England, at a total cost of £18.1 million. However, an epidemiological study conducted in 1995 found that treatment remained sub-optimal (Lepine *et al.*, 1997). Only a third of people with major depression in the UK received a prescription usually, but not always, for an antidepressant drug. The number of prescriptions for antidepressant drugs dispensed in England has been increasing steadily since 1992 and reached 23.3 million in 2002. Spend on antidepressant drugs reached £380.9 million in 2002. Details of numbers of prescriptions and cost of individual drugs are on the Prescription Pricing Authority website (www.ppa.gov.uk).

7.2.2 Dose

Studies of prescribing practice have generally taken 125 mg of TCAs (except lofepramine) and licensed doses of SSRIs to be 'an effective dose' and compared prescribing in practice with this ideal. It is generally accepted that response to TCAs is partially dose-related but no such effect has been demonstrated for SSRIs. SSRIs are consistently found to be prescribed 'at an effective dose' in a much greater proportion of cases than TCAs. For example, a UK prescribing study that included data from over 750,000 patient records found that, if lofepramine was excluded, the mean doses prescribed for individual TCAs fell between 58 mg and 80 mg. Only 13.1% of TCA prescriptions were for 'an effective dose' compared with 99.9% of prescriptions for SSRIs (Donoghue *et al.*, 1996). A further UK study that followed prescribing for 20,195 GP patients found that at least 72% of those prescribed TCAs never received 'an effective

dose' compared with 8% of those prescribed SSRIs (MacDonald *et al.*, 1996). The prescribing of TCAs in this way is known to be pervasive across different countries and over time (Donoghue, 2000; Donoghue & Hylan, 2001).

7.2.3 Duration

In a UK study of 16,204 patients who were prescribed TCAs or SSRIs by their GP, 33% of those prescribed an SSRI completed 'an adequate period of treatment' compared with 6% of those prescribed a TCA (2.8% if lofepramine was excluded) (Dunn *et al.*, 1999). 'An adequate period of treatment' was defined by the authors as: prescriptions covering at least 120 days' treatment within the first six months after diagnosis.

There is some evidence that the mean figure quoted for SSRIs may mask important differences between drugs: Donoghue (2000) found that in a GP population of 6150 patients who were prescribed SSRIs, 27% of fluoxetine patients were still receiving prescriptions after 120 days compared with 23% of paroxetine patients and 13.5% of sertraline patients. Of course, prescribing patterns cannot be directly linked with outcome in studies of this type.

An RCT conducted in the US randomised 536 adults to receive desipramine, imipramine or fluoxetine (Simon *et al.*, 1996). 60% of the fluoxetine patients completed six months of treatment compared with less than 40% of the TCA patients. Those who discontinued one antidepressant were offered another. There were no differences in overall completers or response rates at endpoint suggesting that initial drug choice did not affect outcome. However, outside of clinical trials, patients may not return to their GP to have their treatment changed and outcome may be less positive. For example: a Swedish study of 949 patients found that 35% only ever received one prescription irrespective of whether it was for a TCA or a SSRI (Isacsson *et al.*, 1999). After six months, 42% of SSRI patients were still receiving prescriptions compared with 27% of TCA patients. There is some evidence from this study that the relapse rate may have been higher in the TCA group: 28% of TCA-treated patients received a subsequent prescription for an antidepressant after a nine-month treatment-free gap compared with 10% of SSRI patients.

7.3 Limitations of the literature: Problems with randomised controlled trials (RCTs) in pharmacology

In RCTs, patients assigned to the 'placebo' arm receive regular visits to their doctor, supportive help, and a kindly interest in their welfare. In some trials the participants are allowed to contact the therapist at any time to report problems. In short, they receive everything except the pharmacological help from the tablet in the 'active drug' arm of the trial. This constitutes a treatment in itself, and almost 30% of patients assigned to placebo respond within six weeks (Walsh *et al.*, 2002). This recovery has two components: the spontaneous recovery of the disorder itself; and the additional recovery due to supportive care.

Spontaneous recovery is a function of severity of the disorder; with lesser degrees of depression the recovery is greater. Unfortunately there is a tendency for investigators to recruit patients with less severe depression to the RCTs, and these are more likely to recover spontaneously (Khan *et al.*, 2002).

Conversely, the more severely depressed patients are less likely to be thought suitable for RCTs (despite being more likely to show a true drug effect (Angst 1993; Khan *et al.*, 2002)), since clinicians are reluctant to allow suicidal patients, or patients with severe degrees of depressive phenomena, to run the risk of an inactive treatment.

Next, of those enrolled into an RCT, typically 20–35% fail to complete the study – either because they dropout of treatment themselves, or they are withdrawn from the RCT by the anxious clinician (for example, Stassen *et al.*, 1993). Worse still, results are often presented only for 'completers', rather than for the full 'intention-to-treat' sample.[12]

Finally, some participants may not be representative of patients seen in clinical practice, as they are recruited by newspaper advertisement and paid for their participation in the study after completing a screening questionnaire (Greist *et al.*, 2002; Thase, 2002).

The inclusion of individuals likely to improve, whatever they are given, as well as those motivated to receive free medication, taken together with the smaller likelihood of severely depressed patients being included, will all reduce the size of the specific drug effect. Confining the study to 'completers' introduces unknown biases into a cloudy picture.

Most studies of the effects of drugs are sponsored by the drug industry, and these have been shown to be more than four times as likely to demonstrate positive effects of the sponsor's drug as independent studies (Lexchin *et al.*, 2003). Finally, the tendency of journal editors to publish only studies with positive results (Kirsch & Scoboria 2001; Melander *et al.*, 2003), and the fact that the same patients may appear in several publications (op. cit.), introduces a severe bias in the other direction.

Despite the limitations of RCTs described above, the bulk of our recommendations are based on RCT evidence. However, we have been careful to consider their application to routine practice as evidenced by our use of both a number of (C) level recommendations and 'Good practice points'.

7.4 The placebo response

In addition to the points made above, in recent years there has been an increasing response to placebo, so that the extent of the placebo response correlates with the year of publication ($r = +0.43$) (Walsh *et al.*, 2002). There is a similar, but less robust, association between extent of the response to active medication and year of publication ($r = +0.26$) (ibid.). This may well indicate an increasing tendency for RCTs to be carried out on people with mild disorders and disorders that would have remitted spontaneously.

[12] See introduction to Appendix 17 on the CD and the use of 'C' to show which studies present end-point data as completer data (analysis method of completer data).

A final important point is that there is evidence that the placebo response is greatest with mild depression, and the drug-placebo difference becomes greater with increasing degrees of severity of depression (Angst, 1993; Khan *et al.*, 2002). This effect cannot be demonstrated in the meta-analyses carried out for the present report since the published studies do not quote data for individual patients, but only for the entire group. Thus, there is considerable overlap between the distributions of HRSD scores between inpatient and outpatient studies, so that the effect is diluted. Further issues concerning placebo response are discussed below.

7.5 Studies considered for review – additional inclusion criteria

In addition to the criteria established for the inclusion of trials for the guideline as a whole, the following specific criteria relating to RCTs of pharmacological treatments were established by the Pharmacology Topic Group.

7.5.1 Diagnosis

- Trials where some participants had a primary diagnosis of bipolar disorder were included provided at least 85% had a primary diagnosis of major depressive disorder and no more than 15% had a primary diagnosis of bipolar disorder. These figures resulted from discussion, expert opinion and involvement with user groups. The GDG considered that these trials would still have adequate validity for determining efficacy in major depressive disorder.

- Trials where some participants had a primary diagnosis of dysthymia were included provided at least 80% of trial participants had a primary diagnosis of major depressive disorder, and no more than 20% had a primary diagnosis of dysthymia.

- Trials where participants had a diagnosis of atypical depression were included provided all had a primary diagnosis of major depressive disorder.

- Studies were included provided data from the HRSD and Montgomery Asberg Depression Rating Scale (MADRS) could be extracted for the following outcomes:

- The number of participants who remitted[13] (achieved below the equivalent 17-item HRSD score of eight)

- The number of participants who responded[14] (achieved at least a 50% reduction in scores)

- Mean endpoint or change scores.

[13] For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not remitting.

[14] For statistical reasons, relative risks for this outcome are framed in terms of the number of participants not responding.

7.5.2 Dose

There is prima facie evidence that doses of tricyclics below 100 mg are less effective than doses above (Blashki *et al.*, 1971; Thompson & Thompson, 1989; Bollini *et al.*, 1999). Studies were included provided there was clear evidence that at least 75% of patients received the standard dose or the mean dose used was at least 105% of the standard dose. The standard dose was either that stated by Bollini *et al.* (1999) or, for drugs not included by Bollini *et al.*, the dose stated by the BNF (March 2003).

7.6 Issues and topics covered by this review

In view of the vast numbers of studies performed investigating pharmacological responses in depression and the limited time available, the Pharmacology Topic Group had to decide which aspects of drug treatment were most important to clinicians and patients. This chapter therefore is not the result of a comprehensive review of all psychopharmacological studies performed in all aspects of the treatment of depression.

7.6.1 Severity

A key issue is whether severity of illness can guide the use of antidepressant medication. Unfortunately there is little data to help with this point. Although most studies report mean baseline HRSD or MADRS, this can be taken only as a guide to baseline severity because of heterogeneous samples with wide standard deviations as well as the fact that results are not presented in a way that allows differential response to be identified.

7.6.2 Setting

Where appropriate studies were categorised by setting: (a) primary care (where this was specifically stated); (b) inpatients – where at least 75% of the patients were initially treated as inpatients; (c) outpatients/secondary care – studies in which this was specified. This is likely to provide some bearing on the issue of setting and type of depression although it is not clear how well setting maps onto severity. A further problem is that because of differences among healthcare systems across the world, the nature of the patients in these different groups varies. Thus considerable uncertainty must be associated with conclusions drawn using these categories.

7.6.3 Issues addressed

In broad terms we have tried to address the issue of the comparative efficacy, acceptability and tolerability of the antidepressants most commonly prescribed in the UK, together with specific pharmacological strategies for dealing with treatment-resistant, atypical and psychotic depression. Within each review, where the data allowed, we have looked at the effect on outcomes of severity, setting and age. In addition, we have looked at some of the issues regarding so-called continuation and maintenance therapy, the cardiac safety of antidepressants, dosage, and issues regarding suicidality and completed suicide with antidepressants. Although the number of trial participants leaving treatment

early was used as a measure of the tolerability of drugs reviewed, this guideline cannot be seen as a comprehensive review of the issue of the safety, pharmacology, pharmokinetics and pharmaceutical advice regarding these drugs. Readers are referred to conventional texts particularly regarding issues of dosage schedules, acceptability and tolerability for individual patients and regarding drug interactions.

7.6.4 Topics covered

The following topics are covered:

This chapter	Review of SSRIs versus placebo
Chapter 8 (Section 8.1)	Use of individual drugs in the treatment of depression – TCAs (amitriptyline and overview of TCA data) – Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline – Monoamine oxidase inhibitors (MAOIs): moclobemide, phenelzine – 'Third-generation' drugs: mirtazapine, reboxetine and venlafaxine – St John's wort
Chapter 8 (Section 8.2)	Factors affecting antidepressant choice – The pharmacological management of depression in older adults – The effect of gender on the pharmacological management of depression – The pharmacological management of psychotic depression – The pharmacological management of atypical depression – The pharmacological management of relapse prevention – Dosage issues – Antidepressant discontinuation symptoms – The cardio-toxicity of antidepressants – Suicidality
Chapter 8 (Section 8.3)	The treatment of treatment-resistant depression – Switching strategies – Venlafaxine for treatment-resistant depression – Augmentation strategies • Augmenting an antidepressant with lithium • Augmenting an antidepressant with anticonvulsants (lamotrigine, carbamazepine or valproate) • Augmenting an antidepressant with another antidepressant • Augmenting an antidepressant with pindolol • Augmenting an antidepressant with T3 • Augmenting an antidepressant with a benzodiazepine • Augmenting an antidepressant with an antipsychotic • Augmenting an antidepressant with buspirone

7.7 Review of SSRIs versus placebo

7.7.1 Introduction

A placebo is an inert or innocuous substance used in controlled trials to test the efficacy of an active drug. Placebos began to be used increasingly in control conditions in clinical trials during the 1950s, although at that time they often contained an active ingredient. The response of patients to the inert substances now used should not be equated with the untreated course of the disorder, as there is a pronounced therapeutic advantage in being seen regularly and being offered clinical care, irrespective of the contents of the tablet or the nature of the psychological intervention.

In two meta-analyses (Kirsch & Sapirstein,1998; Kirsch *et al.*, 2002a) it was argued that up to 80% of the effect of antidepressants may be duplicated by placebo – i.e. that 80% of the effect of antidepressants is placebo response. Although the earlier meta-analysis was criticised because it included only a limited number of published trials, the later work analysed all data submitted to the US Food and Drug Administration (FDA) for the licensing of new antidepressants, including the SSRIs and venlafaxine, although it is not clear how many of the trials involved have subsequently been published.

Many commentators attribute this finding to expectancy effects. There is also the problem of 'breaking the blind' as a result of the side effects of antidepressants (Rabkin *et al.*, 1986, in Kirsch *et al.*, 2002b) leading to possible bias in placebo-controlled clinical trials. One way round this problem is to use an active placebo. A meta-analysis of trials using this technique indicated that the placebo effect of antidepressants may be even stronger than that indicated by analyses of trials using inactive placebos. However, there are few trials of active placebo using modern diagnostic criteria and widely accepted ratings (Moncrieff *et al.*, 2001). Psychological factors arising from trial methodology influencing the placebo response include the encouraging effect of being in treatment (Andrews, 2001), demand characteristics (Salamone, 2000) and even the trial recruitment and assessment process itself (ibid.).

It has been suggested that response rates to both placebo and active drugs are increasing at a rate of 7% a year (Walsh *et al.*, 2002). This may be due in part to increased trial recruitment via media advertising, the fact that participants in RCTs are often paid, and the reluctance of trialists to offer placebos to severely ill patients. The resulting participants in RCTs tend to have milder, less chronic depression, which is more responsive to placebo compared with that in participants from clinical referral (ibid.). Once placebo response rates are above 40%, an active drug effect becomes harder to detect, particularly since many trials are underpowered (Thase, 2002). Other methodological problems are highlighted by inter-site differences found in many multi-site trials probably resulting from subtly different procedures being adopted by different researchers (Schneider & Small, 2002).

Non-methodology-related explanations for the placebo response include the effect of spontaneous remission (which may be as high as 50% within an eight-week period, the length of many trials; Andrews, 2001).

The placebo response may also be short-lived, with more patients on placebo relapsing compared with those on antidepressants (Ross *et al.*, 2002). Longer trials are required to be able to fully elucidate the contributions of placebo and the treatment to clinical response. Dago & Quitkin (1995) suggest that greater placebo response is more likely when the presenting episode occurs within the context of a psychosocial stressor.

There is convergent evidence that the placebo response is less marked as clinical severity increases, and the size of the drug/placebo difference becomes greater (Elkin *et al.*, 1989; Angst, 1993; Khan *et al.*, 2002). Thus, the additional therapeutic effects of antidepressants may be submerged by the size of non-specific effects when mainly mildly depressed patients are studied. The published data did not allow the GDG to address this problem systematically since most RCTs merely give mean depression scores (with standard deviations) of large groups of patients, so that there is very considerable overlap between baseline depression scores of patients in different studies. It was therefore only possible to address important questions relating to the effects of severity, age and gender with relatively weak information about patient characteristics. Nonetheless, our findings are in favour of greater drug/placebo differences with increasing severity (see below). It should also be borne in mind that there are non-mood-related benefits of prescribing antidepressants, for example in helping patients to sleep better and in dealing with anxiety-related symptoms. Improving these factors may help patients to cope with their daily lives thereby contributing to a reduction in depression symptoms.

7.7.2 Studies considered for review[15,16]

One-hundred-and-three studies were found in a search of electronic databases with 48[17] being included and 55 being excluded by the GDG.

Six studies were of citalopram (BURKE01, FEIGHNER99, MENDELS1999, MONT'MERY01, MONT'MERY92A, STAHL00); 17 of fluoxetine (ANDREOLI2002, BYERLEY88, COHN1985, COLEMAN01, DUNLOP1990, FEIGHNER89A, MCGRATH00, O'FLYNN1991, RICKELS1986, RUDOLPH99, SIL'STNE99, SRAMEK95, STARK85, THAKORE1995, VALDUCCI1992, WERNICKE1987, WERNICKE1988); 12 of fluvoxamine (CLAGHORN1996, CONTI1988, DOMINGUEZ85, FABRE1996, FEIGHNER1989, ITIL1983, KASPER95, LYDIARD1989, LAPIERRE1987, NORTON1984, ROTH90, WALCZAK1996); eight of paroxetine (CLAGHORN92A, EDWARDS93, FEIGHNER92, HACKETT1996, MILLER1989, RICKELS1989, RICKELS1992, SMITH1992) and five of sertraline (COLEMAN1999, CROFT1999, FABRE95, RAVINDRAM1995, REIMHERR90). These provided data from up to 7460 trial participants.

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[15] Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17 on the CD, which also contains a list of excluded studies with reasons for exclusions.

[16] Here and elsewhere in the guideline, each study considered for review is referred to by a 'study ID' made up of first author and publication date in capital letters (unless a study is in press or only submitted for publication, when first author only is used). References for these studies are in Appendix 18 on the CD.

[17] This figure includes a multicentre trial (KASPER1995) as well as two of its constituent trials published independently (DOMINGUEZ1985, LAPIERRE1987) because 'number of participants leaving the study early for any reason' was not extractable from KASPER1995. See SSRI versus placebo evidence table in Appendix 17 on the CD.

All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.75 weeks), with 16 trials of eight weeks or longer. Three studies were of inpatients, 31 of outpatients, one in primary care and 13 either mixed or unspecified. In no study were more than 80% of study participants aged 65 years and over. It was possible to determine baseline severity in 19 studies, with four being classified as moderate, six as severe and nine as very severe.

Visual inspection of funnel plots of the meta-analyses of the above studies indicated the possibility of publication bias. It was planned to combine these data with the FDA data reported by Kirsch *et al.* (2002a). However, it was not possible to determine which of the FDA data had been subsequently published.

Since it is possible that a placebo response is only short-lived, a sub-analysis of studies which lasted eight weeks or longer was undertaken.

7.7.3 Evidence statements[18]

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 17[19]; *n* = 3143; RR = 0.73; 95% CI, 0.69 to 0.78).

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3[20]; *n* = 729; RR = 0.75; 95% CI, 0.65 to 0.87).

In severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 5; *n* = 619; RR = 0.63; 95% CI, 0.54 to 0.73).

In very severe depression there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 6; *n* = 866; RR = 0.72; 95% CI, 0.65 to 0.8).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs over placebo on increasing the likelihood of achieving remission as measured by the HRSD (N = 3; *n* = 468; Random effects RR = 0.8; 95% CI, 0.61 to 1.06).

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[18] The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on th CD.

[19] Fifteen studies were excluded from all efficacy outcomes because >50% left treatment early (CLAGHORN1996, COHN1985, CONTI1988, DOMINGUEZ85, EDWARDS93, FABRE95, FABRE1996, FEIGHNER1989, FEIGHNER92, ITIL1983, LAPIERRE1987, SMITH1992, STAHL00, STARK85, WALZAK1996).

[20] Studies were excluded from sub-analyses of severity if mean baseline scores were not available.

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 16; *n* = 2223; Random effects SMD = –0.34; 95% CI, –0.47 to –0.22).

In moderate depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 2; *n* = 386; SMD = –0.28; 95% CI, –0.48 to –0.08).

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD (N = 4; *n* = 344; SMD = –0.61; 95% CI, –0.83 to –0.4).

In very severe depression there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms, as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N = 5; *n* = 726; SMD = –0.39; 95% CI, –0.54 to –0.24).

Acceptability and tolerability of treatment

There is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early but the size of this difference is unlikely to be of clinical significance (N = 39[21]; *n* = 7274; RR = 0.94; 95% CI, 0.88 to 0.99).

There is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 39; *n* = 7460; RR = 2.45; 95% CI, 2.08 to 2.89).

There is some evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of patients reporting side effects (N = 11; *n* = 2290; RR = 1.19; 95% CI, 1.13 to 1.25).

Sub-analysis of trials lasting eight weeks or longer

In order to assess whether the placebo effect was short-lived, trials lasting eight weeks or longer were analysed separately.

Effect of treatment on efficacy outcomes in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 8; *n* = 1764; RR = 0.72; 95% CI, 0.66 to 0.79).

[21] One study (COHN1985) was removed from the meta-analysis to remove heterogeneity from the data set.

In moderate depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 729; RR = 0.75; 95% CI, 0.65 to 0.87).

In severe depression in trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 535; RR = 0.63; 95% CI, 0.53 to 0.74).

In very severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N= 1; *n*= 299; RR= 0.72; 95% CI, 0.59 to 0.88).

In trials lasting eight weeks or longer, there is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and placebo on increasing the likelihood of achieving remission as measured by the HRSD (N = 2; *n* = 456; RR = 0.85; 95% CI, 0.67 to 1.07).

In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 7; *n* = 1369; Random effects SMD = –0.28; 95% CI, –0.44 to –0.11).

In moderate depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 2; *n* = 386; SMD = –0.28; 95% CI, –0.48 to –0.08).

In severe depression in trials lasting eight weeks or longer, there is some evidence suggesting that there is a clinically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD (N = 1; *n* = 237; SMD = –0.53; 95% CI, –0.79 to –0.27).

In very severe depression in trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring SSRIs over placebo on reducing depression symptoms as measured by the HRSD but the size of this difference is unlikely to be of clinical significance (N = 1; *n* = 283; SMD = –0.43; 95% CI, –0.67 to –0.2).

Acceptability and tolerability of treatment in trials lasting eight weeks or longer

In trials lasting eight weeks or longer, there is evidence suggesting that there is no clinically significant difference between SSRIs and placebo on reducing the likelihood of leaving treatment early (N = 13; *n* = 3069; Random effects RR =0.95; 95% CI, 0.83 to 1.09).

In trials lasting eight weeks or longer, there is strong evidence suggesting that there is a clinically significant difference favouring placebo over SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 13; *n* = 3069; Random effects RR = 1.93; 95% CI, 1.23 to 3.03).

In trials lasting eight weeks or longer, there is evidence suggesting that there is a statistically significant difference favouring placebo over SSRIs on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 7; *n* = 1378; RR = 1.09; 95% CI, 1.03 to 1.16).

7.7.4 Clinical summary

There is strong evidence that antidepressants have greater efficacy than placebo on achieving a 50% reduction in depression scores in severe and very severe depression. There is some evidence for a similar effect in moderate depression. The effect was similar in longer trials. These results should be treated with caution because of publication bias (i.e. that studies with statistically significant findings are more likely to be published than those with non-significant findings).

There is insufficient evidence on the effect on remission because of heterogeneity in the meta-analysis, but the trend is towards a small effect size. There appears to be no difference between SSRIs and placebo on mean endpoint or change scores.

SSRIs produced more side effects than placebo, with more people leaving treatment early because of adverse events. This was also the case in trials lasting eight weeks or longer.

8 Pharmacological interventions in the treatment and management of depression

This chapter is in three sections:

- Use of individual drugs in the treatment of depression
- Factors that influence choice of antidepressant
- The pharmacological treatment of treatment-resistant depression

8.1 Use of individual drugs in the treatment of depression

8.1.1 Introduction

This section reviews the relative efficacy of individual antidepressants in the treatment of depression. Where there were sufficient data, the effect of patient setting (inpatient, outpatient or primary care) on choice of drug was also examined. It covers the following drugs:

- Tricyclic antidepressants (TCAs)
  - Amitriptyline
  - An overview of TCAs*
- Selective serotonin reuptake inhibitors (SSRIs)
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline

* Many studies in the above reviews used a TCA as a comparator treatment. These data were combined in a review of TCAs to enable the GDG to gain an overview of this class of drugs.

- Monoamine oxidase inhibitors (MAOIs)
  - Moclobemide
  - Phenelzine
- 'Third-generation' drugs
  - Mirtazapine
  - Reboxetine
  - Venlafaxine
- Herbal preparations
  - St John's wort.

8.1.2 Tricyclic antidepressants (TCAs)

8.1.2.1 Introduction

TCAs have been used to treat depression for over 40 years. Currently nine TCAs are available in the UK. They are thought to exert their therapeutic effect by inhibiting the re-uptake of monoamine neurotransmitters into the presynaptic neurone thus enhancing noradrenergic and serotonergic neurotransmission. Although all TCAs block the reuptake of both amines, they vary in their selectivity with, for example, clomipramine being primarily serotonergic and imipramine noradrenergic.

All TCAs cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, sweating), sedation and postural hypotension. These side effects necessitate starting with a low dose and increasing slowly. In many patients a 'therapeutic dose' is never reached either because the patient cannot tolerate it or because the prescriber does not titrate the dose upwards.

All TCAs, except lofepramine, are toxic in overdose with seizures and arrhythmias being a particular concern (see Sections 8.2.9 and 8.2.10). This toxicity, and the perceived poor tolerability of these drugs in general, has led to a decline in their use in the UK over the last decade.

8.1.2.2 Amitriptyline

Although amitriptyline was not the first TCA and is not the best tolerated or the most widely prescribed, it is the standard drug against which new antidepressants are compared with respect to both efficacy and tolerability. Amitriptyline may be marginally more effective than other antidepressants, a potential benefit that is offset by its poorer tolerability (Barbui & Hotopf, 2001). Efficacy benefits may be more marked in hospitalised patients (Anderson *et al.*, 2000).

8.1.2.2.1 Studies considered for review[22,23]

The GDG used an existing review (Barbui & Hotopf, 2001) as the basis for this section, for which the authors made their data available to the NCCMH team. The original review included 184 studies of which 144 did not meet the inclusion criteria set by the GDG. Eight additional studies were identified from searches undertaken for other sections of this guideline. Thus 48 trials are included in this section providing tolerability data from up to 4484[24] participants and efficacy data from up to 2760 participants. A total of 177 trials were excluded. The most common reason for exclusion was an inadequate diagnosis of depression.

All included studies were published between 1977 and 1999 and were between three and 10 weeks long (mean = 5.71 weeks). Sixteen studies were of inpatients, 22 of outpatients and two were undertaken in primary care. In the remaining eight, it was either not clear from where participants were sourced or they were from mixed sources. In three studies all participants were over the age of 65 years (COHN1990, GERETSEGGER1995, HUTCHINSON1992). Studies reported mean doses of equivalent to at least 100 mg of amitriptyline.

Data were available to compare amitriptyline with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amoxapine, desipramine, dothiepin/dosulepin, doxepin, imipramine, lofepramine, minaprine[25], nortriptyline, trimipramine, maprotiline, mianserin, trazodone, phenelzine and mirtazapine.

The original systematic review on which this section is based included two outcome measures, responders and mean endpoint scores. It did not include data on remission and this has not been extracted for the present review.

8.1.2.2.2 Evidence statements[26,27]

Effect of treatment on efficacy[28]

There appears to be no clinically important difference in efficacy between amitriptyline and other antidepressants, either when compared together or by class:

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[22] Full details of the search strategy for this and other reviews in the guideline are available on request from the NCCMH. Details of standard search strings used in all searches are in Appendix 7. Information about each study along with an assessment of methodological quality is in Appendix 17 on the CD, which also contains a list of excluded studies with reasons for exclusions.

[23] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

[24] It is not always possible to extract data for all outcomes from each study, therefore the figures given are for the outcome with the largest number of participants.

[25] Not available in the UK.

[26] The full list of all evidence statements generated from meta-analyses are in Appendix 20 on the CD; the forest plots are in Appendix 19 on the CD.

[27] The authors of the review on which this review is based entered data into Review Manager so that amitriptyline is on the right-hand side of the forest plot and comparator treatments on the left.

[28] Where it made a difference to results the following studies were removed from efficacy analyses because >50% left treatment early: COHN1990, FAWCETT1989, GUY1983, PRESKORN1991, SHAW1986, STUPPAECK1994, WILCOX1994.

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression scores as measured by the HRSD (N = 16; *n* = 1541; RR = 1.06; 95% CI, 0.96 to 1.18).

There is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N = 32; *n* = 2760; SMD = 0.09; 95% CI, 0.01 to 0.16).

There is evidence suggesting that there is no clinically significant difference between:

- other TCAs and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 5; *n* = 285; SMD = 0.04; 95% CI, –0.19 to 0.27)

- SSRIs and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 9; *n* = 837; RR = 1.09; 95% CI, 0.95 to 1.25)

- SSRIs and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 19; *n* = 1648; SMD = 0.06; 95% CI, –0.03 to 0.16).

There is insufficient evidence to determine whether there is a clinically significant difference between other TCAs and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 2; *n* = 68; RR = 0.96; 95% CI, 0.60 to 1.53).

Effect of setting on treatment efficacy

There appears to be no clinically important difference between amitriptyline and other antidepressants in different treatment settings:

In inpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 6; *n* = 600; RR = 1.08; 95% CI, 0.9 to 1.29).

In inpatients there is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N = 11; *n* = 752; SMD = 0.16; 95% CI, 0.02 to 0.30).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring amitriptyline over other antidepressants on reducing depression symptoms as measured by the HRSD and MADRS, but the size of this difference is unlikely to be of clinical significance (N = 9; *n* = 1,002; SMD = 0.13; 95% CI, 0.00 to 0.25).

In outpatients there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 7; *n* = 666; RR = 1.03; 95% CI, 0.89 to 1.2).

In patients in primary care there is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 2; *n* = 132; SMD = –0.09; 95% CI, –0.44 to 0.27).

Acceptability and tolerability of treatment

When compared with all antidepressants, amitriptyline appears to be equally tolerable in terms of leaving treatment early for any reason. However, patients taking other antidepressants report fewer side effects:

There is evidence suggesting that there is no clinically significant difference between amitriptyline and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 43; *n* = 4884; RR = 0.92; 95% CI, 0.84 to 1.003).

There is strong evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of leaving the study early due to side effects (N = 34; *n* = 4034; RR = 0.71; 95% CI, 0.61 to 0.83).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of patients reporting side effects (N = 5; *n* = 773; RR = 0.78; 95% CI, 0.65 to 0.93).

Acceptability and tolerability of treatment by setting

For inpatients, there appears to be little difference between the tolerability of amitriptyline and other antidepressants:

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving the study early for any reason (N = 15; *n* = 1320; RR = 0.96; 95% CI, 0.82 to 1.13).

There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of inpatients leaving treatment early due to side effects (N = 8; *n* = 855; RR = 0.78; 95% CI, 0.55 to 1.1).

There is evidence suggesting that there is no clinically significant difference between paroxetine and amitriptyline on reducing the likelihood of inpatients reporting side effects (N = 2; *n* = 131; RR = 0.88; 95% CI, 0.68 to 1.12).

Amitriptyline was less well tolerated in outpatients.

There is evidence suggesting that there is no clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of outpatients leaving

treatment early for any reason (N = 19; *n* = 2647; Random effects RR = 0.87; 95% CI, 0.72 to 1.06).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over amitriptyline on reducing the likelihood of outpatients leaving treatment early due to side effects (N = 18; *n* = 2396; RR = 0.75; 95% CI, 0.62 to 0.9).

There is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of outpatients reporting side effects (N = 2; *n* = 552; RR = 0.8; 95% CI, 0.61 to 1.04).

Although much of the evidence was too weak to make a valid comparison of tolerability in primary care, more patients reported side effects in amitriptyline than paroxetine, which was the only comparator drug available:

In patients in primary care there is insufficient evidence to determine whether there is a clinically significant difference between other antidepressants and amitriptyline on reducing the likelihood of leaving treatment early either for any reason or due to side effects.

There is some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline on reducing the likelihood of primary care patients reporting side effects (N = 1; *n* = 90; RR = 0.55; 95% CI, 0.35 to 0.86).

8.1.2.2.3 Clinical summary

Amitriptyline is as effective as other antidepressants, although patients taking the drug report more adverse events and tend to leave treatment early due to side effects.

8.1.2.3 Tricyclic antidepressants – an overview of selected data

This section combines data from other reviews where a TCA was used as a comparator treatment. It is, therefore, not a systematic review since a systematic search for all trials of TCAs was not conducted. It specifically does not include comparisons of TCAs with other TCAs.

8.1.2.3.1 Studies considered for review

In all, 94 studies from other reviews included a TCA as a comparator drug. Seventy studies were sourced from the review of SSRIs (Section 8.1.3), seven from the review of mirtazapine (Section 8.1.5.1), eight from phenelzine (Section 8.1.4.3), three from reboxetine (Section 8.1.5.2) and six from venlafaxine (Section 8.1.5.3). Data were available from the following TCAs: clomipramine, doxepin, desipramine, imipramine, dothiepin/dosulepin, nortriptyline, amineptine and lofepramine. Efficacy data were available from up to 6848 patients, and tolerability data from up to 8967 patients.

All included studies were published between 1981 and 2002. Twenty-four studies were of inpatients, 48 of outpatients and three undertaken in primary care. In the remaining 19, it was either not clear from where participants were sourced or they were from mixed sources. In 11 more than 80% of study participants were aged 65 years and over, and, in two, participants had depression with additional atypical features (MCGRATH2000, QUITKIN1990).

8.1.2.3.2 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference between other antidepressants and TCAs on:

- increasing the likelihood of achieving a 50% reduction in symptoms as measured by the HRSD or the MADRS (N = 15[29]; *n* = 2364; RR = 0.91; 95% CI, 0.83 to 1.01)
- increasing the likelihood of achieving remission as measured by the HRSD (N = 3[30]; *n* = 534; RR = 0.98; 95% CI, 0.84 to 1.15)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 70; *n* = 6,848; SMD = 0.02; 95% CI, –0.03 to 0.07).

Effect of setting on treatment efficacy

Inpatients

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms in inpatients as measured by the HRSD (N = 4[31]; *n* = 765; RR = 0.98; 95% CI, 0.82 to 1.18).

There is evidence suggesting that there is a statistically significant difference favouring TCAs over alternative antidepressants on reducing depression symptoms, as measured by the HRSD or the MADRS, in inpatients by the end of treatment, but the size of this difference is unlikely to be of clinical significance (N = 20; *n* = 1681; SMD = 0.12; 95% CI, 0.03 to 0.22).

Outpatients

There is some evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 5; *n* = 733; RR = 0.74; 95% CI, 0.64 to 0.87).

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[29] BRUIJN1996 and QUITKIN1990 were removed from the meta-analysis to remove heterogeneity from the imipramine data set.

[30] QUITKIN1990 was removed from the meta-analysis to remove heterogeneity from the imipramine data set.

[31] BRUIJN1996 was removed from the meta-analysis to remove heterogeneity from the imipramine data set.

There is evidence suggesting that there is no clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS (N = 33; *n* = 3275; SMD = –0.03; 95% CI, –0.1 to 0.04).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and nortriptyline on increasing the likelihood of achieving remission in outpatients by the end of treatment as measured by the HRSD (N = 1[32]; *n* = 60; RR = 1.28; 95% CI, 0.78 to 2.09).

Primary care

There is insufficient evidence to determine whether there is a clinically significant difference between TCAs and alternative antidepressants on reducing depression symptoms in patients in primary care by the end of treatment as measured by the HRSD or MADRS (N = 2; *n* = 213; SMD = –0.14; 95% CI, –0.42 to 0.13).

Acceptability and tolerability of treatment

There is evidence suggesting that there are statistically significant differences favouring alternative antidepressants over TCAs on the following outcomes, but the size of these differences is unlikely to be of clinical significance:

- on reducing the likelihood of leaving treatment early for any reason (N = 83; *n* = 8967; RR = 0.88; 95% CI, 0.83 to 0.94)
- on reducing the likelihood of patients reporting adverse effects (N = 25; *n* = 3007; Random effects RR = 0.91; 95% CI, 0.86 to 0.96).

There is strong evidence suggesting that there is a clinically significant difference favouring alternative antidepressants over TCAs on reducing the likelihood of leaving treatment early due to side effects (N = 80; *n* = 8888; RR = 0.71; 95% CI, 0.65 to 0.78).

When TCAs were examined individually, only dothiepin/dosulepin appears to be more acceptable than alternative antidepressants:

There is some evidence suggesting that there is a clinically significant difference favouring dothiepin/dosulepin over alternative antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 5; *n* = 336; RR = 1.42; 95% CI, 1.02 to 1.98) and on reducing the likelihood of leaving treatment early due to side effects (N = 5; *n* = 336; RR = 2.02; 95% CI, 1.09 to 3.76).

8.1.2.3.3 Clinical summary

TCAs have equal efficacy compared with alternative antidepressants but are less well tolerated particularly in outpatients.

[32] QUITKIN1990 was removed from the meta-analysis to remove heterogeneity from the imipramine data set.

8.1.3 Selective serotonin reuptake inhibitors (SSRIs)

8.1.3.1 Introduction

The selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin into the presynaptic neurone thus increasing neurotransmission. Although they 'selectively' inhibit serotonin reuptake, they are not serotonin specific. Some of the drugs in this class also inhibit the reuptake of noradrenaline and/or dopamine to a lesser extent.

As a class, they are associated with less anticholinergic side effects and are less likely to cause postural hypotension or sedation. Dosage titration is not routinely required so subtherapeutic doses are less likely to be prescribed. They are also less cardiotoxic and much safer in overdose than the TCAs or MAOIs. These advantages have led to their widespread use as better-tolerated first-line antidepressants.

The most problematic side effects of this class of drugs are nausea, diarrhoea and headache. Fluvoxamine, fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes (Mitchell, 1997) precipitating many significant drug interactions. Sertraline is less problematic although enzyme inhibition is dose-related and citalopram is relatively safe in this regard.

There are other important differences among the SSRIs (Anderson & Edwards, 2001), as outlined below.

Citalopram

Citalopram is the most serotonin selective of the SSRIs included in this section. In animals, one of its minor metabolites is cardiotoxic (Van der Burght, 1994) and it is pro-convulsant at high dose (Boeck *et al.*, 1982). The issue of its safety in overdose is discussed below (see Section 8.2.9.3). It is available as a generic preparation.

Escitalopram

Citalopram is a racemic mixture of s-citalopram and r-citalopram. With respect to SSRI potency, escitalopram (s-citalopram) is 100 times more potent than r-citalopram. The observation that escitalopram 10 mg is as effective as citalopram 20 mg confirms that escitalopram is responsible for most or perhaps all of the antidepressant efficacy of citalopram (Waugh & Goa, 2003). It has been suggested that r-citalopram contributes only to side effects and by using the active isomer only, efficacy will be maintained and side effects reduced.

Fluoxetine

Fluoxetine is the most widely prescribed SSRI. It is associated with a lower incidence of nausea than fluvoxamine but a higher incidence of rash. It has a long half-life, which may cause problems with washout periods when switching to other antidepressant drugs but has the advantage of causing less discontinuation symptoms. It is available as a generic preparation.

Fluvoxamine

Fluvoxamine was the first of the currently available SSRIs to be marketed in the UK. It is associated with a higher incidence of nausea than the other SSRIs and so is not widely prescribed.

Paroxetine

Paroxetine is associated with a higher incidence of sweating, sedation and sexual dysfunction than other SSRIs and more problems on withdrawal (Anderson & Edwards, 2001; see also Section 8.2.8 on antidepressant discontinuation/withdrawal symptoms). It is available as a generic preparation.

Sertraline

Sertraline is a well-tolerated SSRI. It is more likely to be associated with upwards dosage titration during treatment than the other SSRIs (Gregor *et al.*, 1994).

8.1.3.2 Studies considered for review

The GDG used an existing review (Geddes *et al.*, 2002) as the basis of this section, for which the authors made their data available to the NCCMH team. Since this review did not cover escitalopram which achieved its UK licence in late 2001, a separate review of this drug was undertaken. The two reviews are presented separately.

Review of SSRIs apart from escitalopram

The Geddes *et al.* (2002) review included 126 studies of which 72 did not meet the inclusion criteria set by the GDG. In addition one trial (Peselow *et al.*, 1989) included in the original review was considered to be part of a multicentre trial (FEIGHNER92) rather than a separate trial. Another (FEIGHNER1989), excluded in the original review, was included in this review because it contained tolerability data (which the original review did not include). A further two trials excluded by the original review were also considered part of the FEIGHNER92 multicentre trial (Dunbar *et al.*, 1991; Feighner & Boyer, 1989).

Since the original review compared SSRIs with TCAs only, 59 additional studies were identified from other reviews undertaken for this guideline, including two identified from hand searching reference lists. Thirty-three of these were included and 26 excluded. Thus 107 trials are included in this review providing data from up to 11,442 participants. A total of 97 trials were excluded.

All included studies were published between 1983 and 2003 and were between four and 24 weeks long (mean = 6.5 weeks). Twenty-four studies were of inpatients, 51 of outpatients and six undertaken in primary care. In the remaining 26, it was either not clear from where participants were sourced, or they were from mixed sources. In 11, more than 80% of study participants were aged 65 years and over (although only eight of these reported extractable efficacy outcomes). In two studies participants had depression with additional atypical features.

In addition to the standard diagnostic criteria, most studies required a minimum baseline HRSD score of between 10 and 22 on the 17-item version (61 studies) or between 18 and 22 on the 21-item version (28 studies). The ten studies reporting MADRS scores required minimum baseline scores of between 18 and 30.

Data were available to compare SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with amineptine, amitriptyline, clomipramine, desipramine,

dothiepin/dosulepin, doxepin, imipramine, lofepramine, nortriptyline, maprotiline, mianserin, trazodone, phenelzine, moclobemide, mirtazapine, venlafaxine and reboxetine.

The original systematic review on which this review is based and for which the data were made available to the GDG included only one outcome measure, mean endpoint scores, and did not include tolerability data. Tolerability data, but not additional efficacy outcomes, have been extracted by the NCCMH team.

Review of escitalopram

A new review was undertaken with two studies being identified from a search of electronic databases, one of which met inclusion criteria. Two further studies were identified from other searches undertaken for this guideline, both of which met inclusion criteria. Two unpublished studies, both of which met inclusion criteria, were supplied by Lundbeck. Thus a total of six studies are included in this review (ALEXOPOULOS2003, BIELSKI2003, BURKE2002, MONTGOMERY2001, MONTGOMERY2002, WADE2002) providing data from up to 2,045 participants. One study (RAPPAPORT2004) was excluded because it reported on the maintenance phase of a trial.

All included studies were published between 2001 and 2003 and were eight weeks long. In two studies participants were classified outpatients, in three primary care and in one the setting was unclear. Participants were aged between 18 years and 85 years, although in no study were all participants over 65 years. Participants received between 10 mg and 20 mg of escitalopram, with two studies specifically comparing 10 mg with 20 mg.

All studies reported mean baseline MADRS scores between 28.7 to 30.7. Three studies reported baseline HRSD scores. These ranged from 25.8 to 28.6.

Data were available to compare escitalopram with citalopram, sertraline, venlafaxine and placebo.

8.1.3.3 Evidence statements for SSRIs apart from escitalopram

Effect of treatment on efficacy

There is no clinically significant difference between SSRIs and other antidepressants, whether combined as a group or divided by drug class:

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 82[33]; *n* = 8,668; SMD = 0.08; 95% CI, 0.03 to 0.12).

[33] Studies where >50% of participants left treatment early were retained in the analysis since removing them made no difference to the results.

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS between:

- SSRIs and TCAs (N = 49; *n* = 4,073; SMD = 0.05; 95% CI, –0.01 to 0.12)
- SSRIs and MAOIs (N = 7; *n* = 469; SMD = 0.03; 95% CI, –0.15 to 0.22).

There is evidence suggesting that there is a statistically significant difference favouring third-generation[34] antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 17; *n* = 3665; SMD = 0.13; 95% CI, 0.06 to 0.19).

Effect of setting on treatment efficacy

In inpatients there is no difference between the efficacy of SSRIs and other antidepressants, apart from third-generation antidepressants:

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms in inpatients as measured by the HRSD or MADRS between:

- SSRIs and other antidepressants (N = 20; *n* = 1258; SMD = 0.09; 95% CI, –0.02 to 0.2)
- SSRIs and TCAs (N = 15; *n* = 970; SMD = 0.12; 95% CI, –0.01 to 0.24).

There is some evidence suggesting that there is a clinically significant difference favouring third-generation antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in inpatients (N = 1; *n* = 67; SMD = 0.58; 95% CI, 0.09 to 1.07).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and MAOIs on reducing depression symptoms as measured by the HRSD or MADRS in inpatients.

In outpatients there is no difference between the efficacy of SSRIs and other antidepressants:

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients but the size of this difference is unlikely to be of clinical significance (N = 38; *n* = 4666; SMD = 0.06; 95% CI, 0 to 0.12).

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms as measured by the HRSD or MADRS in outpatients between SSRIs and TCAs (N = 24; *n* = 2304; SMD = 0.02; 95% CI, –0.07 to 0.1).

[34] Mirtazapine, venlafaxine and reboxetine.

There is evidence suggesting that there is a statistically significant difference favouring 'third-generation' antidepressants over SSRIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients, but the size of this difference is unlikely to be of clinical significance (N = 9; *n* = 2096; SMD = 0.13; 95% CI, 0.05 to 0.22).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs and MAOIs on reducing depression symptoms as measured by the HRSD or MADRS in outpatients.

There is a similar picture in primary care:

There is evidence suggesting that there is no clinically significant difference between SSRIs and other antidepressants on reducing depression symptoms as measured by the HRSD or MADRS in primary care (N = 4; *n* = 922; SMD = 0.08; 95% CI, –0.05 to 0.21).

Acceptability and tolerability of treatment

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N = 97; *n* = 11442; RR = 0.91; 95% CI, 0.87 to 0.96).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N = 89; *n* = 10898; RR = 0.78; 95% CI, 0.71 to 0.85).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over alternative antidepressants on reducing the likelihood of patients reporting adverse effects but the size of this difference is unlikely to be of clinical significance (N = 42; *n* = 5658; RR = 0.94; 95% CI, 0.91 to 0.97).

A sub-analysis against TCAs showed similar results:

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early for any reason but the size of this difference is unlikely to be of clinical significance (N = 62; *n* = 6446; RR = 0.88; 95% CI, 0.82 to 0.93).

There is strong evidence suggesting that there is a clinically significant difference favouring SSRIs over TCAs on reducing the likelihood of patients leaving treatment early due to side effects (N = 59; *n* = 6145; RR = 0.69; 95% CI, 0.62 to 0.77).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs over TCAs on the likelihood of patients reporting adverse events but the size of this difference is unlikely to be of clinical significance (N = 17; *n* = 1846; RR = 0.86; 95% CI, 0.81 to 0.9).

8.1.3.4 Evidence statements for escitalopram compared with placebo

Effect of treatment on efficacy outcomes (all doses)

There is strong evidence suggesting that there is a clinically significant difference favouring escitalopram over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the MADRS (N = 3; *n* = 1056; RR = 0.73; 95% CI, 0.65 to 0.81).

There is some evidence suggesting that there is a clinically significant difference favouring escitalopram over placebo on increasing the likelihood of patients achieving remission as measured by the MADRS (N = 1; n = 380; RR = 0.81; 95% CI, 0.68 to 0.95).

There is evidence suggesting that there is a statistically significant difference favouring escitalopram over placebo on reducing depression symptoms as measured by the MADRS at the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 2; *n* = 619; Random effects SMD = –0.36; 95% CI, –0.57 to –0.15).

Effect of treatment on efficacy outcomes (10 mg)

There is strong evidence suggesting that there is a clinically significant difference favouring escitalopram (10 mg) over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the MADRS (N = 2; *n* = 621; RR = 0.74; 95% CI, 0.64 to 0.86).

There is some evidence suggesting that there is a clinically significant difference favouring escitalopram (10 mg) over placebo on increasing the likelihood of patients achieving remission as measured by the MADRS (N = 1; *n* = 380; RR = 0.81; 95% CI, 0.68 to 0.95).

There is evidence suggesting that there is a statistically significant difference favouring escitalopram (10 mg) over placebo on reducing depression symptoms as measured by the MADRS at the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 2; *n* = 614; SMD = –0.3; 95% CI, –0.46 to –0.14).

Effect of treatment on efficacy outcomes (20 mg)

There is strong evidence suggesting that there is a clinically significant difference favouring escitalopram (20 mg) over placebo on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the MADRS (N = 1; *n* = 247; RR = 0.68; 95% CI, 0.55 to 0.84).

There is some evidence suggesting that there is a clinically significant difference favouring escitalopram (20 mg) over placebo on reducing depression symptoms as measured by the MADRS at the end of treatment (N = 1; *n* = 242; WMD = –4.5; 95% CI, –6.86 to –2.14).

Acceptability and tolerability of treatment

On reducing the likelihood of patients leaving treatment early for any reason, there is insufficient evidence to determine if there is a clinically significant difference between

- escitalopram (all doses) and placebo (N = 3; *n* = 1056; RR = 0.96; 95% CI, 0.73 to 1.26)
- escitalopram (10 mg) and placebo (N = 2; *n* = 621; RR = 0.94; 95% CI, 0.67 to 1.31)
- escitalopram (20 mg) and placebo (N = 1; *n* = 247; RR = 1.17; 95% CI, 0.77 to 1.77).

On reducing the likelihood of patients leaving treatment early due to side effects, there is some evidence suggesting that there is a clinically significant difference favouring:

- placebo over escitalopram (all doses) (N = 3; *n* = 1056; RR = 2.48; 95% CI, 1.17 to 5.26)
- placebo over escitalopram (10 mg) (N = 2; *n* = 621; RR = 2.82; 95% CI, 1.03 to 7.75)
- placebo over escitalopram (20 mg) (N = 1; *n* = 247; RR = 4.23; 95% CI, 1.24 to 14.47).

There is evidence suggesting that there is a statistically significant difference favouring placebo over escitalopram (all doses) on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 3; *n* = 1056; RR = 1.13; 95% CI, 1.03 to 1.23).

There is some evidence suggesting that there is a clinically significant difference favouring placebo over escitalopram (20 mg) on reducing the likelihood of patients reporting side effects (N = 1; *n* = 247; RR = 1.21; 95% CI, 1.06 to 1.39).

There is evidence to suggest that there is no clinically significant difference between escitalopram (10 mg) and placebo on reducing the likelihood of patients reporting side effects (N = 2; *n* = 621; RR = 1.08; 95% CI, 0.97 to 1.22).

8.1.3.5 Evidence statements for escitalopram compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is a statistically significant difference favouring escitalopram over other antidepressants, although the size of this difference is unlikely to be of clinical significance, on:

- increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the MADRS (N = 5; *n* = 1389; RR = 0.87; 95% CI, 0.76 to 0.98)

- reducing depression symptoms as measured by the HRSD at the end of treatment (N = 2; *n* = 443; SMD = –0.2; 95% CI, –0.39 to –0.02).

There is evidence to suggest that there is no clinically significant difference between escitalopram and other antidepressants on increasing the likelihood of patients achieving remission as measured by the MADRS (N = 4; n = 1020; RR = 0.89; 95% CI, 0.79 to 1.02).

There were similar results or 'insufficient evidence' in comparisons of escitalopram (any dose, 10 mg or 20 mg) with SSRIs and venlafaxine separately.

Acceptability and tolerability of treatment

There is evidence to suggest that there is no clinically significant difference between escitalopram and other antidepressants on:

- reducing the likelihood of patients leaving treatment early for any reason (N = 5; *n* = 1389; RR = 0.96; 95% CI, 0.77 to 1.20)

- reducing the likelihood of patients reporting side effects (N = 3; *n* = 979; RR = 0.98; 95% CI, 0.91 to 1.06).

There is some evidence suggesting that there is a clinically significant difference favouring escitalopram over other antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N = 5; *n* = 1389; RR = 0.61; 95% CI, 0.4 to 0.91).

There were similar results or 'insufficient evidence' on all outcomes in comparisons of escitalopram (any dose, 10 mg or 20 mg) with SSRIs and venlafaxine separately. However, there is evidence to suggest that there is no clinically significant difference between escitalopram and venlafaxine on reducing the likelihood of patients reporting side effects (N = 1; *n* = 293; RR = 0.94; 95% CI, 0.81 to 1.1).

8.1.3.6 Clinical summary

SSRIs are relatively well-tolerated drugs with equal efficacy compared with alternative antidepressants. They are particularly suitable for women who may respond preferentially to SSRIs (see gender, section 8.2.3) and for those with suicidal intent, due to their safety in overdose (see section 8.2.10).

8.1.4 Monoamine oxidase inhibitors (MAOIs)

8.1.4.1 Introduction

Monoamine oxidase inhibitors (MAOIs) exert their therapeutic effect by binding irreversibly to monoamine oxidase, the enzyme responsible for the degeneration of monoamine neurotransmitters such as noradrenaline and serotonin. This results in increased monoamine neurotransmission. The first antidepressant drug synthesised was an irreversible MAOI and drugs in this class have been available in the UK for nearly 50 years.

All MAOIs have the potential to induce hypertensive crisis if foods containing tyramine (which is also metabolised by MAO) are eaten (Merriman, 1999) or drugs that increase monoamine neurotransmission are co-prescribed (Livingstone & Livingstone, 1996). These foods and drugs must be avoided for at least 14 days after discontinuing MAOIs. Reversible inhibitors of MAO (RIMAs) are also available. Moclobemide is the only RIMA licensed in the UK.

Dietary restrictions, potentially serious drug interactions and the availability of safer antidepressants have led to the irreversible MAOIs being infrequently prescribed in the UK, even in hospitalised patients. However, MAOIs are still widely cited as being the most effective antidepressants for the treatment of atypical depression (see Section 8.2.5).

For this class of drugs the GDG chose to review phenelzine and moclobemide.

8.1.4.2 Moclobemide

8.1.4.2.1 Introduction

Moclobemide is a reversible selective inhibitor of monoamine oxidase A (a RIMA) as opposed to the traditional MAOIs that inhibit both MAO A and MAO B irreversibly. It has the advantages over the traditional MAOIs that strict dietary restrictions are not required, drug interactions leading to hypertensive crisis are less problematic and shorter washout periods are required when switching to other antidepressants. Moclobemide is generally well-tolerated as it is associated with a low potential for producing anticholinergic side effects, weight gain and symptomatic postural hypotension. It is not widely prescribed in the UK.

8.1.4.2.2 Studies considered for review

Forty-four studies were found in a search of electronic databases with twelve meeting the inclusion criteria set by the GDG and 32 being excluded. Twenty-seven additional studies were identified from other searches undertaken for this guideline, 14 of which met inclusion criteria with 13 being excluded. Thus a total of 26 studies are included in this review (BAKISH1992, BARRELET1991, BEAUMONT1993, BECKERS1990, BOUGEROL1992, CASACCHIA1984, DUARTE1996, GATTAZ1995, GEERTS1994, GUELFI1992, HEBENSTREIT90, HELL1994, JOUVENT1998, KOCZKAS1989, KRAGHSORENSEN95, LAPIERRE1997, LARSEN1989, LECRUBIER1995, NAIR1995, NEWBURN1990, OSE1992, REYNAERT1995, SILVERSTONE94, TANGHE1997, VERSIANI1989, WILLIAMS1993) providing efficacy data from up to 1742 participants and tolerability data from up to 2149 participants. A total of 45 studies were excluded.

Sixteen studies compared moclobemide with TCAs (BAKISH1992, BEAUMONT1993, BECKERS1990, GUELFI1992, HEBENSTREIT90, HELL1994, JOUVENT1998, KOCZKAS1989, KRAGHSORENSEN95, LARSEN1989, LECRUBIER1995, NAIR1995, NEWBURN1990, SILVERSTONE94, TANGHE1997, VERSIANI1989), eight with SSRIs (BARRELET1991, BOUGEROL1992, DUARTE1996, GATTAZ1995, GEERTS1994, LAPIERRE1997, REYNAERT1995, WILLIAMS1993) and seven with placebo (BAKISH1992, CASACCHIA1984, LARSEN1989, NAIR1995, OSE1992, SILVERSTONE1994, VERSIANI1989).

All included studies were published between 1984 and 1998 and were between four and seven weeks long (mean length = 5.34 weeks). In seven studies participants were classified inpatients, in a further seven, outpatients, in two, primary care and in 10 they were either a mixture of inpatients and outpatients or the setting was unclear. In one study (NAIR1995) the patients were exclusively older adults (aged 60 to 90). None of the included studies described participants as having depression with atypical features. Participants received between 150 mg and 600 mg of moclobemide with most receiving at least 300 mg.

Data were available to compare moclobemide with amitriptyline, clomipramine, dothiepin/dosulepin, imipramine, nortriptyline, fluoxetine, fluvoxamine and placebo.

8.1.4.2.3 Evidence statements for moclobemide compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 3; *n* = 490; Random effects SMD = –0.6; 95% CI, –1.13 to –0.07).

There is some evidence suggesting that there is a clinically significant difference favouring moclobemide over placebo on increasing the likelihood of achieving at least a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 606; Random effects RR = 0.7; 95% CI, 0.5 to 0.99).

There is insufficient evidence to determine whether there is a clinically significant difference between moclobemide and placebo on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 2; *n* = 111; RR = 0.88; 95% CI, 0.73 to 1.05).

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and placebo on:

- reducing the likelihood of leaving treatment early for any reason (N = 7; *n* = 819; Random effects RR = 0.95; 95% CI, 0.74 to 1.22)
- reducing the likelihood of leaving treatment early due to side effects (N = 6; *n* = 785; RR = 1.11; 95% CI, 0.6 to 2.04)
- reducing the likelihood of patients reporting side effects (N = 5; *n* = 615; Random effects RR = 1.12; 95% CI, 0.94 to 1.32).

8.1.4.2.4 Evidence statements for moclobemide compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on:

- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 13[35]; *n* = 1222; SMD = 0; 95% CI, –0.12 to 0.11)
- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 5; *n* = 402; RR = 1; 95% CI, 0.86 to 1.18)
- increasing the likelihood of achieving at least a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 13; *n* = 2070; RR = 1.02; 95% CI, 0.93 to 1.13).

Similar results were found in sub-analyses by antidepressant class and setting.

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between moclobemide and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 20; *n* = 2458; RR = 0.97; 95% CI, 0.85 to 1.11).

Similar results were found in sub-analyses by antidepressant class and setting.

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over other antidepressants on reducing the likelihood of leaving treatment due to side effects (N = 18; *n* = 2292; RR = 0.57; 95% CI, 0.44 to 0.75).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over other antidepressants on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 12; *n* = 1472; RR = 0.85; 95% CI, 0.79 to 0.92).

Similar results were found in sub-analyses by setting but not by antidepressant class:

There is evidence suggesting that there is no clinically significant difference between moclobemide and SSRIs on reducing the likelihood of patients reporting side effects (N = 6; *n* = 519; RR = 0.9; 95% CI, 0.79 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference between moclobemide and SSRIs on reducing the likelihood of leaving treatment early due to side effects (N = 6; *n* = 660; RR = 0.96; 95% CI, 0.59 to 1.57).

[35] Two studies (DUARTE1996 and TANGHE1997) were removed from this analysis to remove heterogeneity from the data set; this did not affect the results.

There is strong evidence suggesting that there is a clinically significant difference favouring moclobemide over TCAs on reducing the likelihood of leaving treatment due to side effects (N = 12; *n* = 1632; RR = 0.46; 95% CI, 0.34 to 0.64).

There is evidence suggesting that there is a statistically significant difference favouring moclobemide over TCAs on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical importance (N = 6; *n* = 953; RR = 0.83; 95% CI, 0.76 to 0.91).

8.1.4.2.5 Clinical summary

There is some evidence that moclobemide is more effective than placebo, but insufficient evidence of its tolerability and acceptability. There is evidence that it is equally as effective as other antidepressants (TCAs and SSRIs). Whilst moclobemide is equally as acceptable and tolerable to patients as SSRIs, there is strong evidence that patients receiving moclobemide are less likely to leave treatment early due to side effects than patients receiving TCAs.

8.1.4.3 Phenelzine

8.1.4.3.1 Introduction

Phenelzine is the best tolerated MAOI. Established side effects include hypotension, drowsiness, dizziness, dry mouth and constipation. It has been associated with hepatotoxicity.

8.1.4.3.2 Studies considered for review

Twenty-seven studies were found in a search of electronic databases with nine being included and 18 being excluded by the GDG.

Eight studies compared phenelzine with TCAs (DAVIDSON81, DAVIDSON87, GEORGOTAS86, QUITKIN1990[36], RAFT1981, ROBINSON1983, SWANN1997, VALLEJO87) and one with SSRIs (PANDE1996). These provided efficacy data from up to 634 trial participants and tolerability data from up to 481 participants.

All included studies were published between 1981 and 1997 and were between three and seven weeks long (mean = 5.56 weeks). Participants were described as outpatients in eight studies and as inpatients in the other study (GEORGOTAS86). This study was also the only one in which all participants were 55 years of age or older (mean age 65 years). Studies reported mean doses of between 30 mg and 90 mg of phenelzine. All participants in PANDE1996 and 67% of those in QUITKIN1990 were diagnosed with depression with additional atypical features.

Data were available to compare phenelzine with amitriptyline, desipramine[37], imipramine, nortriptyline and fluoxetine.

[36] The data from QUITKIN1990 was supplied as raw individual patient data by the authors to the NCCMH review team.

[37] Not licensed for use in the UK.

8.1.4.3.3 Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 2; *n* = 325; RR = 0.66; 95% CI, 0.52 to 0.83).

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 7; *n* = 634; Random effects SMD = –0.02; 95% CI, –0.33 to 0.28).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and other antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 3; *n* = 385; Random effects RR = 0.97; 95% CI, 0.55 to 1.70).

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and SSRIs on any efficacy measure, or between phenelzine and TCAs on reducing the likelihood of achieving remission by the end of treatment.

There is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 1; *n* = 285; RR = 0.66; 95% CI, 0.52 to 0.83).

There is evidence suggesting that there is no clinically significant difference between phenelzine and TCAs on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 6; *n* = 594; Random effects SMD = –0.07; 95% CI, –0.40 to 0.27).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and other antidepressants on reducing the likelihood of leaving treatment early for any reason and on reducing the likelihood of leaving treatment early due to side effects.

There is evidence suggesting that there is no clinically significant difference between phenelzine and other antidepressants on reducing the likelihood of patients reporting adverse effects (N = 1; *n* = 60; RR = 0.97; 95% CI, 0.87 to 1.09).

A sub-analysis by antidepressant class gave similar results.

8.1.4.3.4 Clinical summary

There is some evidence suggesting a superior efficacy for response for phenelzine compared with other antidepressants. These findings are probably explained by the high proportion of patients with depression with atypical features in the studies reporting response (71% of patients had depression with atypical features) and remission (56% of patients had depression with atypical features). A separate review of the pharmacological treatment of atypical depression is provided in Section 8.2.5.

There is no difference in mean endpoint scores between the two groups of treatments in patients with major depressive disorder regardless of additional atypical features. This is also evident in comparisons with TCAs alone. Evidence from studies comparing phenelzine with SSRIs was too weak to draw any conclusions.

There is insufficient evidence to draw any conclusions on the comparative tolerability of phenelzine against alternative antidepressants.

8.1.5 Third-generation antidepressants[38]

This diverse group of antidepressants was marketed after the SSRIs. The aim was to broaden the mechanism of action beyond serotonin in order to improve efficacy without incurring the side effects or toxicity in overdose associated with the TCAs.

8.1.5.1 Mirtazapine

8.1.5.1.1 Introduction

Mirtazapine is a noradrenaline and specific serotonin antidepressant (NaSSA) which blocks presynaptic alpha 2 receptors on both NA and 5HT neurones and also blocks postsynaptic 5HT2 (less sexual dysfunction but possible worsening of the symptoms of obsessive compulsive disorder) and 5HT3 (less nausea) receptors. It can cause weight gain and sedation.

8.1.5.1.2 Studies considered for review

Twenty-five studies were found in a search of electronic databases and details of a study in press were provided by Organon Laboratories Ltd (WADE2003). Fifteen were included (although the efficacy data from one of these, WADE2003, were excluded because more than 50% of participants left treatment early) and 11 excluded by the GDG.

Nine studies compared mirtazapine with TCAs and related antidepressants (BREMNER1995, BRUIJN1996, HALIKAS1995, MARTTILA1995, MULLIN1996, RICHOU1995, SMITH1990, VANMOFFAERT95, ZIVKOV1995), five compared it with SSRIs (BENKERT2000, LEINONE1999, SCHATZBERG02, WADE2003, WHEATLEY1998), and one with venlafaxine (GUELFI2001). These provided efficacy data from up to 2491 trial participants and tolerability data from up to 2637 participants.

[38] Although these are classified 'other antidepressants' by the *BNF*, to avoid confusion with the guideline's use of 'other antidepressants' to mean all other antidepressants, the GDG uses the term 'third-generation antidepressants' to describe this group of drugs.

All included studies were published between 1990 and 2003 and were between five and 24 weeks long (mode = six weeks). In five studies participants were described as inpatients, in six as outpatients, one was from primary care and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (SCHATZBERG2002) all participants were 65 years of age or older). Studies reported mean doses of between 22 mg and 76.2 mg of mirtazapine.

Data were available to compare mirtazapine with amitriptyline, clomipramine, doxepin, imipramine, trazodone, citalopram, fluoxetine, paroxetine and venlafaxine.

8.1.5.1.3 Evidence statements

Effect of treatment on efficacy outcomes

There is no difference between the efficacy of mirtazapine and other antidepressants for which comparisons were available:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N = 14[39]; *n* = 2440; RR = 0.92; 95% CI, 0.84 to 1.01)

- reducing depression symptoms by the end of treatment as measured by the HRSD or the MADRS (N = 14; *n* =2314; SMD = –0.03; 95% CI, –0.11 to 0.05).

There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over other antidepressants on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N = 4; *n* = 819; RR = 0.91; 95% CI, 0.83 to 0.99).

Similar results were found in sub-analyses by antidepressant class, other than for SSRIs:

There is evidence suggesting that there is a statistically significant difference favouring mirtazapine over SSRIs on reducing depression symptoms by the end of treatment, but the size of this difference is unlikely to be of clinical significance (N = 4; *n* = 888; SMD = –0.13; 95% CI, –0.27 to 0.00).

Effect of setting on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on:

- reducing depression symptoms by the end of treatment in inpatients as measured by the HRSD or MADRS (N = 5; *n* = 854; Random effects SMD = 0.05; 95% CI, –0.15 to 0.24)

[39] One study (WADE2003) was removed because >50% of participants left the study early.

- increasing the likelihood of achieving remission in outpatients by the end of treatment (N = 2; *n* = 387; RR = 0.93; 95% CI, 0.81 to 1.05)

- reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or the MADRS (N = 6; *n* = 915; SMD = –0.1; 95% CI, –0.23 to 0.03).

In outpatients there is evidence suggesting that there is a statistically significant difference favouring mirtazapine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (N = 6; *n* = 957; RR = 0.86; 95% CI, 0.73 to 1).

In inpatients there is insufficient evidence to determine whether there is a clinically significant difference between mirtazapine and other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms or on achieving remission.

No data were available to determine efficacy in patients in primary care.

Acceptability and tolerability of treatment

Mirtazapine appears to be as acceptable to patients as other antidepressants, except that fewer patients leave treatment early due to side effects:

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on reducing the likelihood of leaving treatment early for any reason (N = 15; *n* = 2637; RR = 0.88; 95% CI, 0.78 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring mirtazapine over other antidepressants on reducing the likelihood of patients leaving treatment early due to side effects (N = 15; *n* = 2637; RR = 0.69; 95% CI, 0.55 to 0.87).

There is evidence suggesting that there is no clinically significant difference between mirtazapine and other antidepressants on reducing the likelihood of patients reporting side effects (N = 6; *n* = 1253; RR = 0.99; 95% CI, 0.93 to 1.05).

Findings were similar in sub-analyses by setting and class of antidepressant.

8.1.5.1.4 Clinical summary

There is no difference between mirtazapine and other antidepressants on any efficacy measure, although in terms of achieving remission mirtazapine appears to have a statistical though not clinical advantage. In addition, mirtazapine has a statistical advantage over SSRIs in terms of reducing depression symptoms, but the difference is not clinically important.

However, there is strong evidence that patients taking mirtazapine are less likely to leave treatment early because of side effects, although this is not the case for patients reporting side effects or leaving treatment early for any reason.

Therefore, although mirtazapine is as effective as other antidepressants, it may have an advantage in terms of reducing side effects likely to lead to patients leaving treatment early.

8.1.5.2 Reboxetine

8.1.5.2.1 Introduction

Reboxetine is a relatively selective noradrenergic reuptake inhibitor. Side effects include insomnia, sweating, dizziness, dry mouth and constipation (Holm & Spencer, 1999). It may also lower serum potassium (ABPI, 2003). It is not licensed for use in older adults.

8.1.5.2.2 Studies considered for review

Eight studies were found in a search of electronic databases, with six (ANDREOLI2002, BAN1998, BERZEWSKI1997, KATONA1999, MASSAN1999, VERSIANI2000B) being included and two excluded.

Three studies compare reboxetine with placebo (ANDREOLI2002, BAN1998, VERSIANI2000B), three with TCAs (BAN1998, BERZEWSKI1997, KATONA1999) and two with SSRIs (ANDREOLI2002, MASSAN1999). These provided efficacy and tolerability data from up to 1068 trial participants.

All included studies were published between 1997 and 2002 and were between four and eight weeks long (mean = 6.66 weeks). In two studies participants were described as inpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (KATONA1999) all participants were aged 65 years and over. Apart from this study where participants received a dose of 6 mg, doses were between 8 mg and 10 mg of reboxetine.

Data were available to compare reboxetine with desipramine, imipramine, fluoxetine and placebo.

8.1.5.2.3 Evidence statements for reboxetine compared with placebo

Effect of treatment on efficacy outcomes

There is strong evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 479; RR = 0.61; 95% CI, 0.51 to 0.73).

There is some evidence suggesting that there is a clinically significant difference favouring reboxetine over placebo on increasing the likelihood of achieving remission by the end of treatment (N = 1; *n* = 254; RR = 0.71; 95% CI, 0.59 to 0.87).

Acceptability and tolerability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and placebo on any measure of acceptability or tolerability.

8.1.5.2.4 Evidence statements for reboxetine compared with other antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 5; *n* = 1068; RR = 0.87; 95% CI, 0.76 to 1.01)
- increasing the likelihood of achieving remission by the end of treatment (N = 4; *n* = 895; RR = 0.96; 95% CI, 0.84 to 1.09)
- reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 3; *n* = 618; SMD = –0.09; 95% CI, –0.24 to 0.07).

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between reboxetine and other antidepressants on increasing the likelihood of patients reporting side effects (N = 4; *n* = 895; RR = 0.98; 95% CI, 0.9 to 1.06).

There is insufficient evidence to determine whether there is a clinically significant difference between reboxetine and other antidepressants on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

8.1.5.2.5 Clinical summary

Reboxetine is superior to placebo and as effective as other antidepressants in the treatment of depression. There is insufficient evidence to comment on reboxetine's tolerability compared with placebo or alternative antidepressants.

8.1.5.3 Venlafaxine

8.1.5.3.1 Introduction

Venlafaxine was the first of the new generation dual-action antidepressants. It inhibits the reuptake of both serotonin and noradrenaline in the same way as the TCAs. At the standard dose of 75 mg it is an SSRI with dual action emerging at doses of 150 mg and above. At higher doses it also inhibits dopamine reuptake.

Venlafaxine has a broad range of side effects similar to those of the TCAs and SSRIs. It can increase blood pressure at higher doses, is associated with a high incidence of discontinuation symptoms (see Section 8.2.8) and is more toxic than the SSRIs in overdose (see Section 8.2.9).

8.1.5.3.2 Studies considered for review

The GDG used an existing review (Smith *et al.*, 2002) as the basis of this review. The original review included 31 studies of which nine did not meet the inclusion criteria set by the GDG. Fifteen additional studies were identified from new searches, and four from another review (Einarson *et al.*, 1999). None of these studies met the inclusion criteria set by the GDG. Two studies were sourced from other reviews in this chapter, both of which met inclusion criteria, and details of ten additional unpublished studies were provided by Wyeth Laboratories, five of which met inclusion criteria. Thus a total of 33 studies are excluded from this review with 29 trials being included (014NEMEROFF, 015SCHATZBERG, 102TSAI, 332RICKELS, 349WYETH, 428CASABONA, 626KORNAAT, 671LENOX-SMITH, ALVES1999, BENKERT96, BIELSKI2003, CLERC1994, COSTA1998, CUN'HAM94, DIERICK96, GUELFI2001, HACKETT96, LECRUBIE97, MAHAPATRA97, MCPARTLIN98, MONTGOMERY2002, POIRIER99, RUDOLPH99, SAMUELIAN98, SCHWEIZER94, SIL'STONE99, SMERALDI98, TYLEE1997, TZANAKAKI00). Together these provide tolerability data from up to 5063 participants and efficacy data from up to 4198 participants.

All included studies were published between 1994 and 2003 and were between four and 13 weeks long (mean = 8.03 weeks). Three studies were of inpatients, 16 of outpatients and four were undertaken in primary care. In the remaining six, it was either not clear from where participants were sourced or they were from mixed sources. In three (MAHAPATRA97, 015SCHATZBERG, SMERLADI98) participants were aged 64 years and over. Mean HRSD scores at baseline ranged from 22.4 to 30.6 (various HRSD versions).

Data were available to compare venlafaxine with clomipramine, dothiepin/dosulepin, imipramine, trazodone, citalopram, escitalopram, fluoxetine, paroxetine and mirtazapine.

Studies reported mean doses equivalent to at least 100 mg of amitriptyline. Eight studies (102TSAI, 428CASABONA, 671LENOX-SMITH, BIELSKI2003, HACKETT96, MONTGOMERY2002, RUDOLPH1999, SIL'STONE99) used 'extended release' (XR) venlafaxine and the remainder 'immediate release' (IR) venlafaxine. Doses ranged from 75 mg to 375 mg. A sub-analysis was performed by dose of venlafaxine, with studies achieving a maximum dose of no more than 150 mg classified low dose (102TSAI, 349WYETH, 428CASABONA, ALVES1999, COSTA1998, DIERICK96, HACKETT96, LECRUIBIE97, MAHAPATRA97, MCPARTLIN98, MONTGOMERY2002, SAMUELIAN98, SMERALDI98, TYLEE1997) and those achieving a minimum dose of no less than 150 mg classified high dose (BENKERT96, BIELSKI2003, CLERC1994, GUELFI2001, POIRIER99, 332RICKELS, TZANAKAKI00). In addition, studies with a dose of 75 mg were analysed separately (102TSAI, 428CASABONA, MCPARTLIN98, TYLEE1997). Some participants in one study, GUELFI2001, received the comparator treatment (mirtazapine) at a dose higher than BNF limits. Where this gave heterogeneity, sub-analyses were performed removing this study. Results are presented only where clinically significant differences were found.

8.1.5.3.3 Evidence statements

Effect of treatment on efficacy

Venlafaxine is no more effective in treating depression than other antidepressants:

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 23; *n* = 4198; Random effects RR = 0.92; 95% CI, 0.83 to 1.02)

- increasing the likelihood of achieving remission as measured by the HRSD (N = 20; *n* = 3849; RR = 0.96; 95% CI, 0.91 to 1.01).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over other antidepressants on reducing depression symptoms, but the size of this difference is unlikely to be of clinical significance (N = 20; *n* = 3637; SMD = –0.09; 95% CI, –0.15 to –0.02).

Similar results were found in sub-analyses by class of antidepressant:

There is evidence to suggest that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving:

- a 50% reduction in depression symptoms (N = 16; *n* = 3268; RR = 0.92; 95% CI, 0.84 to 1.005)

- remission (N = 19; *n* = 3692; RR = 0.95; 95% CI, 0.9 to 1.002).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over SSRIs on reducing depression symptoms by the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 13; *n* = 2741; SMD = –0.10; 95% CI, –0.17 to –0.02).

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and TCAs on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 6; *n* = 773; Random effects RR = 0.91; 95% CI, 0.71 to 1.17).

There is evidence suggesting that there is no clinically significant difference between venlafaxine and TCAs on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 6; *n* = 744; SMD = –0.12; 95% CI, –0.27 to 0.02).

Effect of setting on treatment efficacy

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine and mirtazapine.

Inpatients

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N = 3; *n* = 383; Random effects SMD = –0.04; 95% CI, –0.46 to 0.38).

There is insufficient evidence to determine whether there is a clinically significant difference between venlafaxine and other antidepressants on either increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 3; *n* = 392; Random effects RR = 1.04; 95% CI, 0.71 to 1.53) or on increasing the likelihood of achieving remission (N = 2; *n* = 225; Random effects RR = 0.85; 95% CI, 0.45 to 1.62).

However, compared with SSRIs, venlafaxine is more effective in inpatients:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over SSRIs on:

- reducing depression symptoms in inpatients by the end of treatment as measured by the HRSD or MADRS (N = 1; *n* = 67; SMD = –0.58; 95% CI, –1.07 to –0.09)

- increasing the likelihood of achieving remission in inpatients as measured by the HRSD (N = 1; *n* = 68; RR = 0.60; 95% CI, 0.39 to 0.92).

Outpatients

Data from studies of venlafaxine in outpatients were available to make comparisons with imipramine, clomipramine, fluoxetine and paroxetine.

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over other antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms in outpatients as measured by the HRSD (N = 11; *n* = 2023; RR = 0.83; 95% CI, 0.74 to 0.93).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine over other antidepressants on reducing depression symptoms in outpatients by the end of treatment as measured by the HRSD or MADRS, but the size of this difference is unlikely to be of clinical significance (N = 9; *n* = 1804; SMD = –0.17; 95% CI, –0.26 to –0.08).

Results were similar against TCAs alone. However, when venlafaxine was compared with SSRIs there is evidence suggesting that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving remission in outpatients (N = 12; *n* = 2199; RR = 0.95; 95% CI, 0.89 to 1.02).

In outpatients, there is evidence suggesting that there are statistically significant differences favouring venlafaxine over SSRIs on the following outcomes, but the size of these differences is unlikely to be of clinical significance on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment (N = 9; *n* = 1775; RR = 0.85; 95% CI, 0.75 to 0.96)

- reducing depression symptoms in outpatients by the end of treatment (N = 7; *n* = 1572; SMD = –0.15; 95% CI, –0.25 to –0.05).

Primary care

Data were available to compare venlafaxine against imipramine, paroxetine and fluoxetine in primary care.

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on reducing depression symptoms by the end of treatment as measured by the HRSD or MADRS (N = 3; *n* = 824; SMD = –0.07; 95% CI, –0.21 to 0.06).

There is evidence suggesting that there is no clinically significant difference between venlafaxine and SSRIs on increasing the likelihood of achieving remission (N = 3; *n* = 995; RR = 0.98; 95% CI, 0.88 to 1.11).

Effect of dose on treatment efficacy

Venlafaxine at 75 mg

Data were available to compare venlafaxine at 75 mg with fluoxetine and paroxetine.

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (75 mg) and SSRIs on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 4; *n* = 882; Random effects RR = 0.87; 95% CI, 0.6 to 1.26).

There is evidence to suggest that there is no clinically significant difference between venlafaxine (75 mg) and SSRIs on:

- increasing the likelihood of patients achieving remission as measured by the HRSD or MADRS (N = 4; *n* = 882; RR = 0.98; 95% CI, 0.88 to 1.09)

- reducing depression symptoms as measured by the HRSD at the end of treatment (N = 3; *n* = 792; SMD = –0.08; 95% CI, –0.21 to 0.06).

Low-dose venlafaxine (mean ≤ 150 mg)

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (≤ 150 mg) and other antidepressants on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 12; *n* = 2418; Random effects RR = 0.86; 95% CI, 0.72 to 1.02).

There is evidence suggesting that there is no clinically significant difference between venlafaxine (≤ 150 mg) and other antidepressants on increasing the likelihood of achieving remission (N = 9; *n* = 2125; RR = 0.98; 95% CI, 0.9 to 1.06).

There is evidence suggesting that there is a statistically significant difference favouring venlafaxine (≤ 150 mg) over other antidepressants on reducing depression symptoms as measured by the HRSD or MADRS at the end of treatment but the size of this difference is unlikely to be of clinical significance (N = 11; *n* = 2256; SMD = –0.11; 95% CI, –0.19 to –0.03).

Results were similar in sub-analyses by antidepressant class.

High-dose venlafaxine (mean ≥ 150 mg)

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (≥ 150 mg) and other antidepressants on increasing the likelihood of patients achieving a 50% reduction in depression symptoms as measured by the HRSD or MADRS (N = 6; *n* = 822; Random effects RR = 1; 95% CI, 0.78 to 1.28).

There is evidence suggesting that there is no clinically significant difference between venlafaxine (≥ 150 mg) and other antidepressants:

- on reducing depression symptoms (N = 6; *n* = 807; Random effects SMD = 0.03; 95% CI, –0.18 to 0.23)

- on increasing the likelihood of achieving remission (N = 6; *n* = 706; Random effects RR = 0.94; 95% CI, 0.79 to 1.12).

Results were similar in sub-analyses by antidepressant class.

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- Reducing the likelihood of leaving treatment early for any reason (N = 23; *n* = 4196; RR = 0.98; 95% CI, 0.88 to 1.08)

- Reducing the likelihood of patients reporting adverse events (N = 21; *n* = 3757; RR = 1.01; 95% CI, 0.97 to 1.05).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over venlafaxine on reducing the likelihood of patients leaving treatment early due to side effects (N = 27; *n* = 5063; RR = 1.21; 95% CI, 1.04 to 1.41).

In sub-analyses by antidepressant class, results were similar for venlafaxine compared with SSRIs, except for fluoxetine:

There is evidence suggesting that there is a statistically significant difference favouring fluoxetine over venlafaxine on reducing the likelihood of patients reporting side effects, but the size of this difference is unlikely to be of clinical significance (N = 10; *n* = 1871; RR = 1.06; 95% CI, 1 to 1.11).

Acceptability and tolerability of treatment by setting

Inpatients

To assess the efficacy of venlafaxine in inpatients, data were available to compare it with imipramine, fluoxetine and mirtazapine. Heterogeneity was a problem in the meta-analysis assessing the tolerability of venlafaxine against all antidepressants in inpatients. This was because in the study comparing venlafaxine with mirtazapine, fewer participants taking mirtazapine left the study early compared with those taking venlafaxine, whereas this was not the case in other studies. Therefore, the result against TCAs and SSRIs only were considered:

There is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over TCAs and SSRIs on reducing the likelihood of inpatients leaving treatment early (N = 2; *n* = 235; RR = 0.61; 95% CI, 0.41 to 0.92).

Outpatients

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- reducing the likelihood of outpatients leaving treatment early for any reason (N =11; *n* = 2021; RR = 0.95; 95% CI, 0.82 to 1.1)

- reducing the likelihood of outpatients reporting side effects (N = 10; *n* = 1736; RR = 1.03; 95% CI, 0.98 to 1.09).

When compared with SSRIs:

There is some evidence suggesting that there is a clinically significant difference favouring SSRIs over venlafaxine on reducing the likelihood of outpatients leaving treatment early due to side effects (N = 11; *n* = 2085; RR = 1.48; 95% CI, 1.16 to 1.90).

Primary care

There is evidence suggesting that there is no clinically significant difference between venlafaxine and other antidepressants on:

- reducing the likelihood of leaving treatment early for any reason (N = 4; *n* = 1148; RR = 0.94; 95% CI, 0.77 to 1.15)

- reducing the likelihood of patients reporting adverse events (N = 3; *n* = 787; RR = 1.08; 95% CI, 0.9995 to 1.16).

Acceptability and tolerability of treatment by dose

Venlafaxine at 75 mg

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine (75 mg) and SSRIs on:

- reducing the likelihood of patients leaving treatment early (N = 3; *n* = 768; RR = 0.93; 95% CI, 0.75 to 1.16)

- reducing the likelihood of patients leaving treatment early due to side effects (N = 3; *n* = 768; Random effects RR = 1.07; 95% CI, 0.68 to 1.7)

- reducing the likelihood of patients reporting side effects (N = 3; *n* = 521; RR = 1.12; 95% CI, 0.996 to 1.25).

Low-dose venlafaxine (≤ 150 mg)

There is evidence suggesting that there is no clinically significant difference between low-dose venlafaxine and other antidepressants on reducing the likelihood of leaving treatment early (N = 12; *n* = 2471; RR = 1.04; 95% CI, 0.91 to 1.19).

There is evidence suggesting that there is a statistically significant difference favouring other antidepressants over low-dose venlafaxine on reducing the likelihood of patients reporting side effects but the size of this difference is unlikely to be of clinical significance (N = 12; *n* = 2224; RR = 1.06; 95% CI, 1.001 to 1.12).

There is some evidence suggesting that there is a clinically significant difference favouring other antidepressants over venlafaxine (<=150 mg) on reducing the likelihood of patients leaving treatment early due to side effects (N = 12; *n* = 2471; RR = 1.25; 95% CI, 1.002 to 1.55).

In sub-analyses by class of antidepressant, results were similar except that:

There is strong evidence that there is a clinically significant difference favouring fluoxetine over low-dose venlafaxine on reducing the likelihood of leaving treatment early due to side effects (N = 5; *n* = 1190; RR = 1.61; 95% CI, 1.15 to 2.24).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose venlafaxine and TCAs on reducing the likelihood of leaving treatment early due to side effects.

High-dose venlafaxine (≥ 150 mg)

There is insufficient evidence to determine whether there is a clinically significant difference between high-dose venlafaxine and other antidepressants on reducing the likelihood of leaving treatment early (N = 6; *n* = 822; Random effects RR = 1; 95% CI, 0.7 to 1.41) or on reducing the likelihood of leaving treatment early due to side effects (N = 7; *n* = 873; Random effects RR = 1.48; 95% CI, 0.71 to 3.05).

There is evidence suggesting that there is no clinically significant difference between high-dose venlafaxine and other antidepressants on reducing the likelihood of patients reporting side effects (N = 6; *n* = 674; RR = 0.95; 95% CI, 0.85 to 1.05).

8.1.5.3.4 Clinical summary

There are no clinically significant differences between venlafaxine (at any dose) and other antidepressants on any efficacy outcome. This was also the case for most acceptability and tolerability outcomes. However, there is some evidence that patients taking venlafaxine are more likely to leave treatment early due to side effects, particularly when low-dose (≤ 150 mg) venlafaxine is compared with fluoxetine.

Results were similar in sub-analyses by setting, other than for inpatients, with those taking venlafaxine being less likely to stop treatment early compared with TCAs and SSRIs. In addition, one small study of inpatients found that venlafaxine was superior to SSRIs on efficacy. In outpatients, there was some evidence for increased efficacy compared with other antidepressants, but only on response.

8.1.6 St John's wort

8.1.6.1 Introduction

St John's wort, an extract of the plant *Hypericum perforatum*, has been used for centuries for medicinal purposes including the treatment of depression. It is not licensed as a medicine in the UK but can be bought 'over the counter' from health food shops, herbalists and community pharmacies. Many different branded preparations are available. St John's wort is licensed in Germany for the treatment of depression.

St John's wort is known to contain at least 10 constituents or groups of components that may contribute to its pharmacological effects (Linde & Mulrow, 2003), but its exact mode of action is unknown. These include naphthodianthrons, flavonoids, xanthons and biflavonoids (Wagner & Bladt, 1994). In common with all herbal preparations, the quantity and proportions of each constituent varies among batches (Wang *et al.*, in press). Most commercial products are standardised with respect to hypericin content but it is not known if this is the only active component. Individual brands or batches of the same brand may, therefore, not be therapeutically equivalent. Many clinically significant drug interactions have been reported (Committee on Safety of Medicines, 2000). St John's wort may also cause photosensitivity.

8.1.6.2 Studies considered for review

Forty studies were found in a search of electronic databases, with 19 being included and 21 being excluded by the GDG.

Ten studies were available for a comparison with placebo (DAVIDSON02, HANSGEN1996, KALB2001, LAAKMANN98, LECRUBIER02, PHILIPP99, SCHRADER98, SHELTON2001, VOLZ2000, WITTE1995); four studies for a comparison with TCAs (PHILIPP99, WOELK2000, BERGMANN1993, WHEATLEY1997); one with TCA-related antidepressants (HARRER94); and six studies for a comparison with SSRIs (BEHNKE2002, BRENNER00, DAVIDSON02, HARRER99, SCHRADER00, VANGURP02)[40]. Data from up to 1520 participants were available from studies comparing St John's wort with placebo, and data from up to 1629 participants were available from comparison with antidepressants.

[40] DAVIDSON02 and PHILIPP99 are 3-arm trials.

All included studies were published between 1993 and 2002 and were between four and 12 weeks long (mean number of weeks = 6.47). In 16 studies participants were described as outpatients and in the other three it was either not clear from where participants were sourced or they were from mixed sources. In one (HARRER99) all participants were aged 60 years and over. All participants had either moderate or severe depression.

It is very difficult to assess the exact content of the preparation of St John's wort used in included studies so no study was excluded on grounds of inadequate dose. Included studies described the following range of preparations:

- 2 x 150 mg (300 mg) @ 0.450 to 0.495 mg total hypericin per tablet
- 900 mg LI 160
- 4 x 200 mg (800 mg) LoHyp-57: drug extract ratio 5–7:1
- 3 x 300 mg (900 mg) WS5572: drug extract ratio 2.5–5:1, 5% hyperforin
- 3 x 300 mg (900 mg) WS5573: 0.5% hyperforin
- 3 x 300 mg (900 mg) WS5570: 0.12–0.28% hypericin
- 3 x 350 mg (1050 mg) STEI 300: 0.2–0.3% hypericin, 2 to 3% hyperforin
- 2 x 200 mg (500 mg) ZE117: 0.5 mg hypericin
- 3 to 6 x 300 mg (900 mg to 1800 mg) @ 0.3% hypericum
- 3 x 300 mg (900 mg) LI 160 = 720–960 mcg hypericin
- 2 x 250 mg (500 mg) ZE117: 0.2% hypericin
- 900 mg to 1500 mg LI 160: standardised to 0.12 to 0.28% hypericin
- 4 x 125 mg (500 mg) Neuroplant
- 200–240 mg Psychotonin forte
- 3 x 30 drops Psychotonin (500 mg)
- 3 x 30 drops Hyperforat: 0.6 mg hypericin.

In addition six studies with low doses of standard antidepressants were also included.

8.1.6.3 Evidence statements for St John's wort compared with placebo

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring St John's wort over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD in:

- the data set as a whole (N = 6[41]; *n* = 995; RR = 0.79; 95% CI, 0.71 to 0.88)
- moderate depression (N = 1; *n* = 162; RR = 0.64; 95% CI, 0.51 to 0.79)
- severe depression (N = 5[42]; *n* = 898; RR = 0.81; 95% CI, 0.72 to 0.9).

There is insufficient evidence to determine if there is a clinically significant difference between St John's wort and placebo on increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 3; *n* = 804; Random effects RR= 0.80; 95% CI, 0.53 to 1.22).

There is evidence suggesting that there is a statistically significant difference favouring St John's wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance in:

- the data set as a whole (N = 6[43]; *n* = 1031; SMD = –0.35; 95% CI, –0.47 to –0.22)
- severe depression (N = 5[44]; *n* = 891; SMD = –0.34; 95% CI, –0.47 to –0.2).

However, in moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John's wort over placebo on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 2; *n* = 299; Random effects SMD = –0.71; 95% CI, –1.28 to –0.13).

Acceptability and tolerability of treatment

There is evidence suggesting that there is no clinically significant difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early for any reason (N = 8; *n* = 1472; RR = 0.96; 95% CI, 0.74 to 1.25).

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[41] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.

[42] Two studies (DAVIDSON02, HANGSEN1996) were removed from the meta-analysis to remove heterogeneity from the data set.

[43] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.

[44] Three studies (DAVIDSON02, HANGSEN1996, SCHRADER98) were removed from the meta-analysis to remove heterogeneity from the data set.

There is insufficient evidence to determine if there is a clinically significant difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early due to adverse effects (N = 5; *n* = 1127; RR = 0.88; 95% CI, 0.32 to 2.41).

There is evidence suggesting that there is no clinically significant difference between St John's wort and placebo on reducing the likelihood of patients reporting adverse effects (N = 7; *n* = 1106; RR = 0.89; 95% CI, 0.72 to 1.1).

8.1.6.4 Evidence statements for St John's wort compared with antidepressants

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically significant difference between St John's wort and antidepressants on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 10; *n* = 1612; Random effects RR = 1.03; 95% CI, 0.87 to 1.22)
- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 224; RR = 1.01; 95% CI, 0.87 to 1.17)
- reducing depression symptoms by the end of treatment as measured by the HRSD (N = 9; *n* = 1168; SMD = –0.02; 95% CI, –0.13 to 0.1).

A sub-analysis by severity found no difference in these results except for response rates in those with moderate depression:

In moderate depression there is some evidence suggesting that there is a clinically significant difference favouring St John's wort over antidepressants on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 3; *n* = 481; RR = 0.77; 95% CI, 0.62 to 0.95).

Sub-analyses by antidepressant class and by antidepressant dose (therapeutic versus low dose) found similar results.

A sub-analysis combining severity and antidepressant dose also found similar results apart from for response rates in severe depression:

In severe depression there is some evidence suggesting that there is a clinically significant difference favouring low dose antidepressants over St John's wort on increasing the likelihood of achieving a 50% reduction in depression symptoms as measured by the HRSD (N = 4; *n* = 521; RR = 1.2; 95% CI, 1 to 1.44).

Acceptability and tolerability of treatment

With regard to reducing the likelihood of patients leaving treatment early for any reason, there is insufficient evidence to determine a difference between St John's wort and either all antidepressants or low dose antidepressants. However, there is some evidence suggesting

that there is a clinically significant difference favouring St John's wort over antidepressants given at therapeutic doses (N = 5; *n* = 1011; RR = 0.69; 95% CI, 0.47 to 1).

There is strong evidence suggesting that there is a clinically significant difference favouring St John's wort over antidepressants on:

- reducing the likelihood of patients leaving treatment early due to side effects (N = 10; *n* = 1629; RR = 0.39; 95% CI, 0.26 to 0.6)
- reducing the likelihood of patients reporting adverse effects (N = 8; *n* = 1358; RR = 0.65; 95% CI, 0.57 to 0.75).

8.1.6.5 Clinical summary

St John's wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing depression symptoms in moderate depression.

There appears to be no difference between St John's wort and other antidepressants, other than in moderate depression where it is better at achieving response and in severe depression where it is less effective than low dose antidepressants in achieving response.

However, St John's wort appears as acceptable as placebo, and more acceptable than antidepressants, particularly TCAs, with fewer people leaving treatment early due to side effects and reporting adverse events.

8.1.7 Recommendations for the use of individual drugs in the treatment of depression

8.1.7.1 Antidepressants are not recommended for the initial treatment of mild depression because the risk-benefit ratio is poor. (C)

8.1.7.2 The use of antidepressants should be considered for patients with mild depression that is persisting after other interventions, and those whose depression is associated with psychosocial and medical problems. (C)

8.1.7.3 The use of antidepressants should be considered when patients with a past history of moderate or severe depression present with mild depression. (C)

8.1.7.4 Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed and the possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. (GPP)

8.1.7.5 Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after two weeks. Thereafter they should be seen on an appropriate and regular basis, for example, at intervals of two to four weeks in the first three months and at longer intervals thereafter, if response is good. (GPPC)

8.1.7.6 When an antidepressant is to be prescribed in routine care, it should be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects. (A)

8.1.7.7 When prescribing an SSRI, consideration should be given to using a product in a generic form. Fluoxetine and citalopram, for example, would be reasonable choices because they are generally associated with fewer discontinuation/withdrawal symptoms. However, fluoxetine is associated with a higher propensity for drug interactions. (C)

8.1.7.8 If a depressed patient being treated with an SSRI develops increased agitation early in treatment, the prescriber should provide appropriate information, and if the patient prefers the drug should be changed to a different antidepressant. Alternatively, a brief period of concomitant treatment with a benzodiazepine should be considered, followed by a clinical review within two weeks. (C)

8.1.7.9 If the response to a standard dose of an antidepressant is inadequate, and there are no significant side effects, a gradual increase in dose should be considered in line with the schedule suggested by the Summary of Product Characteristics. (C)

8.1.7.10 Prescribers should consider switching to another antidepressant if there has been no response at all after one month, but if there has been a partial response, a decision to switch can be postponed until six weeks. (C)

8.1.7.11 If an antidepressant has not been effective or is poorly tolerated and – after consideration of a range of other treatment options – the decision is made to offer a further course of antidepressants, then another single antidepressant should be prescribed. (C)

8.1.7.12 Reasonable choices for a second antidepressant include a different SSRI or mirtazapine, but consideration may also be given to other alternatives, including moclobemide, reboxetine, and tricyclic antidepressants (except dosulepin). (B)

8.1.7.13 Before prescribing mirtazapine, practitioners should take into account its propensity to cause sedation and weight gain. (A)

8.1.7.14 Before prescribing moclobemide, practitioners should take into account the need to wash out previously prescribed antidepressants. (A)

8.1.7.15 Before prescribing reboxetine, practitioners should take into account the relative lack of data on side effects. Patients taking reboxetine should be monitored carefully. (B)

8.1.7.16 Before prescribing tricyclic antidepressants, practitioners should take into account their poorer tolerability compared with other equally effective antidepressants, the increased risk of cardiotoxicity and their toxicity in overdose. (B)

8.1.7.17 Dosulepin should not be initiated routinely because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose. (C)

8.1.7.18 When a patient's depression fails to respond to the first antidepressant prescribed, the prescriber should check that the drug has been taken regularly and in the prescribed dose. (GPP)

8.1.7.19 When switching from one antidepressant to another, prescribers should be aware of the need for gradual and modest incremental increases of dose, of interactions between antidepressants and the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed. Features include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus. (C)

8.1.7.20 Where a tricyclic is chosen as an antidepressant, lofrepramine is a reasonable choice because of its relative lack of cardiotoxicity. (C)

8.1.7.21 Dosulepin, phenelzine, combined antidepressants, and lithium augmentation of antidepressants should only be routinely initiated by specialist mental health practitioners, including General Practitioners with a Special Interest in Mental Health. (GPP)

8.1.7.22 Venlafaxine treatment should only be initiated by specialist mental health medical practitioners, including General Practitioners with a Special Interest in Mental Health. (C)

8.1.7.23 Venlafaxine treatment should only be managed under the supervision of specialist mental health medical practitioners, including General Practitioners with a Special Interest in Mental Health. (C)

8.1.7.24 Before prescribing venlafaxine, practitioners should take into account the increased likelihood of patients stopping treatment because of side effects, compared with equally effective SSRIs. (A)

8.1.7.25 Before prescribing venlafaxine, practitioners should take into account its higher propensity for discontinuation/withdrawal symptoms if stopped abruptly, its toxicity in overdose and its higher cost. (C)

8.1.7.26 Although there is evidence that St John's wort may be of benefit in mild or moderate depression, healthcare professionals should not prescribe or advise its use by patients because of uncertainty about appropriate doses, variation in the nature of preparations and potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anticonvulsants). (C)

8.1.7.27 Patients who are taking St John's wort should be informed of the different potencies of the preparations available and the uncertainty that arises from this. They should also be informed of the potential serious interactions of St John's wort with other drugs (including oral contraceptives, anticoagulants and anticonvulsants. (C)

8.2 Factors that influence choice of antidepressant

8.2.1 Introduction

Whilst the previous section reviewed the relative efficacy of different antidepressants, this section looks at factors that may affect the choice of antidepressant.

The section reviews the following:

- The pharmacological management of depression in older adults
- The effect of gender on the pharmacological management of depression
- The pharmacological management of psychotic depression
- The pharmacological management of atypical depression
- The pharmacological management of relapse prevention
- Dosage issues
- Antidepressant discontinuation symptoms
- The cardiotoxicity of antidepressants
- Depression, suicide and antidepressants.

8.2.2 The pharmacological management of depression in older adults

8.2.2.1 Introduction

Depression is the most common mental health problem of later life affecting approximately 15% of older people (Beekman *et al.*, 1999). Untreated it shortens life and increases healthcare costs, as well as adding to disability from medical illnesses, and is the leading cause of suicide amongst older people (Lebowitz *et al.*, 1997). Most depression in older adults is treated in primary care (Plummer *et al.*, 1997) but there is evidence of poor detection (ibid.) and sub-optimal treatment (Iliffe *et al.*, 1991). In this population the monitoring of self-harm is particularly important. It is also very important to educate the patient and caregivers about depression and involve them in treatment decisions. Older adults are at risk of co-existing physical disorders, sensory deficits and other disabilities and, therefore, medication needs to be carefully monitored in these groups.

The efficacy of antidepressants in older adults has been summarised in a Cochrane systematic review (Wilson *et al.*, 2001). There is some evidence that older people take longer to recover than younger adults and adverse events need to be carefully monitored for, since they might substantially affect function in a vulnerable individual.

There are a variety of potential differences in older adults in terms of absorption and metabolism of drugs and increased potential for interaction with other drugs. The maxim is, therefore, to start low and increase slowly but it is clear that much more research involving older patients with depression is required on this and other points.

It was possible to review the following pharmacological strategies for the treatment of depression in older adults:

- Use of individual antidepressants: amitriptyline, TCAs as a group, SSRIs, phenelzine, mirtazapine, venlafaxine and St John's wort (studies were also available for reboxetine but, since this drug is not licensed for the treatment of depression in older adults, this drug is not reviewed)
- Augmentation of an antidepressant with lithium
- Strategies for relapse prevention.

8.2.2.2 Use of individual antidepressants in the treatment of depression in older adults

8.2.2.2.1 Studies considered for review

This review brings together studies from other reviews undertaken for this guideline where more than 80% of study participants were aged 65 years and over.
A separate systematic search of the literature was not undertaken and, therefore, studies undertaken with elderly populations using drugs not reviewed for this guideline are not included.

In all, 15 studies from other reviews of individual antidepressants enrolled participants who were at least 60 years of age (COHN1990, DORMAN1992, FEIGHNER1985A, GEORGOTAS86, GERETSEGGER95, GUILLIBERT89, HARRER99, HUTCHINSON92, LAPIA1992, MAHAPATRA97, PELICIER1993, PHANJOO1991, RAHMAN1991, SCHATZBERG02, SMERALDI98). Ten studies were sourced from the review of SSRIs, two from venlafaxine and one each from mirtazapine, phenelzine and St John's wort. Studies were included provided the mean dose achieved was at least half the 'standard' adult dose. Efficacy data were available from up to 1083 patients, and tolerability data from up to 1620 patients.

All included studies were published between 1985 and 2002. Two were classified as inpatient, eight as outpatient and one as primary care. In four, participants were either from mixed sources or it was not possible determine the source. Studies ranged from five to eight weeks long.

8.2.2.2.2 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference on reducing depression symptoms in older adults:

- between amitriptyline and paroxetine (N = 2; *n* = 126; SMD = –0.1; 95% CI, –0.46 to 0.27)
- between SSRIs and alternative antidepressants (N = 8; *n* = 602; SMD = –0.01; 95% CI, –0.17 to 0.15)
- between venlafaxine and TCAs (N = 2; *n* = 202; SMD = 0.02; 95% CI, –0.26 to 0.29)
- between alternative antidepressants and TCAs (N = 6, *n* = 443; SMD = 0.00; 95% CI, –0.19 to 0.19)
- between St John's wort and fluoxetine (N = 1; *n* = 149; SMD = –0.04; 95% CI, –0.36 to 0.28)
- between mirtazapine and paroxetine (N = 1, *n* = 254; SMD = –0.12; 95% CI, –0.37 to 0.13).

There is insufficient evidence to determine if there is a clinically significant difference in older adults on increasing the likelihood of achieving a 50% reduction in depression symptoms between:

- amitriptyline and paroxetine
- venlafaxine and TCAs
- alternative antidepressants and TCAs
- St John's wort and fluoxetine
- mirtazapine and paroxetine.

There is evidence suggesting that there is no clinically significant difference between mirtazapine and paroxetine on increasing the likelihood of achieving remission in older adults (N = 1, *n* = 254; RR = 0.87; 95% CI, 0.73 to 1.03).

There is insufficient evidence to determine if there is a clinically significant difference in older adults on increasing the likelihood of achieving remission:

- between phenelzine and nortriptyline
- alternative antidepressants and TCAs.

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring mirtazapine over paroxetine on reducing the likelihood of older adults leaving treatment early due to side effects (N = 1, *n* = 254; RR = 0.57; 95% CI, 0.34 to 0.94).

There is evidence suggesting that there is no clinically significant difference between alternative antidepressants and TCAs on reducing the likelihood of older adults reporting adverse effects (N = 7, *n* = 581; RR = 0.89; 95% CI, 0.79 to 1.02).

There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of older adults leaving treatment early between:

- amitriptyline and SSRIs (N = 3; *n* = 422; RR = 0.89; 95% CI, 0.7 to 1.12)
- SSRIs and alternative antidepressants (N = 10; *n* = 1,115; RR = 0.96; 95% CI, 0.82 to 1.13)
- alternative antidepressants and TCAs (N = 10; *n* = 1058; RR = 0.97; 95% CI, 0.83 to 1.13).

There is evidence suggesting that there is no clinically significant difference between SSRIs and alternative antidepressants on reducing the likelihood of older adults leaving treatment early due to side effects (N = 10; *n* = 1154; RR = 1; 95% CI, 0.81 to 1.23).

There is evidence suggesting that there is no clinically significant difference on reducing the likelihood of older adults reporting adverse events between:

- SSRIs and alternative antidepressants (N = 8; *n* = 717; RR = 0.95; 95% CI, 0.85 to 1.05)
- phenelzine and nortriptyline (N = 1; *n* = 60; RR = 0.97; 95% CI, 0.87 to 1.09
- mirtazapine and paroxetine (N = 1, *n* = 254; RR = 0.97; 95% CI, 0.86 to 1.09).

There is insufficient evidence to determine if there is a clinically significant difference between other drug comparisons on other tolerability measures.

Effect of setting on treatment efficacy and tolerability

There is evidence suggesting that there is no clinically significant difference between SSRIs and TCAs on reducing depression symptoms in older inpatients (N = 2; *n* = 95; SMD = –0.07; 95% CI, –0.48 to 0.33).

There is insufficient evidence to determine any difference on any efficacy measure in older outpatients or patients in primary care.

There is some evidence suggesting that there is a clinically significant difference favouring paroxetine over amitriptyline on reducing the likelihood of older adults in primary care reporting adverse effects (N = 1; *n* = 90; RR = 0.55; 95% CI, 0.35 to 0.86).

There is insufficient evidence to determine any difference on tolerability measures for any other patient setting.

8.2.2.3 Augmentation of an antidepressant with lithium in older adults

8.2.2.3.1 Studies considered for review

In the review of lithium augmentation all participants in one study (JENSEN1992) were aged 65 years or over. This was of inpatients, and compared nortriptyline (25 to 100 mg, median = 75 mg) plus lithium with nortriptyline (50 to 100 mg, median = 75 mg) plus placebo.

8.2.2.3.2 Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on increasing the likelihood of achieving remission in older adults (N = 1; *n* = 44; RR = 2.28; 95% CI, 1.09 to 4.78).

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring nortriptyline alone over nortriptyline plus lithium on reducing the likelihood of older adults leaving treatment early (N = 1; *n* = 44; RR = 5.02; 95% CI, 1.26 to 20.07).

There is insufficient evidence to determine if there is a clinically significant difference between nortriptyline plus lithium and nortriptyline alone on reducing the likelihood of older adults leaving treatment early due to side effects (N = 1; *n* = 44; RR = 5.48; 95% CI, 0.72 to 41.82).

8.2.2.4 Relapse prevention in older adults

8.2.2.4.1 Studies considered for review

Five studies looked at relapse prevention in older adults (all at least 65 years of age or with a mean age of 65 years) (ALEXOPOULOS2000, COOK1986, GEORGOTAS1989, KLYSNER2002, WILSON2003), one in patients in primary care (WILSON2003) and four in outpatients (ALEXOPOULOS00, COOK1986, GEORGOTAS1989, KLYSNER2002).

8.2.2.4.2 Evidence statements

In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo there is strong evidence suggesting that there is a clinically significant difference favouring continuing treatment with antidepressants over discontinuing antidepressants on reducing the likelihood of relapse in elderly patients (N = 5; *n* = 345; RR = 0.55; 95% CI, 0.43 to 0.71).

Where there was sufficient evidence, there was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

8.2.2.5 Clinical summary

There is no difference in the efficacy of the various antidepressants for which studies have been undertaken in older adults. There is also no evidence of differences in acceptability. There is no evidence that there is a difference by setting, apart from in primary care, where fewer patients taking paroxetine report adverse events compared with those taking amitriptyline.

With regard to augmenting an antidepressant with lithium, elderly patients appear to be more likely to achieve remission without the addition of lithium. These patients are also less likely to leave treatment early.

It appears to be worthwhile continuing pharmacological treatment in elderly patients with multiple depressive episodes in order to avoid relapse.

These results are similar to those found in the reviews of studies for all adult patients elsewhere in this guideline.

8.2.2.6 Recommendations for the pharmacological management of depression in older adults

8.2.2.6.1 For older adults with depression, antidepressant treatment should be given at an age-appropriate dose for a minimum of six weeks before treatment is considered to be ineffective. If there has been a partial response within this period treatment should be continued for a further six weeks. (C)

8.2.2.6.2 Healthcare professionals should be aware of the increased frequency of drug interactions when prescribing an antidepressant to older adults who are taking other medications. (GPP)

8.2.2.6.3 When prescribing antidepressants – in particular tricyclics – for older adults with depression, careful monitoring for side effects should be undertaken. (C)

8.2.2.6.4 Depression in patients with dementia should be treated in the same way as depression in other older adults. (C)

8.2.2.6.5 Healthcare professionals should be aware that depression responds to antidepressants even in the presence of dementia. (C)

8.2.2.7 Research recommendations

8.2.2.7.1 Further research is needed on all aspects of the pharmacological treatment of depression in the elderly, in particular in those older than 80 years. There is a special need for research evidence on optimum treatment and maintenance doses for elderly people.

8.2.3 The effect of gender on the pharmacological management of depression

8.2.3.1 Introduction

Although the female preponderance in the prevalence of unipolar depression has been well established (Weissman *et al.*, 1993) little attention has been paid to gender differences in treatment response to antidepressant medication. A meta-analysis of 35 studies published between 1957 and 1991 that reported imipramine response rates separately by gender reported that men responded more favourably to imipramine than did women (Hamilton *et al.*, 1996). Kornstein *et al.* (2000) in a study of 635 patients with chronic depression showed a trend towards men responding more positively to imipramine compared with sertraline (RR = 0.76, 95% CIs 0.55 to 1.02), whilst there was some evidence that women responded more positively to sertraline rather than imipramine (RR = 0.80, 95% CIs 0.66 to 0.98). In this study women taking imipramine were more likely to leave the study early compared with those taking sertraline (n = 400; RR = 0.53, 95% CIs 0.35 to 0.80); this difference was not present for men. A study which compared tricyclic antidepressants and monoamine oxidase inhibitors found that in patients with atypical depression and associated panic attacks, women showed a more favourable response to MAOIs and men to tricyclic antidepressants (Davidson & Pelton, 1986). These differential response patterns suggest that gender should be considered when making treatment decisions. There are a number of possible mechanisms whereby gender may influence treatment response. Drugs with effects on the serotonergic system may be relevant for younger women since serotonergic agents have demonstrated efficacy in disorders such as premenstrual dysphoric disorder (Thase *et al.*, 2000). Secondly the presence of atypical depression may modify treatment responsivity and women are more likely to present with atypical depressive symptoms (Kornstein, 1997). Another explanation is that female reproductive hormones may play a permissive or inhibitory role in antidepressant activity. For example, oestrogen may enhance serotonergic activity (Halbreich *et al.*, 1995).

8.2.3.2 Data reviewed

The data used in this section comprised individual patient data from published trials undertaken by Quitkin and colleagues and supplied by them to the NCCMH review team. This is, therefore, not a systematic review. The data included gender, diagnosis, study drug, and baseline and endpoint HRSD scores. Patient data was included only from those diagnosed with major depressive disorder regardless of additional diagnoses (67% of patients were diagnosed with depression with atypical features). The study drugs included were TCAs and phenelzine. These were compared with placebo and with each other. The data were analysed for men and women separately.

8.2.3.3 Evidence statements for TCAs versus placebo

In men there is evidence suggesting that there is no clinically significant difference between TCAs and placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms (n = 157; RR = 0.89; 95% CI, 0.75 to 1.06).

In women there is some evidence suggesting that there is a clinically significant difference favouring TCA over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms (n = 246; RR = 0.82; 95% CI, 0.7 to 0.95).

In men there is insufficient evidence to determine whether there is a clinically significant difference between TCAs and placebo on increasing the likelihood of achieving remission (n = 157; RR = 0.87; 95% CI, 0.73 to 1.04).

In women there is evidence suggesting that there is a statistically significant difference favouring TCAs over placebo on increasing the likelihood of achieving remission in women, but the size of this difference is unlikely to be of clinical significance (n = 246; RR = 0.84; 95% CI, 0.73 to 0.97).

In men there is evidence suggesting that there is no clinically significant difference between TCAs and placebo on reducing depression symptoms as measured by the HRSD (n = 157; WMD = –1.29; 95% CI, –2.87 to 0.28).

In women there is evidence suggesting that there is a statistically significant difference favouring TCAs over placebo on reducing depression symptoms as measured by the HRSD, but the size of this difference is unlikely to be of clinical significance (n = 246; WMD = –1.62; 95% CI, –2.84 to –0.4).

8.2.3.4 Evidence statements for phenelzine versus placebo

Women do slightly better on phenelzine compared with placebo than men:

In men there is strong evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms in men (n = 134; RR = 0.64; 95% CI, 0.48 to 0.84).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms in women (n = 188; Random effects RR = 0.53; 95% CI, 0.31 to 0.91).

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on:

- increasing the likelihood of achieving remission (n = 134; RR = 0.66; 95% CI, 0.5 to 0.86)
- reducing depression symptoms as measured by the HRSD (n = 134; Random effects WMD = –5.02; 95% CI, –9.68 to –0.35).

In women there is strong evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on reducing depression symptoms as measured by the HRSD (n = 188; WMD = –6.27; 95% CI, –8.15 to –4.4).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over placebo on increasing the likelihood of achieving remission (n = 188; Random effects RR = 0.47; 95% CI, 0.25 to 0.89).

8.2.3.5 Evidence statements for TCAs versus phenelzine

It appears that women may do better on phenelzine than on TCAs compared with men:

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms (n = 131; RR = 1.41; 95% CI, 1.05 to 1.9).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms (n = 154; Random effects RR = 1.52; 95% CI, 0.92 to 2.52).

In men there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving remission (n = 131; RR = 1.32; 95% CI, 1 to 1.75).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on increasing the likelihood of achieving remission in women (n = 154; Random effects RR = 1.76; 95% CI, 1.01 to 3).

In men there is insufficient evidence to determine whether there is a clinically significant difference between phenelzine and TCAs on reducing depression symptoms as measured by the HRSD (n = 131; Random effects WMD = 3.21; 95% CI, –0.14 to 6.57).

In women there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs on reducing depression symptoms as measured by the HRSD (n = 154; WMD = 4.43; 95% CI, 2.47 to 6.4).

8.2.3.6 Clinical summary

In patients with chronic depression, women respond better to SSRIs than to TCAs, whereas there is some indication that men may respond better to TCAs. Imipramine was associated with less tolerability than sertraline in women; this was not the case for men.

Women treated in a specialist tertiary depression centre, the majority of whom have atypical depression, respond better to treatment with antidepressants than men, particularly to phenelzine. Men with this disorder treated in the same setting do not respond to TCAs, but do respond to phenelzine, although to a lesser extent than women.

Note that all this data comes from specific populations rather than a representative sample of people with major depressive disorder.

8.2.3.7 Recommendations for gender

8.2.3.7.1 When considering which antidepressants to prescribe for female patients, the fact that they have poorer tolerance of imipramine should be taken into account. (B)

8.2.3.7.2 Phenelzine should be considered for women whose depression is atypical, and who have not responded to, or who cannot tolerate, an SSRI. However, its toxicity in overdose should be considered when prescribing for patients at high risk of suicide. (C)

8.2.3.7.3 For male patients with chronic depression who have not responded to an SSRI, consideration should be given to a tricyclic antidepressant because men tolerate the side effects of tricyclic antidepressants reasonably well. (C)

8.2.4 The pharmacological management of psychotic depression

8.2.4.1 Introduction

Major depression with psychotic features is a disorder with considerable morbidity and mortality. In the epidemiologic catchment area study (Johnson *et al.*, 1991), 14.7% of patients who met the criteria for major depression had a history of psychotic features. The prevalence is higher in samples of elderly patients. The disorder is often not diagnosed accurately because the psychosis may be subtle, intermittent or concealed. There has been a long-standing debate as to whether major depression with psychotic features is a distinct syndrome or represents a more severe depressive subtype. The weight of evidence suggests that severity alone does not account for the differences in symptoms, biological features and treatment response (Rothschild, 2003). The systematic study of major depression with psychotic features has been limited by the fact that the disorder does not exist as a distinct diagnostic subtype in DSM-IV and because of the difficulties in enrolling such patients in research studies. As a result there are few controlled studies on the acute treatment of psychotic depression and no long-term maintenance studies. There is some evidence that patients with major depression with psychotic features exhibit more frequent relapses or recurrences than patients with non-psychotic depression though not all studies are in agreement (see Rothschild, 2003). Patients with major depression with psychotic features demonstrate more severe psychomotor disturbance more frequently than patients without psychosis.

8.2.4.2 Studies considered for review

Twenty studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985, ZANARDI1996, ZANARDI2000) and 14 of which did not, mainly because too many participants had been diagnosed with bipolar depression and, therefore, fell outside the inclusion criteria set by the GDG.

Four studies (ANTON1990, BELLINI1994, MULSANT2001, SPIKER1985) looked at augmenting an antidepressant with an antipsychotic and two (ZANARDI1996, ZANARDI2000) compared a single antidepressant with another. The following comparisons were possible:

- Amitriptyline plus perphenazine versus amoxapine
- Nortriptyline plus perphenazine versus nortriptyline plus placebo

[45] Four-armed trial (BELLINI1994).

- Amitriptyline plus perphenazine versus amitriptyline
- Desipramine plus haloperidol versus desipramine plus placebo[45]
- Fluvoxamine plus haloperidol versus fluvoxamine plus placebo[45]
- Paroxetine versus sertraline
- Fluvoxamine versus venlafaxine.

In comparisons involving antipsychotic augmentation, efficacy data were available from up to 103 participants and tolerability data from up to 87 participants. In comparisons comparing single antidepressants, both efficacy and tolerability data were available from up to 60 participants. All included studies were published between 1985 and 2001 and were between four days and 16 weeks (mean = 7.17 weeks).

All studies were of inpatients, and in one all patients were at least 50 years of age (mean 71) (MULSANT2001). Participants had a diagnosis of major depressive disorder with psychotic features. In two studies (ANTON1990, ZANARDI2000) up to 25% (the limit allowed in the inclusion criteria set by the GDG is 15%) of participants were diagnosed with bipolar disorder. Two sets of analyses were performed including and excluding these two studies. There was no difference in results, so statements from the analysis excluding these studies are presented below.

8.2.4.3 Evidence statements

Effect of treatment on efficacy

There is some evidence suggesting that there is a clinically significant difference favouring sertraline over paroxetine on increasing the likelihood of achieving remission as measured by the HRSD in patients with psychotic depression (N = 1; *n* = 32; RR = 2.83; 95% CI, 1.28 to 6.25).

There is insufficient evidence on any efficacy measure to determine if there is a clinically significant difference between a TCA plus an antipsychotic and either amoxapine or a TCA in patients with psychotic depression.

Acceptability and tolerability of treatment

There is insufficient evidence to determine if there is a clinically significant difference on the acceptability of treatment between:

- perphenazine augmentation of a tricyclic antidepressant and tricyclic monotherapy
- paroxetine and sertraline.

8.2.4.4 Clinical summary

There is no good quality evidence for pharmacological treatments of psychotic depression. However, there are practical problems in recruiting sufficient numbers of patients with psychotic depression and, therefore, practitioners may wish to consider lower levels of evidence.

8.2.4.5 Recommendations for the pharmacological management of psychotic depression

8.2.4.5.1 For patients with psychotic depression, augmenting the current treatment plan with antipsychotic medication should be considered, although the optimum dose and duration of treatment are unknown. (C)

8.2.4.6 Research recommendations for the pharmacological management of psychotic depression

8.2.4.6.1 An adequately powered RCT reporting all relevant outcomes should be undertaken to assess the efficacy of antipsychotics (both singly and in combination with antidepressants) in the treatment of psychotic depression.

8.2.5 The pharmacological management of atypical depression

8.2.5.1 Introduction

Depression with atypical features is described in DSM-IV (APA, 1994). The introduction of a formally defined type of depression with atypical features was in response to research and clinical data indicating that patients with atypical depression have specific characteristics. The classical atypical features are over-eating and over-sleeping (sometimes referred to as reverse vegetative symptoms). The syndrome is also associated with mood reactivity, leaden paralysis and a long-standing pattern of interpersonal rejection sensitivity. In comparison with major depressive disorder without atypical features, patients with atypical depression are more often female, have a younger age of onset and a more severe degree of psychomotor slowing. Co-existing diagnoses of panic disorder, substance misuse and somatisation disorder are common. The high incidence and severity of anxiety symptoms in these patients increases the likelihood of their being misclassified as having an anxiety disorder. The major treatment implication of atypical depression is that patients are said to be more likely to respond to a monoamine oxidase inhibitor than to tricyclic drugs. However, the significance of atypical features remains controversial as does the preferential treatment response to monoamine oxidase inhibitors. The absence of specific diagnostic criteria has limited the ability to assess the aetiology, prevalence and validity of the condition.

8.2.5.2 Studies considered for review

This section brings together studies from other reviews undertaken for this guideline where participants were diagnosed with atypical depression. A separate systematic search of the literature was not undertaken and, therefore, studies undertaken with atypical depression using drugs not reviewed for this guideline are not included.

In all, three studies from other reviews were of atypical depression (MCGRATH2000, PANDE1996, QUITKIN1990). Two came from the review of phenelzine and one from the review of SSRIs. Data were available to look at the efficacy of phenelzine compared with imipramine/desipramine or with fluoxetine, and fluoxetine compared with imipramine. But there was only tolerability data available for phenelzine compared with fluoxetine. Efficacy data were available from up to 334 patients, and tolerability data from up to 40 patients. All included studies were published between 1990 and 2000. Two were classified outpatient studies and in the other it was not possible to determine the source.

8.2.5.3 Evidence statements

Effect of treatment on efficacy

In people with atypical depression there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over other antidepressants (imipramine/desipramine and fluoxetine) on increasing the likelihood of achieving a 50% decrease in depression symptoms by the end of treatment as measured by the HRSD (N = 2; *n* = 232; RR= 0.69; 95% CI, 0.52 to 0.9).

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between phenelzine and other antidepressants on:

- increasing the likelihood of patients achieving remission by the end of treatment as measured by the HRSD (N = 2; *n* = 232; Random effects RR = 0.83; 95% CI, 0.39 to 1.75)

- reducing depression symptoms as measured by the HRSD (N = 2; *n* = 232; Random effects SMD = –0.31; 95% CI, –0.88 to 0.26).

In a sub-analysis by antidepressant class, there is some evidence suggesting that there is a clinically significant difference favouring phenelzine over TCAs (imipramine/desipramine) on:

- increasing the likelihood of patients achieving a 50% decrease in depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 192; RR = 0.68; 95% CI, 0.52 to 0.9)

- increasing the likelihood of patients achieving remission by the end of treatment as measured by the HRSD (N = 1; *n* = 192; RR = 0.65; 95% CI, 0.49 to 0.87)

- reducing depression symptoms as measured by the HRSD (N = 1; *n* = 192; WMD = –3.15; 95% CI, –4.83 to –1.47).

Compared with SSRIs (fluoxetine), there is evidence suggesting that there is no clinically significant difference between phenelzine and fluoxetine on reducing depression symptoms by the end of treatment as measured by the HRSD (N = 1; *n* = 40; WMD = 0.20; 95% CI, –2.11 to 2.51).

There is insufficient evidence to determine if there is a clinically significant difference between phenelzine and fluoxetine, or between fluoxetine and TCAs on any other efficacy measure.

Acceptability and tolerability of treatment

In people with atypical depression there is insufficient evidence to determine if there is a clinically significant difference between phenelzine and fluoxetine on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

8.2.5.4 Clinical summary

In patients with atypical depression there is some evidence suggesting a clinical advantage for phenelzine over TCAs (imipramine/desipramine) in terms of achieving remission and response. However, compared with SSRIs (fluoxetine), there is evidence of no difference on mean endpoint scores, and insufficient evidence on other outcome measures. There is insufficient evidence for the acceptability and tolerability of any antidepressant.

8.2.5.5 Recommendations for the pharmacological management of atypical depression

8.2.5.5.1 Patients whose depression has atypical features should be treated with an SSRI. (C)

8.2.5.5.2 All patients receiving phenelzine require careful monitoring (including taking blood pressure) and advice on interactions with other medicines and foodstuffs, and should have their attention drawn to the product information leaflet. (C)

8.2.5.5.3 Referral to mental health specialists should be considered for patients with atypical depression and significant functional impairment who have not responded to an SSRI. (GPP)

8.2.6 The pharmacological management of relapse prevention

8.2.6.1 Introduction

Major depressive disorder is among the most important causes of death and disability worldwide in both developing and developed countries (Murray & Lopez, 1997). Because of the long-term nature of depressive disorder, with many patients at substantial risk of later recurrence, there is a considerable need to establish how long such patients should stay on antidepressants. Existing clinical guidelines recommend that treatment should be continued for four to six months after the acute episode (Anderson *et al.*, 2000; American Psychiatric Association, 2000b; Bauer *et al.*, 2002a). There is a considerable variation in practice, suggesting that many patients do not receive optimum treatment. Recently Geddes *et al.* (2003a) reviewed all published and unpublished trials available for review by August 2000 in which continued antidepressant drug therapy was compared with placebo in patients who had responded to acute treatment with antidepressants. It was found that antidepressants reduced the risk of relapse in depressive disorder and continued treatment with antidepressants appeared to benefit many patients with recurrent depressive disorder. The treatment benefit for an individual patient depended on their absolute risk of relapse with greater absolute benefits in those at higher risk. It was estimated that for patients who were still at appreciable risk of recurrence after four to six months of treatment with antidepressants, another year of continuation treatment would approximately halve their risk. The authors found no evidence to support the contention that the risk of relapse after withdrawal from active treatment in the placebo group was due to a direct pharmacological effect (e.g. 'withdrawal' or 'rebound') since there was not an excess of cases within a month of drug discontinuation.

8.2.6.2 Studies considered for review

The GDG used the review by Geddes *et al.* (2003a) as the basis for this section. The original review included 37 studies of which 20 met the inclusion criteria set by the GDG. An additional five studies were identified in new searches, one of which was excluded. Another study was identified through searching journal tables of contents and a further study was identified from searches undertaken for the review of lithium augmentation elsewhere in this guideline. Both of these were included. Therefore, 26 studies form the basis of this review (ALEXOPOULOUS2000, BAUER2000, COOK1986, DOOGAN1992, FEIGER1999, FRANK1990, GEORGOTAS1989, GILABERTE2001, HOCHSTRASSER2001, KELLER1998, KISHIMOTO1994, KLYSNER2002, KUPFER1992, MONTGOMERY1988, MONTGOMERY1992, MONTGOMERY1993, PRIEN1984, REIMHERR1998, ROBERT1995, ROBINSON1991, SACKHEIM2001, SCHMIDT2000, TERRA1998, THASE2001, VERSIANI1999, WILSON2003) and 18 were excluded.

Studies included a pre-maintenance phase during which participants continued to receive medication after they had achieved remission. This was followed by a maintenance phase in which participants who had achieved remission were randomised either to pharmacological treatment or to placebo. Studies were included provided participants were classified as remitted only if they no longer met diagnosis for major depression or had achieved an HRSD or MADRS score below the cut-off for mild depression. Similarly, studies were included only if participants had been assessed as having relapsed using some kind of formal criteria such as exceeding a specific HRSD or MADRS score or meeting formal diagnostic criteria for depression rather than clinical judgement alone.

A single outcome, number of study participants experiencing relapse, was extracted. Since the length of both the pre-maintenance and the maintenance phase varied between studies, sub-analyses were undertaken splitting the data set as follows:

- by length of continuation treatment (i.e. length of time continued with medication after remission but before randomisation) – less than or more than six months
- by length of maintenance treatment – less than or more than 12 months.

The longest maintenance phase was two years. Further sub-analyses were undertaken combining these factors – for example, studies with pre-maintenance treatment of less than six months and maintenance treatment of less than 12 months.

Twelve studies used an SSRI as the maintenance treatment (2342 participants), seven studies used a TCA (363 participants), and five studies used other antidepressants (651 participants). Three studies (BAUER2000, PRIEN1984, SACKHEIM2001) compared lithium (with and without an antidepressant) with an antidepressant or placebo[46]. Twenty-one studies used the same treatment in both acute and maintenance phases, and three did not.

All included studies were published between 1984 and 2003. In 17 studies participants were described as outpatients, one was from primary care and in the other eight it was either not clear from where participants were sourced or they were from mixed sources. There were no studies of inpatients. Five studies were classified elderly, and none was of atypical depression.

[46] One four-arm trial (PRIEN1984) has both antidepressant and lithium treatment groups.

Of the 24 trials of antidepressant medication, 12 (BAUER2000, COOK1986, FRANK1990, GILABERTE2001, HOCHSTRASSER2001, KISHIMOTO1994, KUPFER1992, MONTGOMERY1988, MONTGOMERY1993, ROBINSON1991, TERRA1998, VERSIANI1999) included only participants who had had at least one previous depressive episode. Five studies (ALEXOPOULOS2000, FEIGER1999, KLYSNER2002, THASE2001, WILSON2003) were of participants with a mix of first episode and previous episode depression. For the purpose of a sub-analysis by number of episodes, two of these (KLYSNER2002, WILSON2003) were classified first episode since more than 70% of participants were in their first episode. In the remaining seven studies (DOOGAN1992, GEORGOTAS1989, KELLER1998, MONTGOMERY1992, ROBERT1995, SCHMIDT2000, SACKHEIM2001) it was not possible to assess the proportion of participants with first or subsequent episode depression. Additional sub-analyses were undertaken by number of previous episodes.

8.2.6.3 Evidence statements

Effect of treatment on relapse

In an analysis of all available data comparing maintenance treatment with an antidepressant with placebo, there is strong evidence suggesting that there is a clinically significant difference favouring continuing antidepressant treatment over discontinuing antidepressant treatment on reducing the likelihood of relapse (N = 24; *n* = 3356; RR = 0.43; 95% CI, 0.39 to 0.48).

There was little difference in the results of sub-analyses by length of pre-randomisation treatment or by post-randomisation treatment, by a combination of these factors, or between results for SSRIs and TCAs analysed separately. Nor was any difference found for patients in their first episode or for those with previous episodes.

With regard to lithium augmentation:

There is some evidence suggesting that there is a clinically significant difference on reducing the likelihood of relapse favouring continuing lithium augmentation of an antidepressant over:

- discontinuing lithium (i.e. continuing on antidepressant monotherapy) (N = 3; *n* = 160; RR = 0.58; 95% CI, 0.37 to 0.92).

- discontinuing lithium and antidepressant treatment (i.e. taking a placebo) (N = 2; *n* = 129; RR = 0.42; 95% CI, 0.28 to 0.64).

In patients who have achieved remission whilst taking an antidepressant plus lithium, there is some evidence suggesting that there is a clinically significant difference favouring discontinuing lithium treatment (i.e. continuing with the antidepressant alone) over discontinuing antidepressant treatment (i.e. continuing lithium alone) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N = 1; *n* = 77; RR = 1.75; 95% CI, 1.03 to 2.96).

In patients who have achieved remission whilst taking an antidepressant plus lithium there is insufficient evidence to determine if there is a clinically significant difference between discontinuing antidepressant treatment (i.e. continuing with lithium alone)

and discontinuing antidepressant and lithium treatment (i.e. taking a placebo) on reducing the likelihood of patients experiencing a relapse in depression symptoms (N =1; *n* =71; RR = 0.88; 95% CI, 0.60 to 1.28).

8.2.6.4 Clinical summary

The majority of study participants had experienced multiple depressive episodes. There is strong evidence that responders to medication, who have had multiple relapses, should stay on medication to avoid relapse, irrespective of the length of treatment pre-response (between six weeks and 12 months). This effect holds true beyond 12 months. From the available data, it is not possible to determine effects beyond two years. These effects were evident with both TCAs and SSRIs. Whether this effect is evident in those recovering from a first episode or with placebo is unknown. Since most studies randomised participants either to continue with medication or to a placebo, there is little data comparing lengths of maintenance treatment with active medication.

It is worthwhile continuing treatment for up to two years. For patients who have achieved remission whilst taking lithium in addition to an antidepressant it appears to be worthwhile continuing treatment. If one or other drug is stopped the evidence suggests that lithium should be stopped in preference to the antidepressant.

8.2.6.5 Recommendations for relapse prevention

8.2.6.5.1 Antidepressants should be continued for at least six months after remission of an episode of depression because this greatly reduces the risk of relapse. (A)

8.2.6.5.2 When a patient has taken antidepressants for six months after remission, healthcare professionals should review with the patient the need for continued antidepressant treatment. This review should include consideration of the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties. (C)

8.2.6.5.3 Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for two years. (B)

8.2.6.5.4 Patients on maintenance treatment should be re-evaluated, taking into account age, comorbid conditions and other risk factors in the decision to continue maintenance treatment beyond two years. (GPP)

8.2.6.5.5 The antidepressant dose used for the prevention of recurrence should be maintained at the level at which acute treatment was effective. (C)

8.2.6.5.6 Patients who have had multiple episodes of depression, and who have had a good response to treatment with an antidepressant and lithium augmentation, should remain on this combination for at least six months. (B)

8.2.6.5.7 When one drug is to be discontinued in a patient taking an antidepressant with lithium augmentation, this should be lithium in preference to the antidepressant. (C)

8.2.6.5.8 The use of lithium as a sole agent to prevent recurrence of depression in patients with previous recurrences is not recommended. (C)

8.2.6.6 Research recommendations

8.2.6.6.1 Long-term trials of maintenance treatment with antidepressants are needed to determine the optimum dose and duration of treatment.

8.2.6.6.2 Adequately powered RCTs reporting all relevant outcomes, including relapse rates and adverse events, comparing the effectiveness of different antidepressants should be undertaken in order to identify differential individual response to treatment, including how this relates to gender and ethnicity.

8.2.7 Dosage issues

8.2.7.1 Low-dose versus high-dose TCAs

There is controversy over whether the existing recommended dosages for TCAs (100 mg/day, Bollini *et al.*, 1999) are too high. Some GPs are criticised for prescribing at doses that are too low, and evidence for dosing levels has not been established (Furukawa *et al.*, 2002a). This review compares the efficacy and tolerability of low and high doses of TCAs. Low doses were those where the mean dose achieved was less than the equivalent of 100 mg of amitriptyline.

8.2.7.2 Studies considered for review

The GDG used an existing review (Furukawa *et al.*, 2002a) as the basis for this review. The original review included 38 studies of which 33 did not meet the inclusion criteria set by the GDG, mainly because of inadequate diagnosis of depression. Therefore, five trials (BURCH1988, DANISH1999, ROUILLON1994, SIMPSON1988, WHO1986) are included in this review providing data from up to 222 participants.

All included studies were published between 1988 and 1999 and were between four and eight weeks long (mean = six weeks). One study was of inpatients and two of outpatients, with none in primary care. Patients in one study were from mixed sources (DANISH1999). It was not possible to discern setting in WHO1986. No study included all elderly participants or those whose depression has atypical features. Study inclusion criteria ensured a minimum HRSD score at baseline of between 16 and 22 or a MADRS score of 15.

Data were available to compare low doses with high doses of clomipramine, amitriptyline, trimipramine and imipramine. Data were also available to compare low-dose clomipramine with placebo.

Mean low dose was 60.8 mg (total range 25 mg to 75 mg) and mean high dose was 161.9 mg (total range 75 mg to 200 mg) (low-dose versus high-dose studies).

8.2.7.3 Evidence statements

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically significant difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving remission by the end of treatment (N = 3; *n* = 222; RR = 0.99; 95% CI, 0.84 to 1.16).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving a 50% reduction in depression symptoms or on reducing depression symptoms as measured by the HRSD.

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and placebo on reducing depressions symptoms by the end of treatment as measured by the MADRS or on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD.

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring low-dose TCAs over high-dose TCAs on leaving the study early due to side effects (N = 1; *n* = 151; RR = 0.35; 95% CI, 0.16 to 0.78).

There is insufficient evidence to determine whether there is a clinically significant difference between low-dose TCAs and high-dose TCAs on reducing the likelihood of patients leaving treatment early.

8.2.7.4 Clinical summary

There is no clinically significant difference on achieving response between low-dose TCAs (mean dose = 60.8 mg) and therapeutic dose TCAs (mean dose = 161.9 mg). Of the four studies that compared low-dose TCA with high-dose TCA, two reported completer data only. Patients receiving a low-dose TCA were less likely to leave treatment early due to side effects.

8.2.7.5 Recommendations on dose

8.2.7.5.1 Patients who start on low-dose tricyclic antidepressants and who have a clear clinical response can be maintained on that dose with careful monitoring. (C)

8.2.7.5.2 Patients started on low-dose tricyclic antidepressants should be carefully monitored for side effects and efficacy and the dose gradually increased if there is lack of efficacy and no major side effects. (GPP)

8.2.8 Antidepressant discontinuation/withdrawal symptoms

8.2.8.1 Introduction

Although antidepressants are not associated with tolerance and craving, such as are experienced when withdrawing from addictive substances such as opiates or alcohol, some patients experience symptoms when stopping antidepressants or reducing the dose. In this guideline they are referred to as discontinuation/withdrawal symptoms.

They may be new or hard to distinguish from some of the original symptoms of the underlying illness. By definition they must not be attributable to other causes. They are experienced by at least a third of patients (Lejoyeux *et al.*, 1996; MHRA, 2004).

The onset is usually within five days of stopping treatment, or occasionally during taper or after missed doses (Rosenbaum *et al.*, 1998; Michelson *et al.*, 2000). This is influenced by a number of factors, which may include a drug's half-life. Symptoms can vary in form and intensity and occur in any combination. They are usually mild and self-limiting, but can occasionally be severe and prolonged, particularly if withdrawal is abrupt. Some symptoms are more likely with individual drugs (Lejoyeux *et al.,* 1996; Haddad, 2001) (see Table 1 below).

Table 1

	MAOIs	**TCAs**	**SSRIs and venlafaxine**
	Common		
Symptoms	Agitation Irritability Ataxia Movement disorders Insomnia Somnolence Vivid dreams Cognitive impairment Slowed speech Pressured speech	'Flu-like symptoms (chills, myalgia, excessive sweating, headache, nausea) Insomnia Excessive dreaming	'Flu-like symptoms 'Shock-like' sensations Dizziness exacerbated by movement Insomnia Excessive dreaming Irritability Crying spells
	Occasional		
	Hallucinations Paranoid delusions	Movement disorders Mania Cardiac arrhythmias	Movement disorders Problems with concentration and memory

8.2.8.2 Factors affecting the development of discontinuation/withdrawal symptoms

Although anyone can experience discontinuation/withdrawal symptoms, the risk is increased in those prescribed short half-life drugs (Rosenbaum *et al.*, 1998), such as paroxetine and venlafaxine (Hindmarch *et al.*, 2000; Fava *et al.*, 1997; MHRA, 2004). They can also occur in patients who do not take their medication regularly. Two-thirds of patients prescribed antidepressants skip a few doses from time to time (Meijer et al, 2001). The risk is also increased in those who have been taking antidepressants for eight weeks or longer (Haddad, 2001); those who developed anxiety symptoms at the start of antidepressant therapy (particularly with SSRIs); those receiving other centrally acting medication (eg antihypertensives, antihistamines, antipsychotics); children and adolescents; and those who have experienced discontinuation/withdrawal symptoms before (Lejoyeux & Ades, 1997; Haddad, 2001).

Discontinuation/withdrawal symptoms may also be more common in those who relapse on stopping antidepressants (Zajecka *et al.*, 1998; Markowitz *et al.*, 2000).

8.2.8.3 Clinical relevance

The symptoms of a discontinuation/withdrawal reaction may be mistaken for a relapse of illness or the emergence of a new physical illness (Haddad, 2001) leading to unnecessary investigations or reintroduction of the antidepressant. Symptoms may be severe enough to interfere with daily functioning. Another point of clinical relevance is that patients who experience discontinuation/withdrawal symptoms may assume that this means that antidepressants are addictive and not wish to accept further treatment. It is very important to counsel patients before, during and after antidepressant therapy about the nature of this syndrome.

8.2.8.4 How to avoid

Generally, antidepressant therapy should be discontinued over at least a four-week period (this is not required with fluoxetine) (Rosenbaum *et al.*, 1998). The half-life of the drug should be taken into account. The end of the taper may need to be slower as symptoms may not appear until the reduction in the total daily dosage of the antidepressant is substantial. Patients receiving MAOIs may need dosage to be tapered over a longer period. Tranylcypromine may be particularly difficult to stop. It is not clear if the need for slow discontinuation/withdrawal of MAOIs, and particularly tranylcypromine, is due to the discontinuation/withdrawal syndrome or the loss of other neurochemical effects of these drugs. Since it is not possible to disentangle these phenomena, the clinical advice is that patients on MAOIs and those at risk patients (see above) need a slower taper (Haddad, 2001).

8.2.8.5 How to treat

There are no systematic randomised studies in this area. Treatment is pragmatic. If symptoms are mild, reassure the patient that these symptoms are not uncommon after discontinuing an antidepressant and that they will pass in a few days. If symptoms are severe, reintroduce the original antidepressant (or another with a longer half-life from the same class) and taper gradually while monitoring for symptoms (Lejoyeux & Ades, 1997; Haddad, 2001).

8.2.8.6 Recommendations regarding discontinuation/withdrawal symptoms

8.2.8.6.1 All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects and of the risk of discontinuation/withdrawal symptoms. (C)

8.2.8.6.2 All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly. (C)

8.2.8.6.3 Patients should be advised to take the drugs as prescribed. This may be particularly important for drugs with a shorter half-life, such as paroxetine, in order to avoid discontinuation/withdrawal symptoms. (C)

8.2.8.6.4 Healthcare professionals should normally gradually reduce the doses of the drug over a four-week period, although some people may require longer periods. Fluoxetine can usually be stopped over a shorter period. (C)

8.2.8.6.5 If discontinuation/withdrawal symptoms are mild, practitioners should reassure the patient and monitor symptoms. If symptoms are severe, the practitioner should consider reintroducing the original antidepressant at the dose that was effective for another antidepressant with a longer half-life from the same class) and reduce gradually while monitoring symptoms. (C)

8.2.8.6.6 Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. (GPP)

8.2.9 The cardiotoxicity of antidepressants

Consistent associations between depression and cardiovascular morbidity and mortality have been identified (Glassman & Shapiro, 1998). Depression is a significant independent risk factor for both first myocardial infarction and cardiovascular mortality with an adjusted relative risk in the range of 1.5 to 2 (Ford *et al.*, 1998). In patients with ischaemic heart disease, depression has been found to be associated with a three- to four-fold increase in cardiovascular morbidity and mortality (Carney *et al.*, 1997). The prevalence of major depression in patients with coronary heart disease is approximately 20% (Glassman *et al.*, 2002).

In view of the above associations and factors it is important to use antidepressant drugs that either reduce or do not increase the cardiovascular risk of the condition itself and to establish a safe and effective treatment strategy for depressed patients with heart disease. There is evidence that adequate treatment of depression appears either to lower (Avery & Winokur, 1976) or not to change (Pratt *et al.*, 1996) the risk of heart disease. However, two large-scale follow-up studies have shown an increase in myocardial infarction in users of antidepressants with an average odds ratio of 5.8 (Penttinen & Valonen, 1996; Thorogood *et al.*, 1992). Recently a similar association has been identified in the UK for dothiepin/dosulepin (Hippisley-Cox *et al.*, 2001).

However, these studies do not distinguish between the effects of drugs and the condition itself. Thus it is necessary to look at the effects of antidepressants on cardiovascular function and what trials are available (Roose, 2003).

8.2.9.1 Tricyclic antidepressants

Sinus tachycardia, postural hypotension and episodic hypertension are side effects frequently observed. ECG changes are frequent, such as lengthening of the QT, PR and QRS intervals relating to alterations in AV conduction and repolarisation (Roose *et al.*, 1989). These effects are due to the wide-ranging pharmacological actions of TCAs that are not correlated with recognised mechanisms of antidepressant action. In healthy patients such changes may be asymptomatic or clinically unimportant, but in those with heart disease they may lead to significant morbidity and mortality (Glassman *et al.*, 1993). For example, prolonged increased heart rate (mean 11%, Roose & Glassman, 1989) could have a major impact in terms of cardiac work (Roose, 2003).
In patients with left ventricular impairment on TCAs, orthostatic hypotension is three to seven times more common and potentially clinically harmful (Glassman *et al*., 1993). The TCA induced prolongation of conduction may be clinically unimportant in healthy patients, but can lead to complications in those with conduction disease, in particular bundle branch block, and these can be severe in 20% of subjects (Roose *et al.*, 1987). TCAs may be regarded as Class I arrhythmic drugs. Evidence suggests that this class of drug is associated with an increase in mortality in post-infarction patients and in patients with a broader range of ischaemic disease, probably because they turn out to be arrhythmogenic when cardiac tissue becomes anoxic. Overdose of TCAs or elevated plasma levels as a result of interactions with other drugs, liver disease and age is associated with serious hypotension and atrial and ventricular arrthymias may arise even to the extent of complete AV block, which in a number of cases may be fatal (deaths from TCAs represent 20% of overdose deaths; Shah *et al.*, 2001).

Individual tricyclics

The tertiary amine tricyclics (amitriptyline, imipramine and clomipramine) have more cardiovascular effects than the secondary amine tricyclics (e.g. nortriptyline). The last drug has been shown to have less postural hypotension and, therefore, may be considered in those with cardiovascular disease and in the elderly in whom postural hypotension can be very hazardous. There is evidence (although not from an RCT) that lofepramine is safer in overdose than other tricyclics (Lancaster & Gonzalez, 1989).
It is thought that lofepramine blocks the cardiotoxic effects of the main metabolite desipramine. Dothiepin/dosulepin has marked toxicity in overdose in uncontrolled studies (Henry & Antao, 1992; Buckley *et al.*, 1994).

8.2.9.2 Selective serotonin reuptake inhibitors

Depression in untreated populations has been demonstrated to increase cardiovascular morbidity and mortality. SSRIs appear to reduce that risk, since two studies have reported no difference in cardiovascular risk between SSRI-treated depressed patients and non-treated non-depressed controls (Cohen *et al.*, 2000; Meier *et al.*, 2001). Recently Sauer *et al.* (2001) compared the rate of MI in patients on an SSRI with those on no antidepressants. The SSRI-treated patients had a significantly lower rate of MI than did the non SSRI-treated patients. Multiple studies (Roose, 2001) reveal no clinically

significant effects of SSRIs on heart rate, cardiac conduction or blood pressure (see further details below). Studies of depressed patients with and without ischaemic heart disease have documented increased platelet activation and aggregation, which potentially contributes to thrombus formation (Musselman *et al*., 1998). Treatment with SSRIs normalises elevated indices of platelet activation and aggregation seen in non-treated patients with depression and IHD. There is evidence that this effect occurs at relatively low doses and before the antidepressant effect (Pollock *et al.*, 2000). However, the effects on platelet serotonin are not always advantageous: SSRIs increase the probability of having a serious GI bleed, particularly in the very old (Walraven *et al.*, 2001).

8.2.9.3 Individual drugs

Citalopram

The cardiac safety of citalopram has been studied in prospective studies in volunteers and patients and in retrospective evaluations of all ECG data from 40 clinical trials (1789 citalopram-treated patients) (Rasmussen *et al.*, 1999). The only effect of citalopram was the reduction in heart rate (of eight beats per minute) but no other ECG change. There have been case reports of bradycardia with citalopram (Isbister *et al.*, 2001) and a low frequency of hypotension and arrhythmias including left bundle branch block (Mucci, 1997).

Fluoxetine

In a seven-week open trial of older adults with cardiac disease, Roose *et al.* (1998b) showed that fluoxetine caused no major cardiovascular change. Strik *et al.* (2000) showed that fluoxetine was safe in 27 patients with recent myocardial infarction (more than three months since the myocardial infarction) and there was no change in cardiovascular indices in these patients compared with placebo. However, fluoxetine did not demonstrate clinical efficacy in this group compared with placebo (n = 54; WMD = –2.50, 95% CI, –5.64 to 0.64). It is noteworthy that fluoxetine has significant potential to interact with drugs commonly used in the management of heart disease (Mitchell, 1997).

Fluvoxamine

Fluvoxamine has not been found to be associated with cardiovascular or ECG changes (Hewer *et al.*, 1995). Fluvoxamine appears to be safe in overdose (Garnier *et al.*, 1993). Cardiotoxicity was not a serious problem; sinus bradycardia requiring no treatment was noted in a few cases.

Paroxetine

20 mg to 30 mg paroxetine daily was compared with nortriptyline (dose adjusted to give plasma concentrations of 80 to 120 mg/ml) in a double-blind study of 41 patients with MDD and IHD (Roose *et al.*, 1998a). Paroxetine was not associated with clinically significantly sustained changes in heart rate, blood pressure or conduction intervals whereas nortriptyline caused 'clinically significant' changes in these measures and 'more serious cardiac events'.

[47] These data were calculated from data in the paper.

Sertraline

Three-hundred-and-sixty-nine patients with either unstable angina (26%) or recent (within 30 days) MI (74%) were randomised to receive either placebo or sertraline (flexible dose, 50 mg to 200 mg per day in a randomised double-blind trial) (Glassman *et al.*, 2002). Sertraline had no significant effect on left ventricular function compared with placebo or on a range of clinical or laboratory investigations. The incidence of severe cardiovascular events was 14.5% with sertraline numerically, but not significantly, less than placebo at 22.4%.

There was no overall difference between sertraline and placebo in terms of antidepressant response in all patients studied. However, in more severely depressed patients (HRSD >=18 and at least two previous depressive episodes), there was some evidence of a greater decrease in depression symptoms in those on SSRIs compared with those on placebo (n = 90; WMD= –3.4, 95% CI, –6.47 to –0.33[47]). However, this study and others in the field are not adequately powered or of sufficient length to determine cardiovascular morbidity or mortality in the longer term.

Overdose

In contrast to the TCAs, the SSRIs, if taken alone, are only rarely lethal in overdose (Barbey & Roose, 1998; Goeringer *et al.*, 2000). Deaths have occurred when citalopram has been ingested in very high doses (Ostrom *et al.*, 1996). However, other studies, whilst reporting complications with high-dose citalopram overdoses, have not reported deaths (Personne *et al.*, 1997b; Grundemar *et al.*, 1997). The mechanisms of the deaths reported by Ostrom *et al.* (1996) are not clear. There is some evidence that high-dose citalopram overdoses have been associated with ECG abnormalities (Personne *et al.*, 1997a) and QTc prolongation (Catalono *et al.*, 2001). However, Boeck *et al.* (1982) did not report cardiotoxicity with high-dose citalopram in the dog, and in the deaths reported by Ostrom *et al.* (1996) levels of the potentially cardiotoxic metabolite were low. Another potential mechanism of toxicity is that high-dose citalopram overdoses induce seizures and this has been shown in animals (Boeck *et al.,* 1982) and man (Grundemar *et al.*, 1997; Personne *et al.*, 1997a). Glassman (1997) suggested that all high dose SSRI overdoses were a cause for concern and advised prudence over the prescription of large amounts of tablets.

8.2.9.4 Other drugs

Lithium

Lithium has a number of cardiac effects and they can be of clinical significance in patients with heart disease, the elderly, those with higher lithium levels, hypokalaemia and when lithium is used with other drugs such as diuretics, hydroxyzine and tricyclic antidepressants (Chong *et al.*, 2001). Common, often subclinical, effects of lithium include the ‘sick sinus’ syndrome, first degree heart block, ventricular ectopics, flattened T-waves and increased QT dispersion (Reilly *et al.*, 2000), but adverse clinical outcomes are rare. Caution and periodic ECG monitoring is advised in those at risk or with cardiac symptoms.

Mianserin

Cardiac effects with mianserin are rare (Peet *et al.*, 1977; Edwards & Goldie, 1983; Jackson *et al.*, 1987) although there have been some reports of bradycardia and complete heart block in overdose (Haefeli *et al.*, 1991; Hla & Boyd, 1987) and, rarely, bradycardia at therapeutic doses (Carcone *et al.*, 1991). Bucknall *et al.* (1988) showed that mianserin was well tolerated in most, but not all, cardiac patients.

Mirtazapine

No significant cardiovascular effects from mirtazapine have been noted (Nutt, 2002). It appears to have a benign safety profile in overdose (Velazquez *et al.*, 2001).

Moclobemide

Moclobemide is not associated with any significant cardiovascular effects (Fulton & Benfield, 1996) and there are no reports of death in overdose with moclobemide as the sole agent.

Phenelzine

Phenelzine causes marked postural hypotension particularly in the early weeks of treatment and it is associated with a significant bradycardia. It does not cause conduction defects (McGrath *et al.*, 1987a). Its fatal toxicity index in overdose appears to be less than most tricyclics (Henry & Antao, 1992). There is no data on the safety or clinical efficacy of phenelzine in patients with ischaemic heart disease.

Reboxetine

No specific clinical or ECG abnormalities have been noted with reboxetine (Fleishaker *et al.*, 2001) and it has relative safety in overdose.

Trazodone

Trazodone is generally believed to have low cardiotoxicity, although there have been some reports of postural hypotension and, rarely, arrhythmias (Janowsky *et al.*, 1983).

Venlafaxine

No obvious laboratory or clinical cardiac changes have been found with venlafaxine in routine use (Feighner, 1995). There is evidence that in higher doses greater than 200 mg, hypertension occurs in a small but significant minority, and others have recommended regular blood pressure monitoring at and above this dose (e.g. Feighner, 1995). There is also evidence that in overdose (greater than 900 mg) venlafaxine is pro-convulsant compared with TCAs and SSRIs (Whyte *et al.*, 2003) and has a higher fatal toxicity index in overdose than SSRIs (Buckley & McManus, 2002). The MHRA also raised concerns about the increased incidence of adverse cardio-vascular events and the use of venlafaxine in individuals with pre-existing cardio-vascular disease (MHRA, 2004).

8.2.9.5 Recommendations regarding antidepressant cardiotoxicity

8.2.9.5.1 When initiating treatment in a patient with a recent myocardial infarction or unstable angina, sertraline is the treatment of choice as it has the most evidence for safe use in this situation. (B)

8.2.9.5.2 Healthcare professionals should take account of the increased risks associated with tricyclic antidepressants in patients with cardiovascular disease. (GPP)

8.2.9.5.3 An ECG should be carried out and blood pressure measurement taken before prescribing a tricyclic antidepressant for a depressed patient at significant risk of cardiovascular disease. (GPP)

8.2.9.5.4 For patients with pre-existing heart disease venlafaxine should not be prescribed. (C)

8.2.9.5.5 Before prescribing venlafaxine, an ECG and blood pressure measurement should be undertaken. (C)

8.2.9.5.6 For patients prescribed venlafaxine, consideration should be given to monitoring of cardiac function. Regular monitoring of blood pressure should be undertaken, particularly for those on higher doses. (C)

8.2.9.5.7 Before initiating lithium augmentation, an ECG should be carried out. (C)

8.2.10 Depression, antidepressants and suicide

8.2.10.1 Introduction

The majority of patients with depression have at least episodic suicidal ideation often linked to general negativity and hopelessness. Two-thirds of people who attempt suicide are suffering from depression, and suicide is the main cause of the increased mortality of depression and is commonest in those with comorbid physical and mental illness. Suicidal behaviour also occurs with milder forms of depression. Harris and Barraclough (1997) found a suicide risk of 12 times that expected in a cohort of patients with dysthymia (DSM-III (APA, 1980), which includes ICD-10 mild depression (WHO, 1992) and ICD-9 (WHO, 1975) neurotic depression). Therefore, the effective recognition and treatment of depression should lead to a fall in the overall suicide rate.

8.2.10.2 Suicidality and antidepressants

There is evidence in many patients of a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment (Jick *et al.*, 2004). It is not clear whether this is the direct result of taking an antidepressant (and the effect was seen with all classes of antidepressant), or because people do not seek help until they are feeling their worst. There is a delay in the onset of effect of antidepressants, and, just after initiation of treatment, mood remains low with prominent feelings of guilt and hopelessness, but energy and motivation can increase and may be related to the increased suicidal thoughts. A similar situation can arise with patients who develop

akathisia or increased anxiety due to a direct effect of some SSRIs and related drugs. The reason for this phenomenon is not yet fully understood but may reflect 5HT2 sensitisation due to an increase in synaptic 5HT. In some patients, it has been hypothesized that this may increase the propensity to suicidal ideation and suicidal behaviour (Healey, 2003). Careful monitoring is therefore indicated when treatment is initiated with an antidepressant. Patients should be monitored regardless of the apparent severity of their depression. It should be noted that the Jick *et al.* (2004) study is based on an analysis of the General Practice Research Database, which relies on general practitioners accurately recording patient and prescription data.

It has been suggested that the overall reduction in suicide rate may be partly due to more effective treatment of depression with newer antidepressants. In particular, it has been argued that the significant reductions in suicide rates in Sweden, Hungary, the USA and Australia have been due to treatment with these drugs (Isacsson *et al.*, 1997; Hall *et al.*, 2003). However, a number of other factors may account for this trend including changing socio-economic circumstances, and demonstrating a causal link between increased antidepressant prescription and falling suicide rates is not straightforward and has not been conclusively established (Gunnell & Ashby, 2004).

The risk-benefit ratio in children and adolescents appears to be different from that with adults, however, and following an earlier review of safety of SSRIs in children and adolescents the MHRA concluded that there was an increased risk of suicidal behaviours in this group for SSRIs when compared with placebo (MHRA, 2004). Other published studies (e.g. Whittington *et al.*, 2004) have supported this view. There is the possibility that this is due to increased prescribing of drugs with lower toxicity (such as SSRIs) to high-risk patients. It also raises the possibility, which was not confirmed or refuted by the MHRA review of treatment in adults, of an increased risk of suicidal behaviour in young adults started on SSRIs, and therefore the MHRA considered it prudent to recommend increased monitoring for young adults (aged under 30).

The use of antidepressants in the treatment of depression is also not without risk not least because of their toxicity in overdose. Antidepressants were involved in 18% of deaths from drug poisoning between 1993 and 2002 (Morgan et al, 2004), with TCAs, which are cardiotoxic in overdose (see section 8.2.9), accounting for 89% of these. This is equivalent to 30.1 deaths per million prescriptions. Dothiepin/dosulepin alone accounted for 48.5 deaths per million prescriptions (ibid). By contrast, over the same period, SSRIs accounted for around 6% of deaths by suicide, and other antidepressants, including venlafaxine, around 3%. This is equivalent to 1 and 5.2 deaths per million prescriptions respectively (ibid). Venlafaxine alone accounted for 8.5 deaths per million prescriptions. Morgan *et al.* (2004) showed an overall reduction in mortality rates over the time period studied, with a fall in rates related to TCAs, little change for SSRIs, but an increase for other antidepressants largely due to venlafaxine. These data are based on analyses of coroners' records for England and Wales, and prescription data for drugs dispensed in England (regardless of the prescription's country of origin). They may be subject to bias because indication is not recorded on prescriptions. Some antidepressants are licensed for conditions such as obsessive-compulsive disorder and post-traumatic stress disorder in addition to depression. Also, coroners record antidepressant information voluntarily and only if they consider the antidepressant contributed to the cause of death (ibid). Interpretation of these data is complicated by the possibility of differential prescribing, that is patients at high risk of suicide may have been prescribed different drugs from those at low risk.

8.2.10.3 Recommendations regarding antidepressants and suicidality

8.2.10.3.1 Patients started on antidepressants who are considered to present an increased suicide risk or are younger than 30 years (because of the potential increased risk of suicidal thoughts associated with the early stages of antidepressant treatment for this group) should normally be seen after one week and frequently thereafter as appropriate until the risk is no longer considered significant. (C)

8.2.10.3.2 For patients at high risk of suicide, a limited quantity of antidepressants should be prescribed. (C)

8.2.10.3.3 Particularly in the initial stages of SSRI treatment, healthcare professionals should actively seek out signs of akathisia, suicidal ideation, and increased anxiety and agitation. They should also advise patients of the risk of these symptoms in the early stages of treatment and advise them to seek help promptly if these are at all distressing. (C)

8.2.10.3.4 In the event that a patient develops marked and/or prolonged akathisia or agitation while taking an antidepressant, the use of the drug should be reviewed. (C)

8.2.10.3.5 Toxicity in overdose should be considered when choosing an antidepressant for patients at significant risk of suicide. Healthcare professionals should be aware that the tricyclic antidepressants (with the exception of lofepramine), are more dangerous in overdose than other equally effective drugs recommended for routine use in primary care. (GPP)

8.2.10.4 Research recommendations

8.2.10.4.1 Suicidal ideas, self-harming behaviour and completed suicide should be carefully and prospectively measured in large, independent multicentre trials using a variety of methods. Particular attention should be paid to the first four weeks of treatment.

8.2.10.4.2 Trials of antidepressants in other disorders (e.g. chronic pain) should similarly monitor for the above negative outcomes.

8.3 The pharmacological treatment of treatment-resistant depression

8.3.1 Introduction

Despite major developments in the management of mood disorders, in clinical practice the problem of treatment resistance continues to be problematic. Numerous outcome studies have demonstrated that approximately one-third of patients treated for major depression do not respond satisfactorily to first-round antidepressant pharmacotherapy.

Follow-up observations reveal that a considerable number of patients have a poor prognosis with as many as 20% remaining unwell two years after the onset of illness (Keller *et al.*, 1986). Even after multiple treatments, up to 10% of patients remain depressed (Nirenberg & Amsterdam, 1990). A range of studies suggests that between 10% and 20% of patients with major depressive disorder have a long-term poor outcome (Winokur *et al.*, 1993; Lee & Murray, 1988).

It is difficult, however, to evaluate the true levels of resistance to treatment for major depressive disorder from these figures. Although treatment resistance is relatively common in clinical practice, a major problem has been the inconsistent way in which it has been characterised and defined, limiting systematic research. The poor level of attention previously paid to any conceptual examination of treatment resistance has resulted in unsystematic research and uncontrolled trials which have led to a degree of confusion. However, more recently, definitions have been agreed that have improved the characterisation of the syndrome, although there is still disagreement on some of the items. The key parameters that characterise and define treatment resistance include the basic criteria used to specify the diagnosis, response to treatment, previous treatment trials and the adequacy of treatment (Nirenberg & Amsterdam, 1990).

For the purposes of making clinical recommendations in this area, the GDG defined people with treatment-resistant depression as those whose depression symptoms had failed to respond to two or more antidepressants at an adequate dose for an adequate duration given sequentially. However, in addition to trials where participants have failed more than one course, trials where participants have failed only one course of antidepressants are considered as part of the evidence base for this section. The term 'acute-phase non-responders' is used for this evidence.

This chapter reviews the following treatment strategies:

- Switching strategies
- Venlafaxine for treatment-resistant depression
- Augmentation strategies:
    - Augmenting an antidepressant with lithium
    - Augmenting an antidepressant with anticonvulsants (lamotrigine, carbamazepine or valproate)
    - Augmenting an antidepressant with another antidepressant
    - Augmenting an antidepressant with pindolol
    - Augmenting an antidepressant with triiodothyronine (T3)
    - Augmenting an antidepressant with a benzodiazepine
    - Augmenting an antidepressant with an antipsychotic
    - Augmenting an antidepressant with buspirone.

The above strategies were reviewed, as there was sufficient evidence to come to a conclusion about efficacy and/or significant clinical usage of such strategies in the UK. There is, however, a wide range of other strategies used in treatment resistance for which either the evidence base is so weak or the clinical usage so low that the GDG did not include them in this review. Examples of these latter strategies includes the use of MAOIs in combination with other drugs such as tricyclics or L-tryptophan and combinations of antidepressants, for example SSRIs and tricyclics, venlafaxine and reboxetine or combinations of venlafaxine, mirtazapine and reboxetine. Details of the available information about these strategies (e.g. case reports, open studies, expert opinion) can be found elsewhere (Bauer *et al.*, 2002b; Price *et al.*, 2001; Thase & Rush, 1997). These papers also include details of the pharmacological issues associated with these strategies. A wide variety of new treatments to augment antidepressants are being developed or are in pilot trial phase. These are beyond the scope of this review and details can be found elsewhere (Tamminga *et al.*, 2002).

MAOIs have been used extensively in the management of treatment-resistant depression for four decades but there is no randomised data on which to base recommendations. Most information and experience is with phenelzine. McGrath *et al.* (1987b) treated patients in a cross-over design with high doses of phenelzine (maximum 90 mg), imipramine (maximum 300 mg) or placebo and found that of the non-responders only four of the 14 patients responded to a tricyclic cross-over with 17 of the 26 patients responding to an MAOI cross-over. There was some evidence of a preferential response in treatment-resistant patients with atypical depression symptoms, but Nolen *et al.* (1988) subsequently showed that not only patients with atypical depressive symptoms but also patients with major depression and melancholia responded to MAOIs, in particular tranylcypramine. It does not appear that moclobemide has the same spectrum of efficacy in treatment resistance as the classical MAOIs. Nolen *et al.* (1994) switched patients with resistant depression stabilised on tranylcypromine to moclobemide. About 60% of the patients showed deterioration and one-third relapsed.

8.3.2 Switching strategies

8.3.2.1 Introduction

Approximately 20% to 30% of patients with depression fail to respond to the first antidepressant prescribed (assuming an adequate dose, duration of treatment and compliance with medication; Cowen, 1998). It is normal clinical practice at this point to increase the dose to the maximum tolerated (within licensed limits) and, if there is still no or minimal response, to switch to an alternative antidepressant (Anderson *et al.*, 2000). Most prescribers select an antidepressant from a different class to the 'failed' drug (Fredman *et al.*, 2000). Randomised studies of switching are difficult to interpret as they either include patients who may be expected to fare poorly on one of the treatments (e.g. patients with atypical depression in a study with a MAOI and TCA arm; McGrath *et al.*, 1993) or employ a cross-over design (Thase *et al.*, 1992; McGrath *et al.*, 1993). Open studies, however, show that approximately 50% of patients who do not respond to their first treatment are likely to respond to the second antidepressant irrespective of whether it comes from the same class or a different one (Thase & Rush, 1997).

8.3.2.2 Studies considered for review

One study met the inclusion criteria set by the GDG (THASE2002). In this study participants were randomised to 12 weeks of treatment with either sertraline or imipramine. Non-responders were then switched to the other drug for a further 12 weeks. The mean dose of sertraline was 163 mg (±48 mg) and that of imipramine 221 mg (±84 mg).

8.3.2.3 Evidence statements

Effect of treatment on efficacy

There is insufficient evidence to determine if there is a clinically significant difference between switching from sertraline to imipramine and switching from imipramine to sertraline on increasing the likelihood of achieving a 50% reduction in depression symptoms or on reducing depression symptoms.

Acceptability of treatment

There is some evidence suggesting that there is a clinically significant difference favouring switching from imipramine to sertraline over switching from sertraline to imipramine on reducing the likelihood of leaving treatment early (N = 1; *n* = 168; RR = 2.53; 95% CI, 1.04 to 6.16).

8.3.2.4 Clinical summary

There is little evidence on which to make an evidence-based recommendation of switching strategies in the treatment of treatment-resistant depression.

8.3.3 Venlafaxine for treatment-resistant depression

8.3.3.1 Introduction

At the standard dose of 75 mg, venlafaxine is an SSRI. At doses of 150 mg/day and above it also inhibits the reuptake of noradrenaline and, to a lesser extent, dopamine. This progression from single to double to triple action is thought to be potentially beneficial in patients with treatment-resistant depression. Venlafaxine is widely believed to be more effective than SSRIs in patients with treatment resistant depression.

8.3.3.2 Studies considered for review

In the section on venlafaxine elsewhere in this guideline only one study (POIRIER1999) included all patients with treatment resistant depression. Here, venlafaxine IR (mean dose 269 mg) is compared with paroxetine (20 to 40 mg). Patients are either inpatients or outpatients aged between 21 and 62. The study was four weeks long.

8.3.3.3 Evidence statements

Effect of treatment on efficacy

In patients whose depression is treatment resistant, there is some evidence suggesting that there is a clinically significant difference favouring venlafaxine over paroxetine on increasing the likelihood of achieving remission (N = 1; *n* = 123; RR = 0.78; 95% CI, 0.62 to 0.97).

In patients with treatment-resistant depression there is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and paroxetine on increasing the likelihood of achieving a 50% reduction in depression symptoms or on reducing depression symptoms.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between venlafaxine and paroxetine on any measure of acceptability in patients whose depression is treatment resistant.

8.3.3.4 Clinical summary

In patients whose depression is treatment resistant, there is some evidence suggesting a clinical advantage for high-dose venlafaxine (mean 269 mg) over paroxetine in terms of achieving remission, but insufficient evidence that this effect is evident with respect to response, mean endpoint scores or tolerability.

8.3.4 Augmentation strategies

8.3.4.1 Augmenting an antidepressant with lithium

8.3.4.1.1 Introduction

Lithium is an established mood stabilising drug that is used in the treatment of mania and the prophylaxis of bipolar affective disorder. It is also widely used to augment antidepressant response in treatment resistant unipolar depression. The mechanism of action of lithium is not clearly understood (Peet & Pratt, 1993).

Lithium is primarily excreted renally and can cause hypothyroidism. Baseline biochemical tests and ongoing monitoring are essential (full details can be found in the Maudsley Prescribing Guidelines, Taylor *et al.*, 2003).

Lithium is a potentially toxic drug. Plasma levels of 0.5 to 1.0 mmol/L are usually considered to be therapeutic. Above 1.5 mmol/L toxicity invariably develops and death may occur at levels as low as 2.0 mmol/L. Many commonly prescribed drugs can interact with lithium to precipitate lithium toxicity (BNF 45; Taylor *et al.*, 2003).

8.3.4.1.2 Studies considered for review

Twenty-eight studies were found in a search of electronic databases, 10 of which were included (BAUMANN1996, BLOCH1997, CAPPIELLO1998, JANUEL2002, JENSEN1992, JOFFE1993A, NIER'BERG03, SHAHAL1996, STEIN1993, ZUSKY1988) and 18 excluded in the present review.

Only studies comparing lithium plus an antidepressant with lithium plus placebo were included in the analyses. In place of the usual inclusion criterion relating to mean dose of study drugs, the GDG included trials only if they achieved a mean blood plasma level of 0.5 mmol/L of lithium. Antidepressants used included clomipramine, desipramine, imipramine, nortriptyline and citalopram. One study used a variety of antidepressants but did not specify them (ZUSKY1988) and two studies used a range of unspecified TCAs (JOFFE1993A, STEIN1993).

All included studies were published between 1988 and 2002 with participants being randomised to an experimental treatment phase of between one and six weeks (mean = 4.2 weeks). BAUMANN1996, JOFFE1993A, STEIN1993 and ZUSKY1988 were classified as acute-phase non-responder trials. In BAUMANN1996 and JOFFE1993A participants were randomised to treatment only if they had not responded to between three and six weeks of open-label antidepressant treatment. In STEIN1993 and ZUSKY1988 failure to respond to at least one course of antidepressant mono-therapy formed part of the trial inclusion criteria. (In addition 62% of those in CAPPIELLO1998 had failed one course of antidepressants.) NIER'BERG03 was classified as a treatment-resistant depression trial since participants were included only if they had already failed between one and five courses of antidepressants and were randomised to treatment only if they failed to respond to an open-label course. The data set was analysed three ways: all available studies, acute-phase non-responder trials and treatment-resistant trials.

In four studies participants were described as inpatients (BAUMANN1996, JANUEL2002, JENSEN1992, SHAHAL1996), in three as outpatients (BLOCH1997, JOFFE1993A, NIER'BERG03), and in the other three it was either not clear from where participants were sourced or they were from mixed sources (CAPPIELLO1998, STEIN1993, ZUSKY1988). No trial was undertaken in primary care. In one (JENSEN1992) all participants were elderly.

Efficacy data were available from up to 237 participants and tolerability data from up to 356 participants. One-hundred-and-forty-six participants were classified acute-phase non-responders and 35 treatment-resistant.

8.3.4.1.3 Evidence statements for the complete data set

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring antidepressants augmented with lithium over antidepressants augmented with placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N = 6; n = 173; RR = 0.82; 95% CI, 0.68 to 0.99).

There is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on increasing the likelihood of achieving remission by the end of treatment (N = 3; *n* = 216; Random effects RR = 1.26; 95% CI, 0.73 to 2.17).

There is evidence suggesting that there is a statistically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing depressions symptoms by the end of treatment as measured by the HRSD and the MADRS, but there is insufficient evidence to determine its clinical significance (N = 7; *n* = 273; SMD = –0.32; 95% CI, –0.56 to –0.08).

Acceptability of treatment

There is strong evidence suggesting that there is a clinically significant difference favouring antidepressants augmented with placebo over antidepressants augmented with lithium on reducing the likelihood of leaving treatment early (N = 7; *n* = 356; RR = 1.79; 95% CI, 1.23 to 2.6).

There is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on either reducing the likelihood of leaving treatment early due to side effects or reducing the likelihood of patients reporting side effects.

8.3.4.1.4 Evidence statements for acute-phase non-responder trials

Effect of treatment on efficacy outcomes

In patients who have failed one course of antidepressants, there is some evidence suggesting that there is a clinically significant difference favouring lithium over placebo on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by HRSD (N = 3; *n* = 76; RR = 0.66; 95% CI, 0.49 to 0.9)

- reducing depression symptoms by the end of treatment as measured by the HRSD and MADRS (N = 4; *n* = 107; SMD = –0.48; 95% CI, –0.86 to –0.09).

Acceptability of treatment

In patients who have failed one course of antidepressants, there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing the likelihood of leaving treatment early (N = 1; *n* = 52; RR = 1.67; 95% CI, 0.56 to 4.97).

8.3.4.1.5 Evidence statements for people whose depression is treatment resistant

Effect of treatment on efficacy outcomes

In patients whose depression is treatment resistant there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented

with lithium and antidepressants augmented with placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by HRSD (N = 1; *n* = 35; RR = 1.08; 95% CI, 0.82 to 1.42).

Acceptability of treatment

In patients whose depression is treatment resistant there is insufficient evidence to determine if there is a clinically significant difference between antidepressants augmented with lithium and antidepressants augmented with placebo on reducing the likelihood of leaving treatment early in patients with treatment-resistant depression (N = 1; *n* = 35; RR = 0.94; 95% CI, 0.15 to 5.97).

8.3.4.1.6 Clinical summary

In a mixed population of patients (45% acute-phase non-responders, 15% people whose depression is treatment resistant, 40% other depressed patients), there is some evidence of a clinically significant advantage of adding lithium to an antidepressant over adding placebo in terms of response rate, although this effect was not found for mean endpoint scores. In acute-phase non-responders there is some evidence suggesting a clinical advantage of adding lithium over adding placebo in terms of response and mean endpoint scores. However, there is insufficient evidence that this effect is evident in people whose depression is treatment resistant.

However, adding lithium to an antidepressant appears to be less acceptable to patients, although there is insufficient evidence to determine whether this is due to side effects.

8.3.4.2 Augmenting an antidepressant with anticonvulsants

8.3.4.2.1 Introduction

Anticonvulsants are increasingly being prescribed in bipolar disorder. There is a growing database on their efficacy in the treatment of depression and mania in bipolar disorder and in the prophylaxis of that condition. These developments, together with research, suggest that anticonvulsants may also help the symptoms of depression in the context of epilepsy, which have led to some trials and quite widespread use of anticonvulsants in unipolar disorder.

8.3.4.2.2 Carbamazepine

Carbamazepine has attracted the most interest since it was the first anticonvulsant to be shown to have efficacy in bipolar disorder and because carbamazepine shares some neurochemical properties with tricyclic antidepressants. However, no RCTs met the inclusion criteria set by the GDG. There are some open studies in major depression (Dietrich & Emrich, 1998) and some in treatment-resistant depression (Ketter *et al.*, 1995; Cullen *et al.*, 1991) that show some benefit. It is noteworthy that in Cullen's study a high percentage of the older patients who responded had to discontinue carbamazepine because of adverse effects.

Carbamazepine has a wide range of side effects, contraindications and interactions with other drugs. In the context of depression, it is noteworthy that carbamazepine co-administration reduces TCA levels by up to 50% (Dietrich & Emrich, 1998) and SSRIs may interfere with carbamazepine metabolism leading to intoxication.

There is a lack of controlled data and a high likelihood of adverse effects or clinically important interactions and, therefore, carbamazepine cannot be recommended in the routine management of treatment-resistant depression.

8.3.4.2.3 Valproate

There are no RCTs of valproate in either major or bipolar depression. Evidence to date suggests that valproate is more effective in preventing hypomanias rather than depressions in bipolar disorder. One open study enrolled 33 patients with MDD in an eight-week study of valproate as monotherapy (Davis *et al.*, 1996). Approximately 50% of the patients achieved remission. Valproate is generally well tolerated and there are few interactions with antidepressant drugs, although fluoxetine may elevate valproate levels by interfering with its metabolism.

There is insufficient data on which to make an evidence-based recommendation for valproate in the treatment of depression. However, it could be used in a case where an anticonvulsant was required for other reasons.

8.3.4.2.4 Lamotrigine

Lamotrigine is an anti-epileptic drug that is used in the treatment of partial and generalised seizures. In clinical trials in epilepsy a positive psychotropic effect was observed and mood, alertness and social interaction improved. Trials have shown that lamotrigine has evidence of efficacy in depression in bipolar disorder and in preventing depressive episodes particularly in bipolar II patients (Hurley, 2002). Hurley reports on an initial study of 437 MDD patients randomised to lamotrigine, desipramine or placebo. On 'last observation carried forward', ratings in these three groups were not significantly different from each other. In another study 40 depressed patients (30 unipolar, 10 bipolar) were studied in a nine-week RCT of lamotrigine (200 mg) added to paroxetine (40 mg) against placebo. There was no difference in HRSD scores at end point compared with placebo alone (Normann *et al.*, 2002). There was a high frequency of adverse effects and dropouts in both groups. Recently, Barbosa *et al.* (2003) reported on a study of 23 depressed patients (65% MDD) who had failed at least one trial of an antidepressant. Patients were placed on fluoxetine 20 mg/day and then randomised to either placebo or 25 mg to 100 mg of lamotrigine. There was no statistical difference in HRSD or MADRS ratings between the two groups at six weeks.

In view of the lack of positive data lamotrigine cannot be recommended for use in unipolar disorder. Although it is generally well tolerated and free of major interactions, it can cause a severe rash that can be life-threatening in a small minority of cases. Its profile in epilepsy and bipolar disorder suggests that further trials of lamotrigine in treatment-resistant depression are worthwhile.

There are no data that indicate that other anticonvulsants – for example, gabapentin or topiramate – can be recommended in depression.

8.3.4.3 Augmenting an antidepressant with another antidepressant

8.3.4.3.1 Introduction

Combining antidepressant drugs with different modes of action is increasingly used in clinical practice. Combinations of serotonergic and noradrenergic drugs may result in a 'dual action' combination while combinations of serotonergic drugs with different modes of action may be expected to increase serotonergic neurotransmission more than either drug alone.

While the efficacy of these combinations may be additive (this is not proven for the majority of combinations), so too may the toxicity. Both pharmacokinetic and pharmacodynamic interactions must be considered. Fluoxetine, fluvoxamine and paroxetine may substantially and unpredictably increase TCA serum levels increasing the risk of adverse effects (Taylor, 1995). Combinations of serotonergic antidepressants increase the risk of developing serotonin syndrome, which can be fatal. Features include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus.

8.3.4.3.2 Studies considered for review

Fifteen trials were found in a search of electronic databases, seven of which met the inclusion criteria set by the GDG (CARPENTER2002, FAVA1994, FAVA2002, FERRERI2001, LICHT2002, MAES1999, TANGHE1997). One study (TANGHE1997) included only people whose depression was treatment-resistant; in another study (MAES1999), 65% of the people had treatment resistant depression. Participants in the remaining studies were acute-phase non-responders. Studies compared outcomes from participants taking two antidepressants together with those taking either a single antidepressant at 'standard' dose (with or without placebo) or a single antidepressant at 'high' dose.
The following combinations were possible:

- SSRIs ('standard' dose) plus mianserin versus SSRIs ('standard' dose, with or without placebo) (FERRERI2001, LICHT2002, MAES1999)
- Various antidepressants ('standard' dose) plus mirtazapine versus various antidepressants ('standard' dose, with placebo) (CARPENTER2002)
- Amitriptyline plus moclobemide versus amitriptyline ('standard' dose) (TANGHE1997)
- Sertraline (100 mg) plus mianserin versus high-dose sertraline (200 mg) (LICHT2002)
- Fluoxetine (20 mg) plus desipramine versus high-dose fluoxetine (40 mg to 60 mg) (FAVA1994, FAVA2002).

In trials comparing two antidepressants with a single antidepressant at 'standard' dose, efficacy data were available from up to 353 participants and tolerability data from up to 293 participants. In trials comparing two antidepressants with a single antidepressant at high dose, efficacy data were available from up to 390 participants and tolerability data from up to 290 participants.

All included studies were published between 1994 and 2002 and were between four and six weeks long (mean = 4.57 weeks). Two studies were of inpatients (MAES1999, TANGHE1997) and four of outpatients (CARPENTER2002, FAVA1994, FAVA2002, LICHT2002) with none in primary care. Participants in FERRERI2001 were from mixed sources. No study included all older participants or those with atypical depression.

The studies were analysed three ways: all available trials, acute-phase non-responders only and people whose depression is treatment resistant only.

8.3.4.3.3 Evidence statements for the complete data set

Effect of treatment on efficacy

There is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on:

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (N = 3; *n* = 293; RR = 0.81; 95% CI, 0.67 to 0.97)

- reducing depression symptoms by the end of treatment as measured by the HRSD or the MADRS (N = 5; *n* = 353; Random effects SMD = –0.53; 95% CI, –0.97 to –0.10).

There is insufficient evidence to determine whether there is a clinically significant difference between two antidepressants over a single antidepressant (with or without placebo) on increasing the likelihood of achieving a 50% reduction in depression symptoms by the end of treatment as measured by the HRSD (N = 4; *n* = 316; Random effects RR = 0.66; 95% CI, 0.43 to 1.02).

There is insufficient evidence to determine whether there is a clinically significant difference between two antidepressants and a single high dose antidepressant on any efficacy measure.

Acceptability of treatment

There is some evidence suggesting that, on reducing the likelihood of patients reporting side effects, there is a clinically significant difference favouring:

- a single antidepressant (with or without placebo) over two antidepressants (N = 1; *n* = 197; RR = 1.68; 95% CI, 1.32 to 2.14)

- a single high-dose antidepressant over two antidepressants (N = 1; *n* = 196; RR = 1.39; 95% CI, 1.13 to 1.71).

There is insufficient evidence to determine if there is a clinically significant difference between either two antidepressants and a single antidepressant (with or without placebo) or between two antidepressants and a single high dose antidepressant on other tolerability measures.

8.3.4.3.4 Evidence statements for acute-phase non-responder trials

Effect of treatment on efficacy

In patients who have failed one course of antidepressants there is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on increasing the likelihood of achieving remission (N = 3; *n* = 293; RR = 0.81; 95% CI, 0.67 to 0.97).

In patients who have failed one course of antidepressants there is insufficient evidence to determine if there is a clinically significant difference between two antidepressants and a single antidepressant (with or without placebo) on increasing the likelihood of achieving a 50% reduction in depression symptoms or on reducing depression symptoms or between two antidepressants and a single high dose antidepressant on any efficacy measure.

Acceptability and tolerability of treatment

In patients who have failed one course of antidepressants, there some evidence suggesting that there is a clinically significant difference favouring:

- a single antidepressant (with or without placebo) over two antidepressants on reducing the likelihood of patients reporting side effects (N = 1; *n* = 197; RR = 1.68; 95% CI, 1.32 to 2.14)

- a single high dose antidepressant over two antidepressants on patients reporting side effects (N = 1; *n* = 196; RR = 1.39; 95% CI, 1.13 to 1.71).

In patients who have failed one course of antidepressants, there is insufficient evidence to determine if there is a clinically significant difference between either two antidepressants and a single antidepressant (with or without placebo) or between two antidepressants and a single high dose antidepressant on reducing the likelihood of leaving treatment early for any reason or on reducing the likelihood of leaving treatment early due to side effects.

8.3.4.3.5 Evidence statements for people whose depression is treatment resistant

Effect of treatment on efficacy

In people whose depression is treatment resistant there is some evidence suggesting that there is a clinically significant difference favouring two antidepressants over a single antidepressant (with or without placebo) on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 1; *n* = 18; RR = 0.34; 95% CI, 0.13 to 0.92)

- reducing depression symptoms (N = 2; *n* = 57; Random effects SMD = –0.99; 95% CI, –1.87 to –0.1).

Acceptability of treatment

There is no evidence on the acceptability of treatment in people whose depression is treatment resistant.

8.3.4.3.6 Clinical summary

In a mixed population of patients there is some evidence that augmenting one antidepressant with another leads to better outcomes on response, remission and mean endpoint scores compared with a single antidepressant at 'standard' dose. There is insufficient evidence to determine whether this is the case when compared with a single antidepressant at high dose.

Since the majority of studies used mianserin as the augmentor, the analyses are weighted towards this drug. Importantly, there are no studies of combinations of a TCA and irreversible MAOI or any two from venlafaxine, mirtazapine and reboxetine.

There is some evidence that combinations of antidepressants are associated with a higher burden of side effects than a single antidepressant at either standard or high dose, but there is insufficient evidence to comment on the number of patients leaving treatment early.

Where there was sufficient evidence similar results were found when trials of acute-phase non-responders and people whose depression is treatment resistant were analysed separately.

8.3.4.4 Augmenting an antidepressant with pindolol

8.3.4.4.1 Introduction

Serotonergic antidepressants inhibit the reuptake of serotonin into the presynaptic neurone thus increasing serotonergic neurotransmission. The immediate effect of this increase is to stimulate serotonin 1a autoreceptors, which results in a decrease in serotonin release. In time, these autoreceptors become desensitised and serotonin release returns to normal. This, in combination with the inhibition of serotonin reuptake, is thought to lead to the onset of antidepressant effect.

Pindolol is primarily an adrenergic b-blocking drug, which also blocks serotonin 1a autoreceptors. The co-administration of pindolol with a serotonergic antidepressant could be expected to result in an immediate increase in serotonin neurotransmission, thus eliminating the delay in onset of antidepressant response.

As well as being used to speed the onset of antidepressant response, pindolol has also been used to augment the efficacy of antidepressant drugs in acute-phase non-responders and treatment-resistant depression.

8.3.4.4.2 Studies considered for review

Twenty-four studies were found in a search of electronic databases, six of which met the inclusion criteria set by the GDG (BORDET1998, MAES1999, PEREZ1997, PEREZ1999, TOME1997, ZANARDI1997) and 18 of which did not.

Only studies comparing pindolol plus an antidepressant with pindolol plus placebo were included in the analyses. Apart from one study (PEREZ1999), which included clomipramine as well as a range of SSRIs, all studies used a single SSRI as the antidepressant. Efficacy data were available from up to 282 participants and tolerability data from up to 333 participants.

All included studies were published between 1997 and 1999 with participants being randomised to an experimental treatment phase of between 10 days and six weeks (mean = 4.25 weeks).

In two studies participants were described as inpatients (MAES1999, ZANARDI1997), in a further two as outpatients (PEREZ1999, TOME1997), in one as primary care (PEREZ1997) and in the remaining trial participants were from mixed sources (BORDET1998). In no trial were participants exclusively older or had atypical depression. The mean dose of pindolol was 9.23 mg, ranging from 7.5 mg to 15 mg.

No trial was classified acute-phase non-responder, and only one was classified treatment-resistant (PEREZ1999). Here patients were randomised to receive augmentation for ten days with either pindolol (7.5 mg) or placebo after receiving fluoxetine (40 mg), fluvoxamine (200 mg), paroxetine (40 mg) or clomipramine (150 mg) for at least six weeks beforehand. In addition participants had already failed between one and four courses of antidepressants (median two). Most patients were outpatients aged 18 to 65. Results from a separate analysis of this trial are presented below.

Outcomes are classified according to when assessment measures were taken. Up to 14 days after treatment was begun was categorised 'early assessment point' and more than 20 days was categorised 'late assessment point'. Three studies (BORDET1998, TOME1997, ZANARDI1997) gave outcomes at both assessment points.

8.3.4.4.3 Evidence statements

Effect of treatment on efficacy

Early assessment point

There is evidence suggesting that there is no clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the 10th day of treatment (N = 2; *n* = 160; RR = 0.95; 95% CI, 0.82 to 1.11).

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on:

- increasing the likelihood of achieving remission by the 10th or 14th day of treatment (N = 3; *n* = 222; Random effects RR = 0.73; 95% CI, 0.44 to 1.20)
- reducing depression symptoms by the 10th or 14th day of treatment (N = 3; *n* = 237; Random effects SMD = –0.30; 95% CI, –0.88 to 0.28).

Late assessment point

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms by the 35th or 42nd day of treatment (N = 3; *n* = 214; RR = 0.75; 95% CI, 0.54 to 1.03).

There is some evidence suggesting that there is a clinically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on increasing the likelihood of achieving remission by the 21st, 28th or 42nd day of treatment (N = 3; *n* = 253; RR = 0.73; 95% CI, 0.55 to 0.98).

There is evidence suggesting that there is a statistically significant difference favouring SSRIs plus pindolol over SSRIs plus placebo on reducing depression symptoms by the 21st, 35th or 42nd day of treatment, but the size of this difference is unlikely to be of clinical significance (N = 4; *n* = 282; SMD = –0.26; 95% CI, –0.49 to –0.02).

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between SSRIs plus pindolol and SSRIs plus placebo on any measure of tolerability.

8.3.4.4.4 Effect of treatment on efficacy for people whose depression is treatment resistant

Early assessment point

For people whose depression is treatment resistant there is evidence suggesting that there is no clinically significant difference when assessment is made between days 10 and 14 between pindolol augmentation and antidepressant monotherapy on:

- increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 1; *n* = 80; RR = 1; 95% CI, 0.85 to 1.18)
- increasing the likelihood of achieving remission (N = 1; *n* = 80; RR = 1.03; 95% CI, 0.88 to 1.2).

There is insufficient evidence to determine if there is a clinically significant difference between pindolol augmentation and antidepressant monotherapy on reducing depression symptoms in people whose depression is treatment resistant (N = 1; *n* = 80; WMD = 1.6; 95% CI, –0.96 to 4.16).

Acceptability of treatment for people whose depression is treatment resistant

There are no data on the acceptability of treatment for people whose depression is treatment resistant.

8.3.4.4.5 Clinical summary

While there is some evidence of an advantage (at 21 to 42 days) favouring the addition of pindolol to antidepressants over adding placebo on achieving remission, this effect is not evident for response or mean endpoint scores. There is no evidence of any effect on outcomes in people whose depression is treatment resistant at early assessment point. No data were available for late assessment points.

There is insufficient evidence to comment on the tolerability of adding pindolol to antidepressants.

It should be noted that there is uncertainty regarding optimum dose and duration of treatment.

8.3.4.5 Augmenting an antidepressant with triiodothyronine (T3)

8.3.4.5.1 Introduction

Consistent with the observations that the prevalence of depression is increased in hypothyroidism (Loosen, 1987), and subclinical hypothyroidism is more prevalent in people who are clinically depressed (Maes *et al.*, 1993), triiodothyronine (T3) has been used as an antidepressant augmenting agent both to increase the speed of onset of antidepressant response and to increase the magnitude of response.

Increase the speed of onset of antidepressant response

T3, at a dose of 25 mcg per day, may hasten response to tricyclics and this effect may be more robust in women (Altshuler *et al.*, 2001). The optimal duration of treatment is unknown although there is a suggestion in the literature that T3 may be safely withdrawn once response has been achieved (Altshuler *et al.*, 2001). There are no studies with SSRIs or any of the newer antidepressants.

Increase the magnitude of antidepressant response

Although the RCT that satisfied the inclusion criteria set by the GDG found T3 and lithium to be equally effective and superior to placebo (see below), several 'negative' non-RCTs also exist (Steiner *et al.*, 1978; Gitlin *et al.*, 1987; Thase *et al.*, 1989). The response rate has been variable across studies (Aronson *et al.*, 1996). All studies used tricyclic antidepressants. There are no studies with SSRIs or any of the newer antidepressants. T4 has been shown to be inferior to T3 in one study (Joffe & Singer, 1990). Most studies used a dose of 37.5 mcg T3 per day. The optimum duration of treatment is unknown.

8.3.4.5.2 Studies considered for review

One study was found in a search of electronic databases (JOFFE1993A), and this met the inclusion criteria set by the GDG. It compares a range of antidepressants augmented with T3 (37.5 mcg) with antidepressants augmented with placebo. Participants are outpatients who have not achieved remission after five weeks' treatment with either desipramine or imipramine.

8.3.4.5.3 Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring T3 augmentation over antidepressant plus placebo on increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 1; *n* = 33; RR = 0.51; 95% CI, 0.27 to 0.94).

There is insufficient evidence to determine if there is a clinically significant difference between T3 augmentation and antidepressant plus placebo on reducing depression symptoms (N = 1; *n* = 33; WMD = –3.9; 95% CI, –8.86 to 1.06).

Acceptability of treatment

There was no evidence on which to assess the acceptability of treatment.

8.3.4.5.4 Clinical summary

There is little evidence on which to make an evidence-based recommendation of augmentation of antidepressants with T3 for the treatment of treatment-resistant depression. The prevalence of cardiovascular disease is increased in people with depression (Glassman & Shapiro, 1998) and T3 should be used with caution in cardiovascular disease. Potential adverse effects include tachycardia, anginal pain and arrhythmias. Tricyclic antidepressants also have cardiac side effects including arrhythmias, tachycardia and postural hypotension. Caution is advised in combining TCAs and T3.

8.3.4.6 Augmenting an antidepressant with a benzodiazepine

8.3.4.6.1 Introduction

Depression and anxiety commonly co-exist and insomnia is a core symptom of depression. Antidepressants usually take two to four weeks to take effect.

Benzodiazepines are effective anxiolytic and hypnotic drugs with an immediate onset of action and therefore could be expected to produce early improvement in some symptoms of depression. They do not have a specific antidepressant effect.

Benzodiazepines are associated with tolerance and dependence and withdrawal symptoms can occur after four to six weeks of continuous use. To avoid these problems, it is recommended that they should not routinely be prescribed for their hypnotic or anxiolytic effects for longer than four weeks (Royal College of Psychiatrists, 1997; BNF 45).

The National Service Framework for Mental Health (Department of Health, 1999b) discourages the use of benzodiazepines and many primary care prescribing incentive schemes include low prescribing rates for benzodiazepines as a marker of good practice. A Cochrane review, however, concludes that early time limited use of benzodiazepines in combination with an antidepressant drug may accelerate treatment response (Furukawa *et al.*, 2002b).

8.3.4.6.2 Studies considered for review

The GDG used an existing review (Furukawa *et al.*, 2002b) as the basis for this section. The original review included nine studies of which four met the inclusion criteria set by the GDG (FEET1985, NOLEN1993, SCHARF1986, SMITH1998). New searches of electronic databases found an additional study (SMITH2002) which was included in the present review. Together these studies provided tolerability data from up to 196 participants and efficacy data from up to 186 participants.

All included studies were published between 1985 and 2002 and were between three and 12 weeks long (mean = seven weeks). One study was of inpatients (NOLEN1993), three of outpatients (FEET1985, SMITH1998, SMITH2002) and in the remaining study (SCHARF1986) participants were from mixed sources. No study was undertaken in primary care, nor was any of exclusively older participants or those with atypical depression. Other than in FEET1985, where participants had been 'treated in general practice without success', study participants were not described as having failed previous courses of antidepressants.

All studies compared an antidepressant plus benzodiazepine with an antidepressant plus placebo. The included trials used the following antidepressant/benzodiazepine combinations:

- Maprotiline or nortriptyline plus flunitrazepam (2 mg) or lormetazepam (2 mg) (NOLEN1993)
- Fluoxetine plus clonazepam (0.5 mg up to 1 mg) (SMITH1998, SMITH2002)
- Imipramine plus diazepam (10 mg) (FEET1985)
- Amitriptyline plus chlordiazepoxide (mean 44 mg) (SCHARF1986)

The mean dose of TCAs was between 122.5 mg and 200 mg, and fluoxetine was given at between 20 mg and 40 mg.

8.3.4.6.3 Evidence statements

Effect of treatment on efficacy

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any efficacy measure.

Acceptability of treatment

There is insufficient evidence to determine whether there is a clinically significant difference between antidepressants plus a benzodiazepine and antidepressants plus placebo on any tolerability measure.

8.3.4.6.4 Clinical summary

There is insufficient evidence to determine whether there is any effect of adding a benzodiazepine to antidepressant treatment in terms of both efficacy and tolerability.

8.3.4.7 Augmenting antidepressants with an antipsychotic

8.3.4.7.1 Introduction

Ostroff and Nelson (1999) reported on eight patients with non-psychotic depression who, having failed to respond to an SSRI, did respond when risperidone was added. In an eight-week, double-blind clinical trial of olanzapine in combination with fluoxetine in patients who were 'stage two treatment resistant', the combination was superior to either agent on its own (Tohen *et al.*, 1999[48]).

8.3.4.7.2 Studies considered for review

A separate search for systematic reviews of antipsychotic augmentation of antidepressants was undertaken (i.e. in addition to the searches undertaken for all systematic reviews for the treatment of depression – see Chapter 3). Since no suitable review was found, the GDG took the decision to search for RCTs only for olanzapine augmentation of fluoxetine. One study was found in a search of electronic databases (SHELTON2001), and this met the inclusion criteria set by the GDG. It compares fluoxetine plus olanzapine with fluoxetine plus placebo. Patients had failed at least two courses of antidepressants before entering the study, and were randomised to augmentation treatment only if they failed to respond to a course of open-label fluoxetine.

8.3.4.7.3 Evidence statements

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically significant difference favouring augmentation of fluoxetine with olanzapine over fluoxetine alone on increasing the likelihood of achieving a 50% reduction in depression symptoms (N = 1; *n* = 20; RR = 0.44; 95% CI, 0.2 to 0.98).

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between augmentation of fluoxetine with olanzapine and fluoxetine alone on reducing the likelihood of leaving treatment early (N = 1; *n* = 20; RR = 0.33; 95% CI, 0.04 to 2.69).

8.3.4.7.4 Clinical summary

There is little evidence on which to make an evidence-based recommendation of antipsychotic augmentation of antidepressants for the treatment of treatment-resistant depression.

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[48] This study is also published as SHELTON2001 which is reviewed below.

8.3.4.8 Augmenting an antidepressant with buspirone

8.3.4.8.1 Introduction

Buspirone is a 5HT1a partial agonist that is licensed for the treatment of anxiety. Its proposed mechanism of action as an augmentor of antidepressant drugs is similar to that of pindolol (see Section 8.3.4.4).

8.3.4.8.2 Studies considered for review

Only studies comparing antidepressant augmentation with buspirone with augmentation with placebo for people whose depression is treatment resistant were considered. One study was included (APPELBERG01). This compared fluoxetine or citalopram augmented with buspirone (20 mg to 60 mg) with fluoxetine or citalopram augmented with placebo in people whose depression had not responded to a single course of antidepressants.

8.3.4.8.3 Evidence statements

Effect of treatment on efficacy

There are no extractable data on the efficacy of buspirone augmentation.

Acceptability of treatment

There is insufficient evidence to determine if there is a clinically significant difference between buspirone augmentation and SSRI monotherapy on any tolerability measure.

8.3.4.8.4 Clinical summary

There is no evidence on which to make an evidence-based recommendation of augmentation of antidepressants with buspirone for the treatment of treatment-resistant depression.

8.3.5 Recommendations for the pharmacological treatment of treatment-resistant depression

8.3.5.1 Where combinations of antidepressants other than mianserin with SSRIs and mirtazapine with SSRIs are considered, healthcare professionals should re-evaluate the adequacy of previous treatments carefully before proceeding and consider seeking a second opinion. Any discussion should be documented in the notes. (C)

8.3.5.2 Where patients are treated with one antidepressant augmented by another, careful monitoring of progress and side effects is advised and the importance of this should be explained to the patient. Particular care should be taken to monitor for serotonin syndrome. (GPP)

8.3.5.3 There is sufficient evidence to recommend the use of benzodiazepine augmentation of antidepressant. (C)

8.3.5.4 Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate the side effects. There is evidence for benefits from the addition of mianserin or mirtazapine to SSRIs. (C)

8.3.5.5 When used to augment another antidepressant, mianserin should be used with caution, particularly in older adults, because of the risk of agranulocytosis. (C)

8.3.5.6 Venlafaxine should be considered for patients whose depression has failed to respond to two adequate trials of other antidepressants. Consideration should be given to increasing the dose up to BNF limits if required, provided patients can tolerate the side effects. (C)

8.3.5.7 A trial of lithium augmentation should be considered for patients whose depression has failed to respond to several antidepressants and who are prepared to tolerate the burdens associated with its use. (B)

8.3.5.8 Phenelzine should be considered for patients whose depression has failed to respond to alternative antidepressants and who are prepared to tolerate the side effects and dietary restrictions associated with its use. However, its toxicity in overdose should be considered when prescribing for patients at high risk of suicide. (C)

8.3.5.9 Augmentation of an antidepressant with carbamazepine, lamotrigine, buspirone, pindolol, valproate or thyroid supplementation is not recommended in the routine management of treatment-resistant depression. (B)

8.3.6 Research recommendations

8.3.6.1 Adequately powered RCTs reporting all relevant outcomes should be undertaken to assess the efficacy of valproate and lamotrigine in the management of treatment-resistant depression.

9 Health economics evidence

9.1 Background

In order to help the decision-making process of the GDG, relevant economic evidence was collected and assessed where available. This process was based on a preliminary analysis of the clinical evidence and had three stages:

- Identification of the areas with likely major cost impacts within the scope of the guideline
- Systematic review of existing data on the economic burden of major depressive disorder and cost-effectiveness evidence of different treatment options for depression
- Primary economic evaluation alongside the guideline development procedure to provide cost-effectiveness evidence where such previous data did not exist.

9.2 Key economic issues

It is widely acknowledged that numerous economic issues exist relevant to the management of major depressive disorder in the UK. However, the GDG in collaboration with the health economist identified four key issues considered to be of particular importance:

- The economic burden of depression in the UK
- Comparative cost-effectiveness of older versus newer antidepressants
- Comparative cost-effectiveness of relapse prevention with maintenance antidepressant treatment versus no maintenance antidepressant treatment for relapse prevention
- Comparative cost-effectiveness of pharmacological, psychological and combination therapies for patients with depression treated in primary or secondary care.

9.3 Systematic literature review

A systematic review of the health economic evidence was conducted. The aim was three-fold:

- To identify all publications with information about the economic burden of depression in the UK

- To identify existing economic evaluations of any psychological, pharmacological, or other physical or service-level interventions for the treatment of major depressive disorder undertaken in the UK

- To find studies with health state utility evidence generalisable to the UK context to facilitate a possible cost-utility modelling process.

Although no attempt was made to systematically review studies with only resource use or cost data, relevant UK-based information was extracted for future modelling exercises if it was considered appropriate.

9.3.1 Search strategy

In September 2002, bibliographic electronic databases (MEDLINE, PreMEDLINE, EMBASE, CINAHL, PsycINFO, CDSR, CCTR, DARE, HTA) and specific health economic databases (NHS EED, OHE HEED) were searched for economic studies. For Medline, PreMedline, Embase, CINAHL, PsycINFO, CDSR, CCTR and DARE, a combination of a specially developed health economics search filter already tested in earlier NCCMH guidelines and a general filter for major depressive disorder was used. Subject headings and free-text searches were combined. HTA, NHS EED and OHE HEED were searched using shorter, database-specific strategies. OHE HEED was searched again in April 2003 to identify recently published economic studies.

Applying similar methodology, secondary searches, focused on a selection of antidepressants chosen as 'class markers', were carried out to identify additional pharmacoeconomic studies. Search strategies and further information on the health economic systematic review are presented in Appendix 14.

In addition to searches of electronic databases, reference lists of eligible studies and relevant reviews were searched by hand, and experts in the field of depression and mental health economics were contacted to identify additional relevant published and unpublished studies. Studies included in the clinical evidence review were also screened for economic evidence.

9.3.2 Review process

The database searches for general health economic evidence for depression resulted in a total of 8570 references. Of these, 1669 were identified as potentially relevant. Secondary searches for additional pharmacoeconomic papers resulted in 1156 references, of which 63 were initially considered relevant. A further 50 potentially eligible references were found by handsearching. A second sift of titles/abstracts by the health economist reduced the overall number of potentially relevant publications to 353. (At this stage inclusion was not limited to papers only from the UK.) Full texts of all potentially eligible studies (including those where relevance/eligibility was not clear from the abstract) were obtained. These publications were then assessed against a set of standard inclusion criteria by the health economist, and papers eligible for inclusion as economic evaluations were subsequently assessed for internal validity. The quality assessment was based on the 32-point checklist used by the *British Medical Journal* to assist referees in appraising economic analyses (Drummond & Jefferson, 1996) (Appendix 15).

9.3.3 Selection criteria

Cost-of-illness/economic burden studies

- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.
- Only studies from the UK were included, as the aim of the review was to identify economic burden information relevant to the national context.
- Selection criteria based on types of clinical conditions and patients were identical to the clinical literature review (see Appendix 8).
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.

Economic evaluations

- Studies were included provided they had used cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis.
- Clinical evidence from a meta-analysis, a randomised controlled trial, a quasi-experimental trial or a cohort study was used.
- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.
- Only studies from the UK were considered, as the aim of the review was to identify economic evaluation information relevant to the national context.
- Selection criteria based on types of clinical conditions, patients, treatments and settings were identical to the clinical literature review (see Appendix 8).
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.

Health state utility studies

- Studies reporting health state utilities for depression were considered for inclusion.
- There was no restriction placed on language or publication status of the papers.
- Studies published between 1980 and 2003 were included.

- Only studies from OECD countries were considered to assure the generalisability of the results to the UK context.

- Selection criteria based on types of clinical conditions, patients, treatments and settings were identical to the clinical literature review (see Appendix 8).

9.3.4 Data extraction

Data were extracted by the health economist. Masked assessment, whereby data extractors are blind to the details of journal, authors, etc., was not undertaken.

9.3.5 Evidence synthesis

9.3.5.1 Cost-of-illness/economic burden studies

Altogether, 12 publications were deemed eligible for a review of the economic burden of depression (Berto *et al.*, 2000; Eccles *et al.*, 1999; Freemantle *et al.*, 1998; Freemantle & Mason, 1995; Goldberg *et al.*, 1996; Henry, 1993; Hughes *et al.*, 1997; Jonsson & Bebbington, 1993; Kind & Sorensen, 1993; Knapp & Ilson, 2002; Lepine *et al.*, 1997; West, 1992). A summary of these papers is presented in Chapter 2.5.

9.3.5.2 Economic evaluations

Not counting multiple publications, 26 papers were selected for data abstraction. Details and results of the included studies are summarised in the form of an evidence table in Appendix 16. Only a short summary of the results is reported here.

Pharmacological interventions

Two studies addressed the cost-effectiveness of maintenance antidepressant therapy (Hatziandreu *et al.*, 1994; Kind & Sorensen, 1995). Kind and Sorensen (1995) compared maintenance antidepressant therapy with the 'watchful waiting approach'. Although the average cost per symptom-free patient was higher for maintenance therapy, the cost difference was minor. The incremental analysis by Hatziandreu *et al.* (1994) confirmed that maintenance therapy is cost-effective compared with acute episodic treatment.

One study with moderate internal validity compared the use of an augmentor (pindolol) versus placebo with SSRI treatment (Tome & Isaac, 1998). The average effectiveness-cost ratio favoured the augmentation treatment option.

Ten papers investigated the comparative cost-effectiveness of newer versus older antidepressants (Borghi & Guest, 2000; Doyle *et al.*, 2001; Freemantle *et al.*, 1994; Freeman *et al.*, 2000; Forder *et al.*, 1996; Jonsson & Bebbington, 1994; Montgomery *et al.*, 1996; Stewart, 1994; Stewart, 1996; Woods & Rizzo, 1997), one of which was an update of an earlier calculation (Stewart, 1996) and another one (Woods & Rizzo, 1997) was a reassessment of the model by Jonsson and Bebbington (1994). Apart from the study by Borghi and Guest (2000) all used modelling techniques for their estimations.

The result of the paper by Freemantle *et al.* (1994) did not support the first-line use of newer antidepressants, the earlier study by Stewart (1994) could not show any cost advantage of SSRIs over TCAs, and the reassessed cost-effectiveness analysis by Woods and Rizzo (1997) did not confirm the superiority of paroxetine over imipramine showed earlier by Jonsson and Bebbington (1994).

The other seven studies showed that SSRIs are more cost-effective than TCAs. Out of these, the study by Montgomery *et al.* (1996) was based on the same model as the analysis of Jonsson and Bebbington (1994) but used a different SSRI as the comparator. There were a further two studies which were based on identical models (Doyle *et al.*, 2001; Freeman *et al.*, 2000). Both studies compared venlafaxine with SSRIs and TCAs and concluded that venlafaxine is more cost-effective than older antidepressants. However, the clinical estimates used for these comparisons were inconsistent with the results of our clinical evidence review. Hence, an opportunity cost approach was taken and information on the primary care cost (medication, staff, dispensing) of different antidepressant treatments over a four-month period was considered alongside the clinical evidence (Table 1). For the cost calculations, resource use information was obtained from the GDG acting as an expert panel. Unit cost data were extracted from multiple sources (BNF 45; Netten *et al.*, 2002). All costs were expressed in £ for the year 2002/03.

Table 1: Antidepressant therapy costs.

Antidepressant	*Average daily dose (mg)*	*Treatment cost per patient (£, 2002/03)*
Amitriptyline	75	70.06
Imipramine (NP)	100	76.90
lofepramine (Gamanil)	140	101.79
Citalopram	20	128.32
Fluoxetine (NP)	20	90.06
Paroxetine (NP)	20	118.90
Phenelzine (Nardil)	45	131.44
Reboxetine (Edronax)	8	135.26
Sertraline (Lustral)	100	173.23
Moclobemide (NP)	300	135.06
Mirtazapine (Zispin)	30	157.89
Venlafaxine (Efexor)	100	196.59

Summary

Based on the published information and on recent clinical evidence showing significantly better outcomes with maintenance therapy, it is likely that antidepressant maintenance therapy is cost-effective to prevent relapse. However, no health economic evidence exists about the optimal length of maintenance therapy.

Current pharmacoeconomic evidence suggests that SSRIs are more cost-effective than TCAs for the first-line treatment of major depression. In contrast to the published evidence on venlafaxine, the first-line use of this drug was not supported by the opportunity cost considerations based on the guideline clinical evidence review.

Overall, the published pharmacoeconomic evidence is not sufficient to inform present guideline recommendations on the single most cost-effective antidepressant for the first-line treatment of major depression in the UK. The availability of resources for the guideline development process did not permit primary modelling of such evidence. In the future, a comprehensive, independent model of the evidence on the cost-effectiveness of newer antidepressants used as first-line treatments is necessary. This should take into consideration that prices of the newer antidepressants are likely to decrease significantly as generic versions of these drugs become available.

Psychological interventions

Eight studies focused on the cost-effectiveness of brief psychological interventions or computerised CBT in primary care compared with usual GP care (Friedli *et al.*, 2000; Kaltenthaler *et al.*, 2002; King *et al.*, 2000; McCrone *et al.*, 2003; Miller *et al.*, 2003; Mynors-Wallis *et al.*, 1997; Scott & Freeman, 1992; Simpson *et al.*, 2000).

Four studies could not find a significant difference either in the outcomes or in the costs between the different alternatives (Friedli *et al.*, 2000; King *et al.*, 2000; Miller *et al.*, 2003; Simpson *et al.*, 2000). We estimated using UK-based unit costs and expert opinion of the GDG and also found that brief psychological interventions would have very similar costs to antidepressant therapy in primary care. (For example, the cost of a standard course of problem-solving therapy provided by a counsellor was estimated at £117 for year 2002/03.)

The cost-effectiveness estimate of Mynors-Wallis *et al.* (1997) favoured usual GP care when a healthcare perspective was used, and found problem-solving therapy provided by community nurses superior in the societal perspective. Scott and Freeman (1992) found counselling provided by social workers more effective than usual GP care, but usual GP care was less costly than any of the specialist treatments assessed in the study (i.e. amitriptyline prescribed by a psychiatrist, CBT, counselling). Due to the small sample sizes of the latter two studies, however, these results should be treated with caution.

One study, not yet published, found computerised CBT superior to routine care (McCrone *et al.*, 2003). Crude estimates of a recent Health Technology Assessment supports this finding (Kaltenthaler *et al.*, 2002), but also show great differences in the cost-effectiveness of the different types of computerised CBT.

In summary, it is likely that the additional costs, if any, of brief psychological interventions provided in primary care are offset by savings on other healthcare costs. Hence, other factors such as clinical benefits, patient preferences and staff availability should be taken into consideration when choosing between these alternatives (King *et al.*, 2000).

Three further studies investigated the cost-effectiveness of psychological interventions on an outpatient basis. The study by Leff *et al.* (2000) showed that couple-focused therapy was superior to antidepressant therapy in terms of clinical outcomes and that the additional costs of couple-focused therapy were offset by savings in other health service use. However, the validity of the results is greatly limited due to the high dropout rate. For the same reason, the study was excluded from the clinical review. The study by Guthrie *et al.* (1999) compared brief psychodynamic interpersonal therapy with usual psychiatrist care. They found psychotherapy to be both more effective and cost saving. A recent study by Scott *et al.* (2003) reported that CBT in combination with antidepressant therapy is likely to be cost-effective for relapse prevention in patients with residual depression.

Electroconvulsive therapy (ECT)

A recent Health Technology Appraisal (NICE, 2003) could not identify any published economic studies relating to ECT. The primary model constructed by the Assessment Group concluded that ECT and pharmacotherapy are likely to be equally cost-effective for the inpatient treatment of adults with severe depression. The authors highlight that a considerable amount of uncertainty exists in the data on which the model was based.

Service provision

One study assessed the efficiency of service provision in hospital or in the community (Goldberg *et al.*, 1996). Using less robust economic methodology, the authors found the latter alternative significantly cost saving, while no difference could be detected between the two options in terms of clinical outcome.

9.3.5.3 Health state utility studies

Among the studies already assessed for eligibility, six publications could be identified reporting information relevant to patient-assigned health state utility values for depression (Bennett *et al.*, 2000; King *et al.*, 2000; Pyne *et al.*, 1997; Pyne *et al.*, 2001; Revicki & Wood, 1998; Whalley & McKenna, 1995).

The paper by Whalley and McKenna (1995) summarised the different quality-of-life instruments for depression and anxiety, and reviewed published studies of quality-of-life in depression and anxiety. They concluded that very few published studies were available on the topic at that time. King *et al.* (2000) based their estimates on a patient population with mixed anxiety/depression, and so these utility values were not suitable to inform a possible cost-utility model for patients with depression only. The paper by Bennett *et al.* (2000) presented a disease specific utility measure. Neither the study from 1997 (Pyne *et al.*, 1997) nor the result of a more recent study by Pyne *et al.* (2001) provided sufficient information for the calculation of QALYs for economic analyses. The earlier study showed that there is a highly significant reduction in the Quality of Well-Being scale (QWB) scores for people with major depressive disorder (MDD) compared with controls and that the scores are inversely correlated with depression severity (Pyne *et al.*, 1997). The latter study revealed that although the overall index score of the QWB scale was not a strong predictor of acute treatment response to inpatient antidepressant therapy, the lower scores on the physical activity and the higher scores on the social activity subscales of QWB are among the strongest predictors of such response (Pyne *et al.*, 2001). The health state utility values reported by Revicki and Wood (1998), however, were deemed suitable to be used for the calculation of QALYs for our model.

Summary

All six studies reported significant impact of depression on the quality-of-life of patients with MDD. People with moderate to severe depression had QWB scores similar to ambulatory AIDS patients and patients with moderate to severe chronic obstructive pulmonary disease (Pyne *et al.*, 1997). A considerable proportion (25%) of the patients with MDD valued the state of severe depression worse than death or equal to death (Revicki & Wood, 1998).

There is an ongoing debate however about the sensitivity and reliability of utility measures for patients with mental health problems (Chisholm *et al.*, 1997). In the lack of several comparable studies investigating this question in patients with major depression, significant uncertainty remains around the current estimates.

9.4 Cost-effectiveness modelling

9.4.1 Background

The literature search did not identify any robust evidence on the comparative cost-effectiveness of individual psychological therapies with pharmacological treatment and the combination of these therapies for the routine secondary care treatment of patients with moderate/severe depression. The only study (Scott, 2003) addressing this question was published only recently and had limited generalisability as it investigated the cost-effectiveness of combination therapy compared with pharmacotherapy for relapse prevention in patients with residual depression. Therefore, it was decided to devise a cost-effectiveness model that summarised the available clinical evidence and combined it with relevant cost data to answer the question outlined above.

Current evidence shows that a course of cognitive behavioural therapy (CBT) or interpersonal therapy (IPT) is effective in treating acute depression and also significantly reduces the risk of relapse. Based on expert advice, CBT was chosen as the form of psychological therapy for this analysis since currently it has the best clinical evidence and it is more widely available than IPT in the UK. Based on the available clinical, utility and cost data, fluoxetine was chosen as the representative antidepressant therapy for inclusion in the model.

9.4.2 Methods

Treatment strategies and model structure

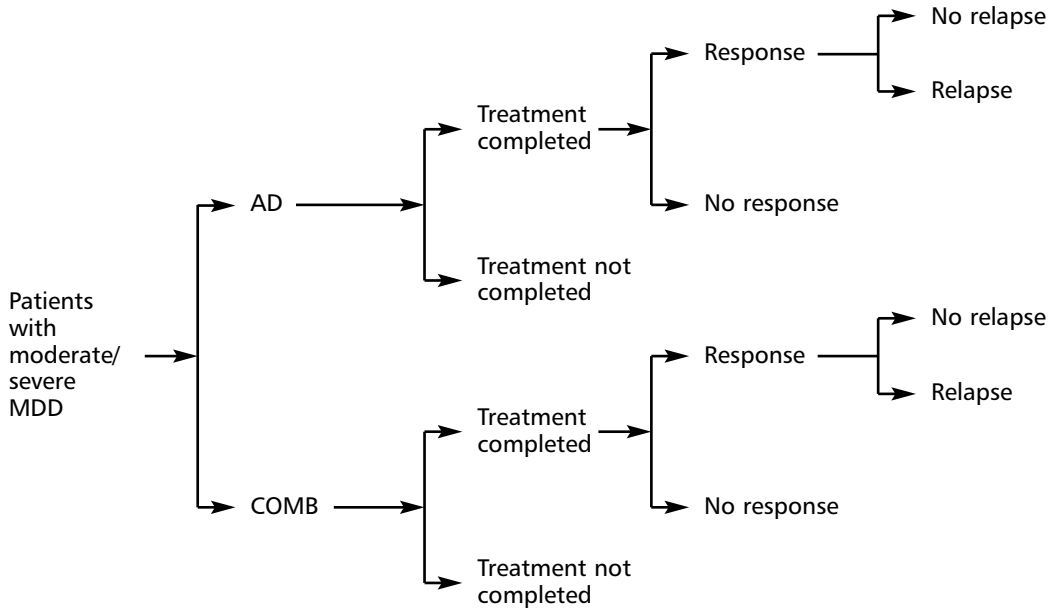
A formal decision analytic model was constructed in order to explore the incremental cost-effectiveness of antidepressant therapy and the combination of antidepressant therapy and CBT for the routine treatment of moderate/severe depression in secondary care. The analysis was undertaken using Microsoft Excel XP. The detailed structure of the decision tree is presented in Figure 1.

Strategy A: Antidepressant treatment given for 12 weeks and 12-month follow-up without maintenance treatment (AD).

Strategy B: Combination of 12 weeks' antidepressant treatment and 16 sessions of CBT and 12-month follow-up without maintenance treatment (COMB).

Originally three specific strategies for the first-line management of depression were considered. However, the clinical evidence review showed no overall superiority for CBT alone on treatment outcomes over antidepressants. The efficacy evidence together with the significantly higher treatment cost of CBT compared with the cost of antidepressants resulted in the exclusion of CBT alone from the final cost-effectiveness analysis.

Figure 1: Structure of the model.



Assumptions of the model

Population

- A cohort of 100 patients in each arm.
- Each patient in the model has moderate/severe depression and is treated in secondary care.

Antidepressant therapy

- Antidepressant therapy: 40 mg/day generic fluoxetine for 12 weeks.
- 'Standard care' is assumed to be antidepressant therapy initiated by a consultant psychiatrist and maintained by a specialist registrar. Initial prescription is for a fortnightly dose of the medication followed by prescriptions of doses for six and four weeks. There are four consultations, each lasting 15 minutes on average.
- Intensive clinical management means weekly sessions of 20 minutes for 12 weeks provided by the psychiatrist.
- The outcome of antidepressant therapy does not depend on whether standard care or intensive clinical management is provided. (The clinical evidence was based on a mixture of studies using formal clinical management or standard care in addition to antidepressant therapy.)
- There is no maintenance therapy.
- Occasionally missed treatment sessions mean that full costs are incurred.

- Those patients who do not complete the treatment do not incur full treatment costs, only a proportion of it corresponding to the mean dropout time. However, they will consume other healthcare resources as a consequence of their depression.

- Average time to dropout is 21 days.

- Patients completing treatment but not responding to it, or relapsing during follow-up, will use further healthcare resources as a consequence of their depression.

- The cost of events such as patients taking an overdose of antidepressants has not been included. The drug protocols used in the two treatment strategies were identical. Hence, it was assumed that such cost would not influence the cost difference between the two strategies significantly.

Combination therapy

- Combination therapy consists of 16 sessions of CBT over 12 weeks and 12 weeks' antidepressant therapy with standard care as described above. One CBT session is 50 minutes in duration. CBT is provided by a suitably qualified and trained clinical psychologist. (In the model, a clinical psychologist was used as a representative example of therapists providing CBT for patients with depression in secondary care.)

- There is no maintenance therapy.

- Occasionally missed treatment sessions mean that full costs are incurred.

- Those patients who do not complete the treatment do not incur full treatment costs, only a proportion of it corresponding to the mean dropout time. However, they will consume other healthcare resources as a consequence of their depression.

- Average time to dropout is 21 days.

- Patients completing treatment but not responding to it, or relapsing during follow-up, will use further healthcare resources as a consequence of their depression.

- The cost of events such as patients taking an overdose of antidepressants would not influence the cost difference between the two strategies significantly, since the drug protocols used in the two treatment strategies are identical.

Clinical outcomes and event probabilities

The number of successfully treated patients was chosen as the primary outcome measure in the economic evaluation. However, a secondary analysis was also carried out using quality-adjusted life years (QALYs) as the outcome measure. No discounting of benefits was necessary since the overall time horizon of the analysis was 15 months.

Clinical parameter estimates were collected as part of the clinical evidence review for the guideline. From the outcome measures used in the clinical effectiveness review, the dichotomous outcome measure of 'no response to treatment' defined by scores greater than six on the 17-item HRSD or more than eight on the 24-item HRSD was chosen as being the most appropriate for the cost-effectiveness analysis.

The event probabilities used in the model were based on intention-to-treat rules. For the base case analysis, absolute risk estimates were taken from the guideline meta-analyses. To determine the minimum/maximum values for sensitivity analysis, the absolute risk ratios of antidepressant therapy and the 95% confidence intervals around the relevant risk differences between antidepressant therapy and combination therapy were combined. Full details of the event probabilities used in the model are given in Table 2.

To estimate benefits in terms of QALYs, utility values were obtained from a published study, which reported patient-assigned health state utilities by depression severity and antidepressant medication (Revicki & Wood, 1998) (Table 2). Uncertainty around these estimates was also explored by sensitivity analysis.

Resource use and unit costs

Since no patient level data were available to calculate costs for the economic evaluation, deterministic costing of the different treatment strategies was carried out. The costs were identified from the perspective of the National Health Service. Non-health service expenditure and indirect costs were not considered in the analysis. All cost data were for the year 2002/03, adjusted using the Hospital and Community Health Service inflation index (Department of Health, UK) where required. As in the case of outcomes, no discounting was applied since the time horizon of the analysis was 15 months.

Resource utilisation data were collected as part of the literature review or from the GDG acting as an expert panel. Unit costs were obtained from a variety of sources including the *British National Formulary 45* (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2003) and the Personal Social Services Research Unit (Netten *et al.*, 2002). The applied staff unit costs were without qualification costs, but included salary costs, salary on-costs, overheads, capital overheads and ongoing training costs. Estimated resource utilisation data were then combined with the relevant unit cost information to give the reference cost associated with each treatment. All treatment costs were adjusted for patients who do not complete the treatment.

The health service costs of depression management for people who either do not complete the treatment, complete but do not respond to treatment, or relapse during follow-up, were also included in the economic evaluation (Borghi & Guest, 2000). Due to the great uncertainty around the original estimates, these parameters were included in the sensitivity analysis.

Details of the model parameters are listed in Table 2 alongside.

Table 2: Model parameters.

Parameter	Strategy	Base case value (mean)	Range (95% CI)	Source
Clinical outcomes				
Probability of not completing treatment	AD	0.30		Guideline meta-analysis
	COMB	0.25		Guideline meta-analysis
Risk difference in not completing treatment		–0.06	(–0.12) – (0.00)	Guideline meta-analysis
Probability of no response when treatment is completed	AD	0.57		Calculated using guideline meta-analysis
	COMB	0.38		Calculated using guideline meta-analysis
Risk difference in no response when treatment is completed		–0.19	(–0.45) – (–0.03)	Calculated using guideline meta-analysis
Probability of relapse at 12-month follow-up	AD	0.55		Simons, 1986 and Blackburn, 1986
	COMB	0.38		Simons, 1986 and Blackburn, 1986
Risk difference in relapse at 12-month follow-up		–0.17	(–0.44) – (–0.10)	Simons, 1986 and Blackburn, 1986
Health state utilities				
Severe depression		0.30	0.23 – 0.37	Revicki & Wood, 1998
Moderate depression		0.63	0.58 – 0.68	Revicki & Wood, 1998
Response, treatment		0.80	0.76 – 0.84	Revicki & Wood, 1998
Response, no treatment		0.86	0.82 – 0.90	Revicki & Wood, 1998
Unit costs (all estimates are in prices £ 2002/03)				
Generic fluoxetine 20 mg per pack		£7.61		BNF 45
Dispensing fee per prescription		£0.95		Prescription Pricing Authority
Consultant psychiatrist (per hour of patient contact)		£207		Netten *et al.*, 2002
Specialist registrar (per hour of patient contact)		£27		Netten *et al.*, 2002
Clinical psychologist (per hour of client contact)		£65		Netten *et al.*, 2002
Five-month cost of depression management for patients discontinuing treatment		£245	£60 – £600	Borghi & Guest, 2000

Incremental cost-effectiveness of COMB versus AD therapy

The incremental cost-effectiveness of COMB compared with AD was evaluated by assessing the difference in costs and the difference in effectiveness of each treatment. The difference in effectiveness was primarily measured as the number of additional successfully treated patients. A secondary analysis based on the number of QALYs gained was also carried out. The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in the expected direct healthcare costs with the difference in the overall effects of the two strategies.

Sensitivity analyses

One-way sensitivity analysis

There was considerable uncertainty about a few parameter estimates used in the base case model. Furthermore, the policy implications of point estimates are usually ambiguous. To explore the effect of uncertainty around individual parameters, a one-way sensitivity analysis was carried out whereby a single parameter was varied between its plausible minimum and maximum values while maintaining all remaining parameters at their base case value.

Probabilistic analysis

To demonstrate the joint uncertainty around the parameters used in the cost-effectiveness model, a probabilistic analysis was conducted. Using the base case estimates and the minimum/maximum values of the different variables, appropriate distributions were assigned to each parameter included in the sensitivity analysis and Monte-Carlo simulations of the incremental costs and effects were carried out. More details of the theoretical basis of probabilistic analysis are described in a publication by Briggs and Gray (1999).

9.4.3 Results

Clinical outcomes

The systematic review of the clinical evidence showed that the number of people not completing treatment is significantly higher for AD than for COMB. The absolute risk per person being 0.30 and 0.25, respectively. Furthermore, the probability of no response when completing treatment is also significantly greater for AD (0.57) than for COMB (0.38). (The latter values were calculated from the overall probability of no response at the end of treatment reported in the clinical evidence review.) The difference in the number of successfully treated patients further increased when relapse values were also considered. Significantly fewer people who responded to the original COMB treatment relapsed during the 12-month follow-up (0.38 vs. 0.55). The analysis revealed that approximately 165 more patients per 100 would be successfully treated in the COMB therapy arm compared with the AD treatment arm over a 15-month period. The result also favoured COMB therapy over AD when benefits were measured in QALYs. The average gain in QALYs was shown to be 0.11 per patient suffering from severe depression and 0.04 per patient suffering from moderate depression.

Costs

Antidepressant treatment costs

The total AD therapy cost included medication cost, staff costs and dispensing fees. Multiple scenarios were considered. The first scenario reflected usual clinical practice (standard care) and revealed that a full course of 12-week antidepressant therapy with standard care would cost on average £162. The second scenario included the costs of intensive clinical management frequently used in clinical trials. Formal clinical management increased the cost of AD therapy to £283. This adjustment did not affect the total cost of combination therapy.

Combination therapy cost

The cost of a full course of CBT was estimated at £867 when provided by a suitably qualified and trained clinical psychologist. The cost of COMB therapy included the cost of AD therapy with standard care as outlined above and the cost of CBT. On average, the total cost of COMB therapy was £1029.

Additional health service costs for the management of depression

It is well known that depressed people who are treated unsuccessfully or relapse will continue to impose considerable extra costs for the healthcare sector as a consequence of their depression. Borghi and Guest (2000) estimated the 5-month cost of the additional healthcare resource use to be £206 (1997/98 prices) for patients with moderate or severe depression who discontinue initial antidepressant treatment. The original estimate was inflated to 2002/03 prices and extrapolated to calculate the total cost of additional health service use over a 15-month period for people not completing initial treatment (£680), completing but not responding to treatment (£580), or relapsing during follow-up (£417).

Incremental cost-effectiveness of COMB versus AD therapy

COMB therapy was estimated to be both significantly more effective and more costly than AD treatment. On average, the strategy of COMB therapy was £637/£539 more costly per patient when not considering/considering the additional costs of intensive clinical management for antidepressant therapy. The resulting base case ICERs were £4056/£3431 per additional successfully treated patient, £5777/£4887 per QALY gained for severe depression and £14,540/£12,299 per QALY gained for moderate depression, respectively (Table 3).

Table 3: Incremental cost-effectiveness of COMB versus AD with standard care for cohorts of 100 people with moderate/severe depression.

	AD	COMB	Difference	ICER (£)	95% CI lower limit	95% CI upper limit
Total costs (£)	65,978	129,654	63,675			
Number of successfully treated patients (at the end of follow-up)	14	29	16	4056	1300	84,900
QALY severe depression	52	63	11	5777	1600	44,800
QALY moderate depression	84	89	4	14,540	4700	148,500

QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio.

Sensitivity analyses

One-way sensitivity analysis

The parameter values used in the sensitivity analyses and the relevant incremental cost-effectiveness ratios are listed in Table 4. The results of the one-way sensitivity analysis showed that the findings are robust when single parameters are varied over their uncertainty ranges. The most significant components of uncertainty around the comparative cost-effectiveness of the two treatment strategies were: (1) the risk difference between AD and COMB therapy for no response when treatment is completed; and (2) the amount of clinical management patients receive during AD therapy. Other factors played a lesser role in the variation of the base case estimate.

Table 4: One-way sensitivity analysis (AD with standard care, severe depression).

Parameter	Range used in the sensitivity analysis (95% CI)	Cost per additional successfully treated patient (£)	Cost per additional QALY (£)
Clinical outcomes			
Risk difference in not completing treatment	(–0.12) – 0.00	4238 – 3884	6036 – 5532
Risk difference in no response when treatment is completed	(–0.45) – (–0.03)	1996 – 13,361	2598 – 33,195
Risk difference in relapse at 12-month follow-up	(–0.44) – (–0.10)	2080 – 24,643	3651 – 11,842
Health state utilities			
Severe depression	0.23 – 0.37	4056	5106 – 6653
Response, treatment	0.76 – 0.84	4056	5855 – 5702
Response, no treatment	0.82 – 0.90	4056	6109 – 5480
Partial improvement for non-responder patients who complete treatment	No–Yes	4056	5777 – 6286
Unit costs (in £ for year 2002/03)			
Five-month cost of depression management for patients discontinuing treatment	£60 – £600	4531 – 3150	6453 – 4486

Probabilistic sensitivity analysis

To report the results of the probabilistic sensitivity analysis, cost-effectiveness acceptability curves were devised (Figures 2–4). The curves indicate the probability of COMB therapy being cost-effective for a range of potential threshold values. The threshold value is the maximum amount of money a decision maker would be willing to pay for a unit of effect, in this case for a successfully treated patient or a QALY.

The probabilistic analysis showed that if decision makers are not willing to pay more for additional health benefit, COMB therapy is unlikely to be cost-effective. If decision makers are willing to pay £30,000 for an additional successfully treated patient with moderate/severe depression, the probability of COMB being cost-effective compared with AD therapy with standard care is 95%. The probability of cost-effectiveness at a £30,000 threshold is very similar when comparing COMB with AD therapy with intensive clinical management (Figure 2).

Figure 2: Cost-effectiveness acceptability curves of COMB therapy when compared with AD therapy for the routine treatment of moderate and severe depression in secondary care (benefits measured in terms of successfully treated patients).

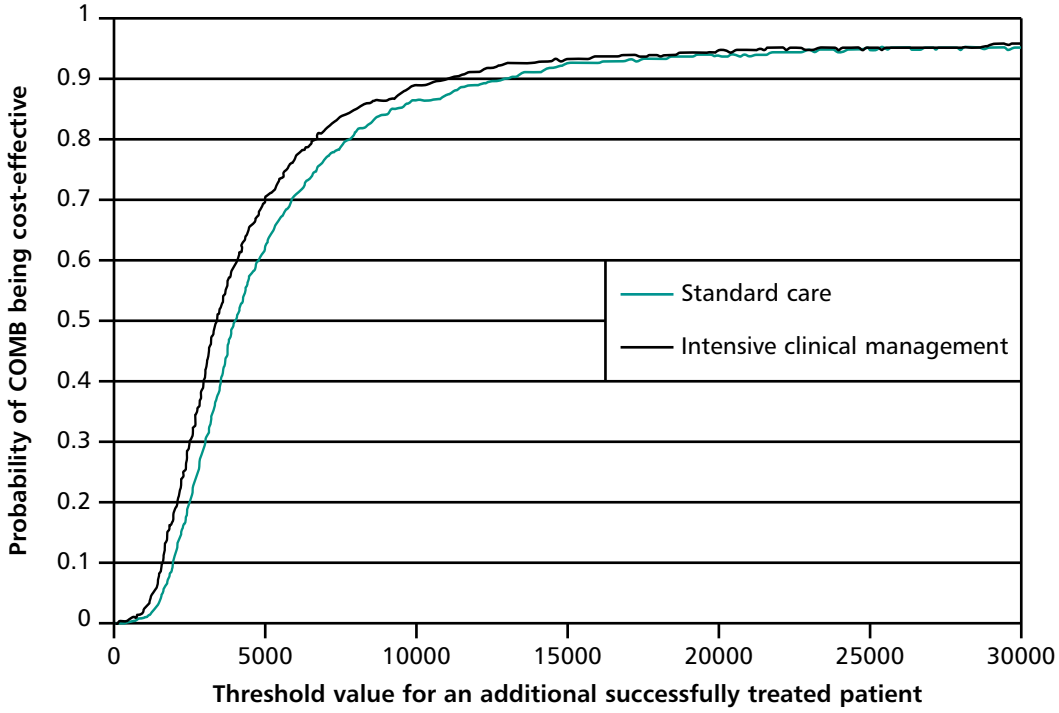
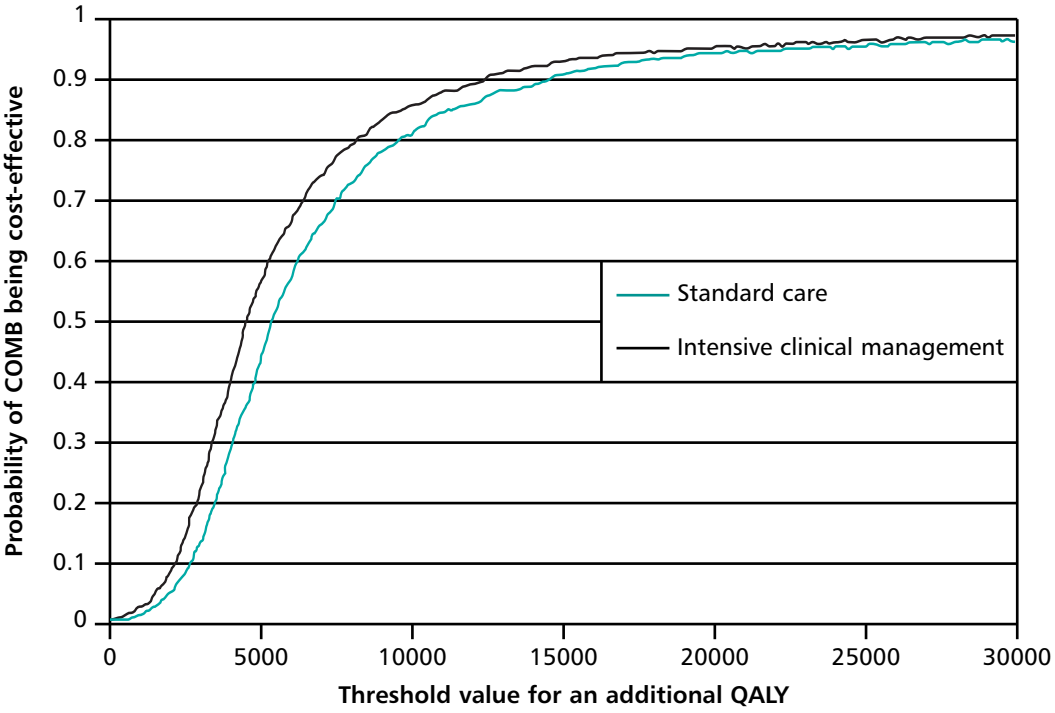


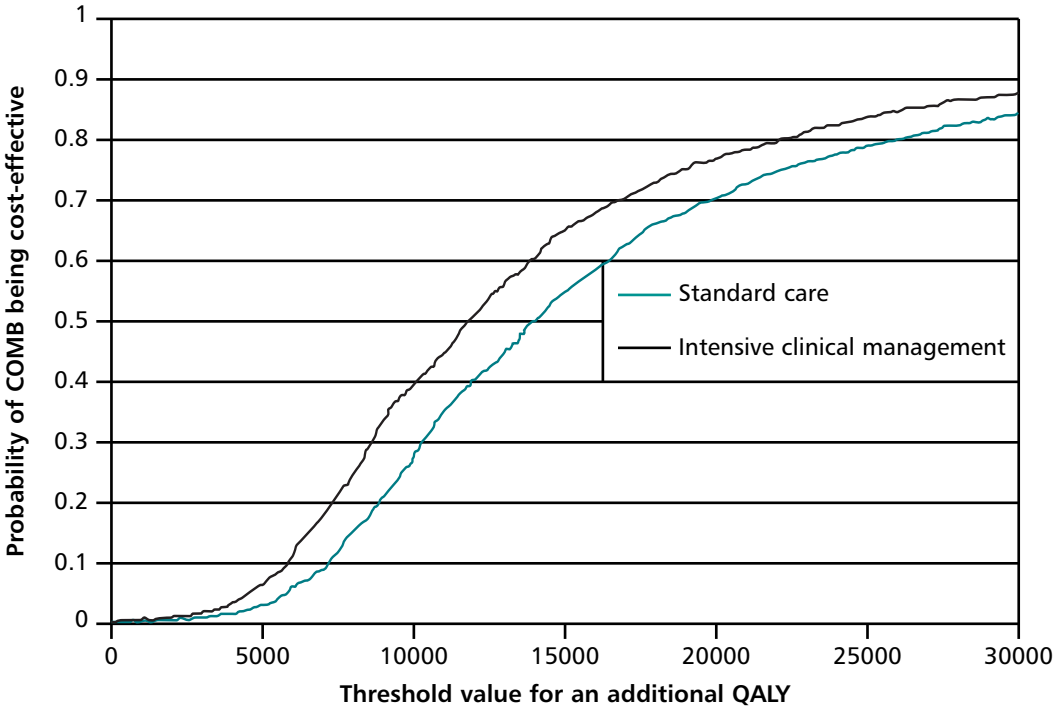
Figure 3: Cost-effectiveness acceptability curves of COMB therapy when compared with AD therapy for the routine treatment of severe depression in secondary care (benefits measured in terms of QALYs).



If we measure health benefits in terms of QALYs, there is over 95% certainty about the cost-effectiveness of COMB compared with AD with standard care for severe depression (Figure 3), but only 85% certainty for moderate depression at the recently quoted If we

measure health benefits in terms of QALYs, there is over 95% certainty about the cost-effectiveness of COMB compared with AD with standard care for severe depression (Figure 3), but only 85% certainty for moderate depression at the recently quoted £30,000 threshold as the decision makers' maximum willingness-to-pay per QALY (Figure 4) (Richardson *et al.*, 2004). Furthermore, in contrast to severe depression, the probability of cost-effectiveness for moderate depression is greatly affected by the threshold value.

Figure 4. Cost-effectiveness acceptability curves of COMB therapy when compared with AD therapy for the routine treatment of moderate depression in secondary care (benefits measured in terms of QALYs).



9.4.4 Discussion

The issue of the routine use of antidepressant therapy, individual psychotherapy or the combination of antidepressant therapy and individual psychotherapy for the secondary care management of people with moderate/severe depression in secondary care was identified as having a possible major cost impact on the NHS, but no existing cost-effectiveness evidence was available to facilitate the GDG's decision-making process.

In the economic evaluation, CBT was chosen as the psychotherapy and fluoxetine as the antidepressant drug being compared. A cost-effectiveness model was constructed to investigate the difference in clinical outcomes and direct healthcare costs between the different strategies. Preliminary analyses showed that CBT alone is likely to be dominated by antidepressant therapy and, therefore, it was excluded from the final model. Combination therapy is both more effective and more costly than antidepressant therapy, and these strategies were compared in a formal cost-effectiveness analysis.

The point estimate of the incremental cost per additional successfully treated patient varied between £4056 and £3431 depending on whether standard clinical support or intensive clinical management was provided with antidepressant therapy. When benefits were measured in terms of QALYs, the base case ICER estimates varied between £5777 and £4887 for severe depression and between £14,540 and £12,299 for moderate depression, respectively. Uncertainty around these estimates was explored by sensitivity analyses, including a probabilistic analysis.

Based on the overall results, CBT alone is unlikely to be a cost-effective first-line therapy for patients with moderate/severe depression treated in secondary care. Combination therapy, however, has been shown to be a cost-effective routine treatment for patients with severe depression. Due to the greater uncertainty, there is not sufficient evidence to support the cost effectiveness of first-line use of combination therapy for moderate depression at the current £30,000/QALY threshold value as decision maker's willingness-to-pay for an additional QALY in the UK.

It is anticipated that the type of antidepressant chosen for the model would not influence the relative cost-effectiveness of the two strategies significantly since the combination and antidepressant strategies include identical medication protocols. The same argument is likely to be valid for the cost of patients taking an overdose of antidepressants.

On the other hand, a wider provision of combination therapy is likely to impose additional training needs for CBT providers, and have considerable additional cost impact for the NHS. Although this needs careful consideration in a cost impact analysis of the guideline, it has not been included in this evaluation.

9.5 Research recommendations

For future research, it is recommended that studies should:

9.5.1 Explore the cost-effectiveness of the different newer antidepressants used as first-line treatments in the UK

9.5.2 Determine the optimal length of maintenance antidepressant therapy

9.5.3 Investigate the comparative cost-effectiveness of IPT versus CBT for the secondary care treatment of depression with regard to the non-disease specific nature and the lower training needs of IPT

9.5.4 Measure the health-related quality-of-life of patients with depression in future studies

9.5.5 Analyse the cost-effectiveness of improving the early detection of depression

9.5.6 Estimate the overall cost impact of the implementation of the guideline.

10 Appendices

Appendix 1: Scope for the development of a clinical guideline on the Management of depression

1 Objective

1.1 The National Institute for Clinical Excellence has commissioned a clinical guideline for patients and clinicians on depression. The guideline will provide advice on effective care using evidence from clinical trials and economic analyses.

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

2 Title

Depression: The management of Depression in Primary, Community and Secondary Care.[1]

3 Clinical need and practice[2]

3.1 Each year, one woman in 15 and one man in 30 will be affected by depression and every GP will see between 60 and 100 people with depression. Most of the 4000 suicides committed each year in England are associated to some extent with depression.

3.2 The rates of depression in people from the African-Caribbean and Asian communities are about 60% higher than that in the white population, with the difference being twice as great in men.

3.3 Antidepressant medications are used for treatment but are not always prescribed in correct doses. Second-line treatments currently include lithium and electroconvulsive therapy. Depression is treated with psychological therapies as well as combinations of pharmaco- and psycho-therapies.

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[1] The title changed in the development of the guideline.

[2] Taken from the National Service Framework for Mental Health.

3.4 A number of guidelines, consensus statements and local protocols exist. This guideline will review evidence of clinical and cost-effective practice, together with current guidelines, and will offer guidance on best practice. The guideline will include the outcome of the Institute's Health Technology Appraisals on electroconvulsive therapy and computerised cognitive behaviour therapy.

4 Population

4.1 The guideline will offer best practice advice on the care of people over 18 years of age who meet the standard diagnostic criteria of depression or related disorders, including dysthymia. There will be no upper age limit.

4.2 The guideline will be relevant to patients with mild, moderate and severe depression and will address primary, chronic and recurring depression.

4.3 The guideline will be sensitive to the varying approaches of different races and cultures and be aware of the issues of both internal and external social exclusion.

4.4 Although the guideline will be of relevance to all patients with depression whether or not it is accompanied by other illnesses, it will not address separately the management of patients with other physical or psychiatric conditions.

4.5 The guidance will be interpreted to ensure that patients have the information they need and the opportunities to discuss with their clinicians the advantages, disadvantages and potential side effects of treatment so that they can make informed choices about the options for their care.

4.6 Depression can affect the whole family and the guideline will recognise the role of the family in the treatment and support of patients.

5 Healthcare setting

5.1 The guideline will cover the care provided by primary, community and secondary healthcare professionals who have direct contact with and make decisions concerning the care of patients with depression.

5.2 This is an NHS guideline. Although it will comment on the interface with other services such as those provided by social services, prison services and the voluntary sector it will not include recommendations relating to the services exclusively provided by these agencies.

5.3 The guideline will include:

- care in general practice and NHS community care
- hospital outpatient and inpatient care

- primary/secondary interface
- crisis and home treatment services
- assertive outreach services
- day hospitals.

6 Diseases, interventions and treatment

6.1 The guideline development will cover the full range of care routinely made available by the NHS.

6.2 While it will not review the evidence on diagnosis or assessment (except where it concerns patients with a diagnosis of resistant depression), it will refer to the diagnostic criteria currently in use and therefore will describe the diagnostic factors which trigger the use of this guideline. The definition of the condition in relation to other affective disorders will be precise.

6.3 It will provide guidance to patients on pathways to treatment.

6.4 The guideline will not address primary prevention but will cover relapse prevention. Risk management and suicide prevention will be included in the guideline which will also address the action which might be taken when patients fail to respond to adequate treatment at any point, including criteria for referral on to other or specialist services.

6.5 The guideline will include appropriate use of pharmacological treatments.

6.5.1 Type

- Tricyclics (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs)
- When and under what circumstances other novel antidepressants should be used as second- or third-line treatments.
- Monoamine oxidase inhibitors
- Mood stabilisers
- Combination/adjuvant therapies
- Pharmacological interventions other than antidepressants including Hypericum (St John's wort)

6.5.2 Dose

6.5.3 Duration and discontinuation

6.5.4 Changing drug regimes and sequencing in non-response

6.5.5 Side effects

6.5.6 Toxicity

6.5.7 Guidance will be based on the best evidence available to the development group. When referring to pharmacological treatments, normally guidelines will recommend within the licence indications. However, where the evidence clearly supports it, recommendations for use outside the licence indications may be made in exceptional circumstances.

6.5.8 It is the responsibility of prescribers to be aware of circumstances where medication is contraindicated. The guideline will assume that prescribers are familiar with the side effect profile and contraindications of medication they prescribe for patients with depression.

6.6 The guideline will include appropriate use of psychological interventions including:

6.6.1 Type

- Cognitive behavioural treatments referring to the Institute's Technology Appraisal due in June 2002
- Interpersonal therapy (e.g. counselling)
- Other psychological interventions.

6.6.2 Frequency

6.6.3 Duration

6.7 The guideline will include appropriate use of combined pharmacological and psychological interventions including, where appropriate, those listed above in Sections 6.5 and 6.6.

6.8 The guideline will include guidance on the appropriate use of electroconvulsive therapy including:

6.8.1 Type

6.8.2 Frequency

6.8.3 Duration

6.8.4 Side effects

6.9 Where the evidence is available to enable robust advice to be formulated, the guideline will address aspects of self-care including diet, exercise, self-help groups and self-medication.

7 Presentation

The guideline will be available in three forms:

7.1 The full guideline containing the evidence base used by the developers.

7.2 A short form version, using a standard template, which will form the Institute's guidance to the NHS, including a clinical practice algorithm.

7.3 A version prepared specifically for patients and their carers which will interpret the recommendations made in the Institute's short form version and which will be designed to help patients to make informed choices about their care.

8 Status

8.1 This scoping statement is subjected to a four week period of consultation with stakeholders. The scope is then re-drafted and submitted to the Guidelines Advisory Committee and subsequently the Institute's Guidance Executive, for approval. Once approved, it is posted on the Institute's website, together with details of the Commissioning Brief and the name of the Collaborating Centre through which the guideline is being commissioned. The development of the guideline will begin in the autumn of 2001.

8.2 Information on the guidelines development process, stakeholder involvement and the progress of this guideline is available on the website http://www.nice.org.uk/.

Appendix 2: Special advisers to the Guideline Development Group

Dr Marie Donaghy
Head of School, Health Sciences, Queen Margaret University College, Leith Campus, Duke Street, Edinburgh EH6 8HF.

Appendix 3: Stakeholders who responded to early requests for evidence

All Wales Medical and Pharmaceutical Advisers Forum

Association of the British Pharmaceutical Industry (ABPI)

Birmingham Dental Hospital, Faculty of Dental Surgery

British Association for Psychopharmacology

British Dietetic Association

Chartered Society of Physiotherapy

College of Occupational Therapists

GlaxoSmithKline UK

Jannsen-Cilag Ltd

Lundbeck Ltd

Manic Depression Fellowship

Merck Pharmaceuticals

Mind

The National Childbirth Trust

National Schizophrenic Fellowship

SANE

Speakability

Trinity Pharmaceuticals Limited

UK Advocacy Network

Wyeth Laboratories

Appendix 4: Stakeholders and experts who responded to the first consultation draft of the guideline

Stakeholders

Age Concern Cymru

Alzheimer's Society

Association of the British Pharmaceutical Industry (ABPI)

Association for Quality in Health & Social Care

Dr Anthony Bateman

British Association of Art Therapists

British Association of Behavioural & Cognitive Psychotherapies (BABCP)

British Association for Psychopharmacology

British Dietetic Association

British Medical Association

British National Formulary (BNF)

Chartered Society of Physiotherapy

CIS'ters

College of Occupational Therapists

Community Practitioners' and Health Visitors' Association

Counselling in Primary Care Trust

Counsellors and Psychotherapists in Primary Care

Philip Cowan, Neurolink

Critical Psychiatry Network

East London and City Mental Health NHS Trust Affective Disorders Clinic (Eleni Palazidou)

Eli Lilly and Company Ltd

GlaxoSmithKline UK

Dr Andy Hershon

Mike Launer

Lundbeck Ltd

MIND

Neurolink

PAPYRUS (Prevention of Young Suicides)

Pfizer Ltd

Roche Diagnostics Ltd

Royal College of General Practitioners

Royal College of Nursing (RCN)

Royal College of Psychiatrists

Mike Scanlan, Northampton PCT

David Shiers (NIHME, West Midlands)

Dr David Smith, Consultant Psychiatrist Derbyshire Mental Health Services

Social Care Institute for Excellence (SCIE)

ST Solutions Ltd

Tavistock and Portman NHS Trust

Ultrasis plc

Victim Support

Wyeth Laboratories

Experts

Dr John Cape

Professor Chris Dowrick

Dr John Geddes

Professor Anthony Kendrick

Dr Irving Kirsch

Dr Chris Williams

Appendix 5: Researchers contacted to request information about unpublished or soon-to-be published studies

Dr Ian Anderson

Professor Ivy Blackburn

Professor Chris Dowrick

Dr Chris Freeman

Dr Linda Gask

Professor Steve Hollon

Dr J. Holmes

Professor Anthony Kendrick

Professor Glynis Parry

Professor Jan Scott

Dr John Swan

Dr Chris Williams

Appendix 6: Clinical questions

A. Service Topic Group

1. Does screening for depression by GPs improve outcomes?
2. In depression, does guided self-help improve outcomes compared to other interventions?
3. Does computerised CBT improve patient outcomes compared to other treatments?
4. Does exercise improve patient outcomes compared to other treatments or TAU?
5. In depression, which model of care produces the best outcomes?
6. Do non-statutory support groups improve outcomes?
7. Do crisis resolution and home treatment teams improve patient outcomes compared to other treatments?
8. Do day hospitals improve patient outcomes compared to other treatments?
9. Does electroconvulsive therapy improve patient outcomes compared to other treatments?

B. Psychology Topic Group

1. Are psychological interventions effective compared to:
    - treatment as usual
    - other psychological interventions
    - medication
2. Is there a benefit in combining psychological interventions with medication?

C. Pharmacology Topic Group

1. Is any single (or class of) antidepressant better in the treatment of depression?
2. Does the choice of antidepressant depend on:
    - Severity of depression (including threshold)
    - Depression sub-type (psychotic depression or depression with atypical features)
    - Side effects
    - Discontinuation symptoms
    - Setting
    - Gender
    - Age
    - Setting
3. What pharmacological strategies are effective in refractory depression?
4. Is St John's wort effective in depression?
    - By severity of depression
    - Compared to antidepressants
5. Which switching strategies are effective?
6. What are the best pharmacological management strategies to prevent relapse?

Appendix 7: Search strategies for the identification of clinical studies

Depression search filter

MEDLINE, CINAHL, EMBASE, PsycINFO, All EBM Reviews – Cochrane DSR, ACP Journal Club, DARE, and CCTR.

1. depressive disorder/ or dysthymic disorder/ or seasonal affective disorder/ or depression, involutional/ or depression/
2. depression/ or dysthymia/ or involutional depression/
3. major depression/ or seasonal affective disorder/ or anaclitic depression/ or dysthymic disorder/ or endogenous depression/ or involutional depression/ or reactive depression/ or recurrent depression/ or treatment resistant depression/
4. depression/ or depression, reactive/ or dysthymic disorder/
5. (seasonal affective disorder$ or depress$ or dysthym$).tw. or melancholi$.mp.
6. or/1-5
7. *manic depressive psychosis/
8. *bipolar disorder/
9. *bipolar depression/
10. or/7-8
11. 6 not 10

Systematic review search filter

MEDLINE, CINAHL, EMBASE, PsycINFO, All EBM Reviews – Cochrane DSR, ACP Journal Club, DARE, and CCTR – OVID interface

1. meta analysis/
2. meta analysis.fc.
3. meta-analysis.pt.

4. (review,academic or review,multicase).pt.

5. exp literature searching/

6. systematic review.pt.

7. (metaanaly$ or meta analy$ or meta?analy$).tw.

8. ((systematic or quantitative or methodologic$) adj (overview$ or review$)).tw.

9. (research review$ or research integration).tw.

10. (handsearch$ or ((hand or manual) adj search$)).tw.

11. (mantel haenszel or peto or dersimonian or der simonian).tw.

12. (fixed effect$ or random effect$ or (pooled adj data)).tw.

13. (medline or embase or scisearch or science citation or isi citation or 'web of science').tw.

14. or/1-13

Randomised controlled trials search filters

MEDLINE, CINAHL, EMBASE, PsycINFO, All EBM Reviews – Cochrane DSR, ACP Journal Club, DARE, and CCTR – OVID interface

RCT

1. exp clinical trials/ or cross-over studies/ or random allocation/or double-blind method/ or single-blind method/

2. random$.pt.

3. exp clinical trial/ or crossover procedure/ or double blind procedure/or single blind procedure/ or randomization/

4. exp clinical trials/ or crossover design/ or random assignment/

5. exp clinical trials/ or double blind method/ or random allocation/

6. random$.mp.

7. (cross-over or cross?over or (clinical adj2 trial$) or single-blind$ or single?blind$ or double-blind or double?blind$ or triple-blind or triple?blind).tw.

8. or/1-7

9. animals/ not (animals/ and human$.mp.)

10. animal$/ not (animal$/ and human$/)

11. meta-analysis/

12. meta-analysis.pt.

13. systematic review/

14. or/9-13

15. 8 not 14

RCT (including systematic reviews)

1. exp clinical trials/ or cross-over studies/ or random allocation/or double-blind method/ or single-blind method/

2. random$.pt.

3. exp clinical trial/ or crossover procedure/ or double blind procedure/or single blind procedure/ or randomisation/

4. exp clinical trials/ or crossover design/ or random assignment/

5. exp clinical trials/ or double blind method/ or random allocation/

6. random$.mp.

7. (cross-over or cross?over or (clinical adj2 trial$) or single-blind$ or single?blind$ or double-blind or double?blind$ or triple-blind or triple?blind).tw.

8. or/1-7

9. animals/ not (animals/ and human$.mp.)

10. animal$/ not (animal$/ and human$/)

11. or/9-10

12. 8 not 11

Update search for systematic reviews

6th November 2002

CINAHL (1982 to October Week 4 2002), EMBASE (1980 to 2002 Week 44), MEDLINE (1996 to October Week 4 2002), MEDLINE Daily Update (October 31, 2002), PsycINFO (2000 to November Week 1 2002)

Hits (after removing duplicates): 268

Systematic review AND **Depression**

NOT	1. animal$/ not (animal$/ and human$/)
	2. animals/ not (animals/ and human$.mp.)
	3. exp neoplasms/
	4. exp neoplasm/
	5. (cancer$ or neoplasm$).tw.
	6. exp reproduction/
	7. exp pregnancy/
	8. or/1-7
AND	limited to yr=2002

Service search filters	**Available on request**
Psychology search filters	**Available on request**
Pharmacology search filters	**Available on request**

Appendix 8: Systematic review and RCT eligibility checklist

Eligibility checklist	**Report reference ID:**	Eligibility ✓ x *(circle one)*
Checklist completed by:	**Date completed:**	
Topic Areas: 1 2 3	*(circle all applicable)*	
Overall assessment		
Comment		

Exclusion criteria	Code options ✓ x ?
Only concerned with:	
● Patients under 18 years of age	
● Diagnosis or assessment, unless for refractory patients	
● Primary prevention, unless relapse prevention	
● Care options not routinely made available by the NHS	
● Depression in conjunction with comorbid physical or mental illness	
Inclusion criteria	
Population	
● Reported results from patients who meet the standard diagnostic criteria of depression	
Topic Area	
1. Pharmacological	
1.1 TCAs	
1.2 Related antidepressants	
1.3 SSRIs	
1.4 MAOIs	
1.5 'Third generation' ADs	
1.6 Augmentation/prophylaxis drugs	
1.7 Benzodiazepines	
1.8 Other treatments	

Continued alongside

Topic Area	Code options ✓ x ?
2. Psychological	
2.1. Behaviour therapy	
2.2. Cognitive behavioural therapy	
2.3. Counselling	
2.4 Interpersonal psychotherapy	
2.5 Systemic/family approaches	
2.6 Couples therapy	
2.7 Group therapy	
2.8 Problem solving	
2.9 Psychodynamic psychotherapy (both short-term and long-term)	
3. Service	
3.1 Screening	
3.2 Guided self help	
3.3 Computerised CBT	
3.4 Exercise	
3.5 Managed care	
3.6 Non-statutory support	
3.7 Crisis resolution and home treatment teams	
3.8 Day hospitals	

Continued overleaf

Primary Outcomes	Code options ✓ x ?
● Adverse effects of treatment	
● Carer/family outcomes	
● Cognitive functioning	
● Compliance with:	
(a) Drug treatment	
(b) Other non-drug treatments	
● Death (any cause and sudden unexpected death or suicide)	
● Economic outcomes	
● Engagement	
● Hospital admission	
● Mental state:	
(a) Criterion-based improvement (as defined in individual studies)	
with reference to the positive and negative symptoms	
of depression	
(b) Continuous measures of mental state	
● Occupational status	
● Other intervention-specific outcomes	
● Patient satisfaction	
● Psychological well being:	
(a) Criterion-based improvement (as defined in individual studies)	
with respect to general psychological well-being, such as	
self-esteem or distress	
(b) Continuous measures of psychological well-being	
● Quality of life	
● Relapse (as defined in the individual studies)	
● Social functioning	
● Any other unexpected or unwanted effect	

Note: ✓ = Yes; x = No; ? = Criterion not described adequately to classify as yes or no.

Appendix 9: Systematic review quality checklist

Quality checklist for a systematic review
(notes for reviewer are presented in italics)

Checklist completed by:		Report reference ID:
SECTION 1: VALIDITY		
Evaluation criteria		**Comments**
1.1	Does the review address an appropriate and clearly focused question?	*Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.*
1.2	Does the review include a description of the methodology used?	*A systematic review should include a detailed description of the methods used to identify and evaluate individual studies. If this description is not present, it is not possible to make a thorough evaluation of the quality of the review, and it should be rejected as a source of Level 1 evidence. (Though it may be useable as Level 4 evidence, if no better evidence can be found.) Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.*
1.3	Was the literature search sufficiently rigorous to identify all relevant studies?	*Consider whether the review used an electronic search of at least one bibliographic database (searching for studies dating at least 10 years before publication of the review). Any indication that hand-searching of key journals, or follow-up of reference lists of included studies, were carried out in addition to electronic database searches can normally be taken as evidence of a well-conducted review.*

Continued overleaf

1.4	Was study quality assessed and taken into account?	*A well-conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. At a minimum, the authors should have checked that there was adequate concealment of allocation, that the rate of drop out was minimised, and that the results were analysed on an 'intention to treat' basis. If there is no indication of such an assessment, the review should be rejected as a source of Level 1 evidence. If details of the assessment are poor, or the methods considered to be inadequate, the quality of the review should be downgraded.*	
SECTION 2: OVERALL ASSESSMENT			
		Comments	**Code**
2.1	Low risk of bias Moderate risk of bias High risk of bias	*All or most criteria met* *Most criteria partly met* *Few or no criteria met*	**A** **B** **C**

Appendix 10: RCT methodological quality checklist

Quality checklist for an RCT
(notes for reviewer are presented in italics)

Report reference ID:			
Checklist completed by:		Date completed:	
SECTION 1: INTERNAL VALIDITY			
Evaluation criteria		**How well is this criterion addressed?**	
1.1	Was the assignment of subjects to treatment groups randomised?	*If there is no indication of randomisation, the study should be rejected. If the description of randomisation is poor, or the process used is not truly random (e.g. allocation by date, alternating between one group and another) or can otherwise be seen as flawed, the study should be given a lower quality rating.*	
1.2	Was an adequate concealment method used?	*Centralised allocation, computerised allocation systems, or the use of coded identical containers would all be regarded as adequate methods of concealment, and may be taken as indicators of a well-conducted study. If the method of concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating, and can be rejected if the concealment method is seen as inadequate.*	
SECTION 2: OVERALL ASSESSMENT			
		Comments	**Code**
2.1	Low risk of bias Moderate risk of bias High risk of bias	*Both criteria met* *One or more criteria partly met* *One or more criteria not met*	**A** **B** **C**

Appendix 11: Clinical study data extraction forms

Topic Area:	**Report reference ID:**
Comparisons:	

Ref List checked		Data entered in Rev Man		Characteristics entered	
Data checked		Reference Manager updated		Excluded	

Randomised?		Blind?		
Age:		Young/Elderly (mean age over 65)		
Setting:		In/Out/Mixed/Primary Care (80% patients)		
Analysis:		Completer/ITT (continuous data)		
Diagnosis			% Dysthymic	
			% Bipolar	
Mean baseline				

Trial length
Interventions (Dose): 1 2 3
Notes

RCT data extraction form

Data extraction form for a randomised controlled trial												
Completed by:					**Report reference ID:**							
1 TREATMENT GROUP:												
Single dichotomous outcomes	Death			Leaving study early			Relapse: treatment end			Relapse: follow-up		
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	
Continuous outcomes post-treatment												
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Continuous outcomes at follow-up												
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Dichotomous outcomes post-treatment												
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	
Dichotomous outcomes at follow-up												
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	
2 TREATMENT GROUP:												
Single dichotomous outcomes	Death			Leaving study early			Relapse: treatment end			Relapse: follow-up		
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	
Continuous outcomes post-treatment												
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Continuous outcomes at follow-up												
	n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Dichotomous outcomes post-treatment												
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	
Dichotomous outcomes at follow-up												
	n	*N*		*n*	*N*		*n*	*N*		*n*	*N*	

RCT data extraction form for pharmacological studies

Data extraction form for a randomised controlled trial (pharmacology)							
Completed by:		**Report reference ID:**					
1 TREATMENT GROUP:							
Dropouts		**Treatment Responders**		**Side Effects (total)**			
n	*N*	*n*	*N*	*n*	*N*	*n*	*N*
Definition of responders							

Post-treatment means											
n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Other data											
n	*N*		*n*	*N*		*n*	*Mean*	*SD*	*n*	*Mean*	*SD*

2 TREATMENT GROUP:							
Dropouts		**Treatment Responders**		**Side Effects (total)**			
n	*N*	*n*	*N*	*n*	*N*	*n*	*N*
Definition of responders							

Post-treatment means											
n	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*
Other data											
n	*N*		*n*	*N*		*n*	*Mean*	*SD*	*n*	*Mean*	*SD*

Comparisons entered:

Appendix 12: Methods for calculating standard deviations

The following formulae were used to impute standard deviations (SD) where these were not available in study reports:

(n = sample size of group)

$$SD = \text{Standard Error} \times \sqrt{n}$$

$$SD = \frac{(\text{upper 95\% Confidence Interval} - \text{mean})}{1.96} \times \sqrt{n}$$

$$SD = \frac{(\text{mean}_1 - \text{mean}_2)}{\sqrt{F}\,(\sqrt{1/n_1} + \sqrt{1/n_2})}$$

(If F ratio is not given, then $F = t_2$)

Appendix 13: Depression rating scales

In the preparation of this guideline, data were considered from three depression rating scales:

- Beck Depression Inventory (Beck *et al.*, 1961)
- Hamilton Rating Scale for Depression (Hamilton, 1960)
- Montgomery Asberg Depression Rating Scale (Montgomery & Asberg, 1979).

Beck Depression Inventory (BDI)

Introduction

The BDI is a 21-item self-report questionnaire first published in 1961 by Beck, Ward, Mendelson, Mock and Erbaugh. Two revisions have been published. The first (BDI-IA) in 1979 by Beck, Rush, Shaw and Emery, eliminated alternative wordings for the same symptoms and double negatives (Beck *et al.*, 1996). The second (BDI-II) was published in 1996 by Beck, Steer and Brown and reflected changes in consecutive versions of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association). There is also a 13-item version (Guy, 1976).

The items in the original version were based on patient descriptions of depression, including mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusations, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation and loss of libido. In addition to other changes, version II replaced body image change, weight loss, somatic preoccupation and work difficulty with agitation, worthlessness, concentration difficulty, and loss of energy (Beck *et al.*, 1996). However, the correlation between the BDI-IA and BDI-II is high ($r = 0.93$, $p < 0.001$, Beck *et al.* (1996), p.25). Since most trials used in the evidence base for this guideline reference the first version, the meta-analyses do not distinguish between versions.

Scoring and levels of depression

Each item is scored 0 to 3, giving a total possible score of 63. With regard to levels of depression, there are discrepancies between researchers, including different papers by Beck. For example, Beck and Beamesderfer (1974) have none or minimal depression as <10; mild to moderate 10–18; moderate to severe is 19–29; and severe 30–63. However, in a personal communication (Beck, 2002), Beck states mild or sub-clinical is 11–16, and moderate is >17. The different cut-offs are listed in Table 1.

Table 1: Suggested cut-offs for levels of depression severity on the BDI.

Reference [BDI version]	*Not depressed*	*Mild*	*Moderate*	*Severe*
Kendall, 1987 *(I)*		10–20	20–30	>30
Beck *et al.*, 1988 *(Ia)*		10–18	19–29	30–63
BDI Website (4) *(Ia)*	Below 4 – possible denial of depression	10–18	19–29	30-63
Family Practice Notebook *(II)*		<15	15–30	>30
Shapiro *et al.*, 1994[1] *(IA?)*		16–20	21–26	>26
Elkin *et al.*, 1989 *(I)*	<=9			
Beck *et al.*, 1996 *(BDI-II)*	0–13 (minimal)	14–19	20–28	29–63
Beck 2002 *(?)*		11–16	17+	
APA (2000a) *(?)*	0–9	10–16	17–29	30–63

The guideline uses the cut-offs recommended by the APA (2000a).

The Hamilton Rating Scale for Depression (HRSD)

Introduction

The HRSD is a 21-item clinician-completed scale, although usually only the first 17 items are scored. There is also a 24-item version.

The items covered are depressed mood, guilt feelings, suicide, insomnia – early, insomnia – middle, insomnia – late, work and activities, retardation – psychomotor, agitation, anxiety – psychological, anxiety – somatic, somatic symptoms GI, somatic symptoms – general, sexual dysfunction – menstrual disturbance, hypochondrias, weight loss – by history and by scales, insight.

The additional items in the 21-item version are diurnal variation, depersonalisation and derealisation, paranoid symptoms, and obsessional and compulsive symptoms.

Since it was developed before RDC or DSM-III criteria for depression, it does not include symptoms that are part of these definitions, such as anhedonia (APA, 2000a). It gives more weight to somatic symptoms than to cognitive ones (APA, 2000a).

Scoring and levels of depression

Items are scored 0–4 or 0–2, giving a total score range of 0–50 on the 17-item version.

[1] The cut-offs given in this paper are from an unpublished manuscript by Beck (1978, Beck Depression Inventory, Unpublished Manuscript, University of Pennsylvania).

Table 2: Suggested cut-offs for levels of depression severity on the HRSD.

	Not depressed	*Mild*	*Moderate*	*Severe*	*Very Severe*
HRSD-website		10–13	14–17	>17	
Elkin *et al.*, 1989	<= 6	10–20	20–30	>30	
Keller *et al.*, 2000	<=8				
APA 2000a	0–7	8–13	14–18	19–22	>23

The guideline uses the cut-offs recommended by the APA (2000a).

The Montgomery Asberg Depression Rating Scale (MADRS)

Background

The MADRS was first published in 1979 (Montgomery & Asberg, 1979). Its 10 items were taken from the 65-item Comprehensive Psychopathological Rating Scale (Asberg *et al.*, 1978), and showed the greatest change with treatment and highest correlation to overall change.

The items covered are apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.

The scale is administered by a clinician, although a self-administered version exists.

The recall time is during the last week OR during the last three days.

Scoring and levels of depression

Each of the 10 items is scored either on predefined steps (0, 2, 4 or 6) or between them (1, 3 or 5) (Montgomery & Asberg, 1979). No levels of depression appear to have been set.

Comparison between scales

The GDG took the view that the HRSD and MADRS measured similar aspects of depression. Where studies for a particular comparison reported the same outcome using either of these scales, meta-analyses were performed combining the data using a standardised mean difference (SMD). However, whereas the HRSD emphasises somatic symptoms and so responds earlier to changes due to pharmacological treatment, the BDI focuses on cognitive symptoms, and so responds later. It could be argued that differences in scales are due to mode of completion. Senra (1995) compared a clinician-completed version of the BDI and a patient-completed version of the HRSD with the original scales to assess the effect of mode of completion on ratings. He concluded that differences between the scales were not due to mode of completion, but to differences in the content of the scales. Where meta-analyses of both HRSD/MADRS and BDI scores for the same comparison were undertaken, but did not produce the same result, recommendations were made based on the HRSD result.

Appendix 14: Search strategies for the identification of health economics studies

Databases searched: MEDLINE, PreMEDLINE, EMBASE (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, Cochrane Database of Systematic Reviews (CDSR), Cochrane Controlled Trials Register (CCTR), Database of Abstracts of Reviews of Effectiveness (DARE)

Search filter: Economic Search Filter AND Depression General Filter

1. (burden adj2 illness).mp.
2. (burden adj2 disease).mp.
3. (cost$ adj2 evaluat$).mp.
4. (cost$ adj2 benefit$).mp.
5. (cost$ adj2 utilit$).mp.
6. (cost$ adj2 minimi$).mp.
7. (cost$ adj2 illness).mp.
8. (cost$ adj2 disease).mp.
9. (cost$ adj2 analys$).mp.
10. (cost$ adj2 assess$).mp.
11. (cost$ adj2 study).mp.
12. (cost$ adj2 studies).mp.
13. (cost$ adj2 allocation).mp.
14. (cost$ adj2 outcome$).mp.
15. (cost$ adj2 consequence$).mp.
16. (cost$ adj2 effect$).mp.
17. (cost$ adj2 treatment$).mp.
18. (economic adj2 evaluat$).mp.
19. (economic adj2 analysis$).mp.
20. (economic adj2 study).mp.
21. (economic adj2 studies).mp.
22. (economic adj2 assess$).mp.
23. (economic adj2 consequence$).mp.
24. (economic adj2 outcome$).mp.
25. (resource$ adj2 allocation$).mp.
26. (resource$ adj2 utili$).mp.
27. expenditure$.mp.
28. exp economics/
29. exp 'costs and cost analysis'/
30. exp 'health economics'/
31. or/1-30

AND

1. depressive disorder/ or dysthymic disorder/ or seasonal affective disorder/ or depression, involutional/ or exp bipolar disorder/ or depression/
2. depression/ or dysthymia/ or involutional depression/ or exp manic depressive psychosis/
3. exp bipolar disorder/ or major depression/ or seasonal affective disorder/ or anaclitic depression/ or dysthymic disorder/ or endogenous depression/ or involutional depression/ or reactive depression/ or recurrent depression/ or treatment resistant depression/
4. depression/ or depression, reactive/ or dysthymic disorder/
5. (seasonal affective disorder$ or depress$ or dysthym$ or (bipolar adj2 disord$)).tw. or melancholi$.mp.
6. or/1-5

Date: September 2002
Hits: 7833

Search filter: Economic Search Filter AND Depression General Filter AND Antidepressant Search String (see below)

Venlafaxine search
venlafaxine/
or
(efexor or effexor or venlafaxine).mp

Fluoxetine search
fluoxetine/
or
(fluoxetine or adofen or afeksin or affectine or affex or astrin or atd or auscap or daforin or deprax or deprexin or deproxin or diesan or digassim or docutrix or erocap or eufor or felicium or fluctin or fluctine or flumed or fluneurin or fluocim or fluohexal or fluox or fluoxac or fluoxemerck or fluoxeren or flouxibene or fluoxifar or fluoxine or fluox-puren or flusol or flutin or flutine or flux or fluxantin or fluxene or fluxet or fluxetil or fluxetin or fluxac or fondur or fontex or fonzac or geroxac or lorien or lovan or magrilan or motvone or mutan or nodepe or norzac or nuzak or nyucoflox or oxetine or oxsac or plinzene or positivum or prizma or prodep or provatine or prozac or prozamel or prozatan or prozyn or psipax or reneuron or salipax or sanzur or sarafem or seromex or seronil or seroscand or siquial or tuneluz or verotina or zactin).mp

Amitriptyline search
amitriptyline/
or
(amitriptyline or adepril or adepsique or adt or amilt-ifi or amineurin or amioxid or amitrip or amitrol or amyline or anapsique or anxipress-d or chlordiazepoxide or deprelio or diapatol or domical or elatrol or elavil or endep or enovil or equilibrin or etrafon or euplit or klotriptyl or laroxyl or lentizol or levate or limbatril or limbitrol or limbitryl or longopax or mutabase or mutabon or neuragon or neurarmonil or nobritol or noriline or novoprotect or novo-triptyn or pantrop or parks-plus or perphenazine or pertriptyl or pms-levazine or polytanol or proavil or redomex or saroten or sarotex or sedans or sylvemid or syneudon or tensorelax or trepiline or triavil or tripta or triptafen or triptizol or triptyl or triptyline or tryptal or tryptanol or tryptil or tryptine or tryptizol).mp
Date: March 2003
Hits: 1145

Databases searched: HTA (Health Technology Assessment), NHS EED (NHS Economic Evaluation Database)

Search filter: depressive disorder/ or dysthymic disorder/ or seasonal affective disorder/ or depression, involutional/ or exp bipolar disorder/ or depression/ or depress*
Date: September 2002
Hits: 209

Search filter: amitriptyline or fluoxetine or venlafaxine
Date: March 2003
Hits: 37

Database searched: OHE HEED (Office of Health Economics Health Economic Evaluations Database)

Search filter: depression or depressed or depressive or mood disorder or affective disorder
Date: October 2002/ April 2003
Hits: 485/ 528

Search filter: amitriptyline or fluoxetine or venlafaxine
Date: March 2003
Hits: 8

Appendix 15: Quality checklists for economics studies

Full economic evaluations

Author: **Date:**

Title:

Study design	*Yes*	*No*	*NA*
1. The research question is stated	●		
2. The viewpoint(s) of the analysis are clearly stated		●	
3. The alternatives being compared are relevant		●	
4. The rationale for choosing the alternative programmes or interventions compared is stated	●		
5. The alternatives being compared are clearly described		●	
6. The form of economic evaluation used is justified in relation to the question addressed		●	
Data collection			
1. The source of effectiveness data used are stated		●	
2. Details of the design and results of effectiveness study are given		●	
3. The primary outcome measure(s) for the economic evaluation are clearly stated	●		
4. Methods to value health states and other benefits are stated		●	
5. Details of the subjects from whom valuations were obtained are given	●		
6. Indirect costs (if included) are reported separately		●	
7. Quantities of resources are reported separately from their unit costs		●	
8. Methods for the estimation of quantities and unit costs are described		●	
9. Currency and price data are recorded		●	
10. Details of currency of price adjustments for inflation or currency conversion are given		●	
11. Details of any model used are given		●	
12. The choice of model used and the key parameters on which it is based are justified		●	
Analysis and interpretation of results			
1. Time horizon of costs and benefits is stated		●	
2. The discount rate(s) is stated		●	
3. The choice of rate(s) is justified		●	
4. An explanation is given if costs or benefits are not discounted	●		

		Yes	No	NA
5.	Details of statistical tests and confidence intervals are given for stochastic data	●		
6.	The approach to sensitivity analysis is given	●		
7.	The choice of variables for sensitivity analysis is given		●	
8.	The ranges over which the variables are varied are stated	●		
9.	Relevant alternatives are compared		●	
10.	Incremental analysis is reported		●	
11.	Major outcomes are presented in a disaggregated as well as aggregated form	●		
12.	The answer to the study question is given		●	
13.	Conclusions follow from the data reported		●	
14.	Conclusions are accompanied by the appropriate caveats		●	

Partial economic evaluations

Author: **Date:**

Title:

Study design		Yes	No	NA
1.	The research question is stated		●	
2.	The viewpoint(s) of the analysis are clearly stated and justified		●	
Data collection				
1.	Details of the subjects from whom valuations were obtained are given	●		
2.	Indirect costs (if included) are reported separately	●		
3.	Quantities of resources are reported separately from their unit costs	●		
4.	Methods for the estimation of quantities and unit costs are described		●	
5.	Currency and price data are recorded	●		
6.	Details of currency of price adjustments for inflation or currency conversion are given	●		
7.	Details of any model used are given	●		
8.	The choice of model used and the key parameters on which it is based are justified	●		
Analysis and interpretation of results				
1.	Time horizon of costs is stated		●	
2.	The discount rate(s) is stated		●	
3.	Details of statistical tests and confidence intervals are given for stochastic data	●		
4.	The choice of variables for sensitivity analysis is given		●	
5.	Appropriate sensitivity analysis is performed		●	
6.	The answer to the study question is given	●		
7.	Conclusions follow from the data reported		●	
8.	Conclusions are accompanied by the appropriate caveats	●		

Appendix 16: Health economics evidence table

Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Pharmacological interventions					
Borghi & Guest, 2000	1. CEA, modelling 2. UK 3. NHS	1. mirtazapine 2. amitriptyline 3. fluoxetine	1. 6/7 months 2. people with moderate/severe depression	1. successfully treated patients (HRSD 17<=7 or reduction in HRSD 17>=50%) 2. meta-analysis	1. direct health service and lost productivity (£, 1997/98) 2. Mirtazapine was found to be dominant compared to amitriptyline. It both reduced the expected direct NHS costs by £35 per patient and increased the proportion of successfully treated patients from 19.2% to 23.2%. However, this result was sensitive to the cost of managing adverse events. When compared to fluoxetine, mirtazapine increased the proportion of successfully treated patients from 15.6% to 19.1% but at an additional cost of £27 per patient. Sensitivity analysis revealed the factors this result was sensitive to. 3. good (26/3/3) 4. yes

Doyle *et al.*, 2001 **Casciano *et al.*, 2001**	1. CEA, modelling 2. multinational (UK) 3. outpatient and inpatient care	1. venlafaxine 2. SSRIs 3. TCAs	1. 6 months 2. people with acute MDD	1. treatment success (>50% reduction in scores on the HRSD), symptom-free days 2. meta-analysis (Einarson *et al.*, 1999)	1. direct health service ($, 1999) 2. Venlafaxine dominates the other two options since its expected total health service costs are the lowest, and it is superior in terms of both success rate and symptom-free days. Sensitivity analysis confirmed the robustness of these findings. 3. good (27/1/3) 4. yes
Forder *et al.*, 1996	1. CEA 2. UK 3. primary care	1. sertraline 2. TCAs	1. 12 months 2. people with MDD	1. GP's rating of the patients: very much improved, somewhat improved, same, worsened 2. quasi-experimental study	1. direct health and social services, informal care (£, 1993/94) 2. Treatment with sertraline appears to be more effective and is also less costly when all costs are included. Although the medication cost was five times greater during the study period for the sertraline group than for the TCA group, the overall cost per successfully treated patient was £24,286 vs. £34,419, respectively. 3. good (23/4/5) 4. yes
Freeman *et al.*, 2000	1. CEA, modelling 2. UK 3. outpatient care	1. venlafaxine 2. SSRIs 3. TCAs	1. 6 months 2. people with MDD	1. symptom-free days 2. meta-analysis (Einarson *et al.*, 1999)	1. direct health service (£, 1998) 2. Treatment with venlafaxine yielded the lowest outpatient cost for a symptom-free day (£10.53), compared with £13.23 for SSRIs and £15.52 for TCAs. Hence, the authors found venlafaxine to be cost-effective in outpatients with MDD and cost saving compared to SSRIs and TCAs. The results of the sensitivity analysis indicated that the findings were robust with respect to assumptions implicit to the model. 3. good (22/6/4) 4. yes

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Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Pharmacological interventions *(continued)*					
Freemantle *et al.*, 1994	1. CEA, modelling 2. UK 3. primary care	1. current antidepressant prescribing pattern 2. first-line treatment with SSRIs 3. first-line treatment with newer TCAs	1. 12 months 2. people with MDD	1. life years saved 2. observational data	1. drug treatment (£, 1992) 2. Additional life years could be saved but only by considerable additional costs, and the results are highly sensitive for the model assumptions (range: £19,412 – £172,908/ life year gained). The policy of switching to newer (less toxic) TCAs is considerably more cost effective than the switch to SSRIs. Broader health service costs (e.g. for non-fatal suicide attempts) were not considered. 3. good (26/4/2) 4. no
Hatziandreu *et al.*, 1994	1. CUA, modelling 2. UK 3. ?	1. 2-year maintenance therapy with sertraline 2. 3-month episodic therapy with dothiepin/dosulepin	1. lifetime 2. women with recurrent MDD	1. QALY 2. physician panels	1. direct mental health service (£, 1991) 2. The incremental cost/QALY is £2712 for the maintenance therapy. The robustness of the result was confirmed by comprehensive sensitivity analysis. 3. good (25/3/4) 4. yes

Jonsson & Bebbington, 1994	1. CEA, modelling 2. UK 3. outpatient care	1. 12-week paroxetine therapy 2. 12-week imipramine therapy	1. 12 months 2. people with MDD	1. successfully treated patients 2. literature	1. direct health service (£, 1990) 2. The average cost per successfully treated patient is lower for paroxetine (£824) than for imipramine (£1024). The marginal cost-effectiveness in the base case was found to be £58/additional successfully treated patient. The results were stable when a sensitivity analysis was applied to the variables in the model. 3. moderate (18/10/4) 4. yes
Kind & Sorensen, 1995	1. CEA, modelling 2. UK 3. outpatient care	1. SSRI maintenance therapy 2. no maintenance therapy	1. 12 months 2. people after their initial episode of MDD	1. symptom-free patients 2. literature	1. treatment (£, 1993/94) 2. The average cost per symptom-free patient is estimated to be £271 under the watchful waiting approach and between £474 and £389 under maintenance strategy. 3. moderate (19/9/4) 4. no
Montgomery *et al.*, 1996	1. CEA, modelling 2. UK 3. outpatient care	1. 12-week nefazodone treatment 2. 12-week imipramine treatment	1. 12 months 2. people with MDD	1. successfully treated patients 2. RCT	1. direct health service (£, 1994) 2. Nefazodone was shown to be more effective than imipramine. The expected cost of treatment was also lower for nefazodone than for imipramine (£218 vs. £254). The average cost per successfully treated patient was £242 for nefazodone and £323 for imipramine. 3. moderate (15/13/4) 4. yes

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Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Pharmacological interventions *(continued)*					
NICE, 2003	1. CUA, modelling 2. UK 3. inpatient care	1. ECT antidepressant therapy	1. 12 months 2. adults with severe MDD	1. QALY 2. literature, expert panel	1. ? 2. Given the small differences in total costs and QALYs between the strategies, ECT and pharmacotherapy are likely to be equally cost-effective. 3. ? 4. ?
Stewart, 1994	1. CEA, modelling 2. UK 3. primary care	1. SSRIs 2. TCAs	1. 12 months 2. people with MDD	1. treatment success 2. literature	1. direct health service (£, 1992/93) 2. The average annual cost per successfully treated patient is shown to be £491.25 for imipramine, £539.00 for amitriptyline, £581.46 for sertraline and £547.65 for paroxetine. However, factors such as antidepressant overdose or cost of any side effect treatment were not included in the analysis and these all would favour SSRIs. The cost advantage of TCAs was lower than usually inferred from acquisition costs, but there was no clear cost advantage in switching from TCAs to SSRIs. 3. good (25/3/4) 4. no

Stewart, 1996 (update)	1. CEA, modelling 2. UK 3. primary care	1. SSRIs 2. TCAs	1. 12 months 2. people with MDD	1. treatment success 2. literature	1. direct health service (£, 1995) 2. At 1995/96 price levels one additional successfully treated patient can be obtained by an extra £2518 when comparing SSRIs to TCAs. This additional cost changes to £383–£1023 in the sensitivity analysis by using clinical data from the study by Montgomery *et al.* (1994) and Song *et al.* (1993) respectively and by adjusting for differences in sub-therapeutic doses. These results advocate the general use of SSRIs. 3. good (26/3/3) 4. no
Tome & Isaac, 1998	1. CEA, modelling 2. UK 3. mental health care	1. SSRI+6-week pindolol augmentation 2. SSRI + placebo	1. 12 months 2. people with moderate to severe MDD	1. change in BDI score 2. RCT	1. direct mental health service (£, 1990) 2. The year cost of the SSRI and augmentor group is less than that of the SSRI and placebo group. Furthermore, the average change in BDI per £ is 0.1271 for the augmentor group and 0.0753 for the placebo group. 3. moderate (15/13/4) 4. yes
Woods & Rizzo, 1997 (reassessment of Jonsson & Bebbington, 1994)	1. CEA, modelling 2. UK 3. outpatient care	1. 12-week paroxetine therapy 2. 12-week imipramine therapy	1. 12 months 2. people with MDD	1. successfully treated patients 2. literature	1. direct health service (£, ?) 2. The revisions suggest that in most scenarios the cost per successfully treated patient for imipramine is lower or equal to that of paroxetine. 3. good (23/6/3) 4. no

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Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Psychological interventions					
Friedli *et al.*, 2000	1. CMA 2. UK 3. primary care	1. non-directive counselling (max. 12 sessions) 2. usual GP care	1. 9 months 2. people with depression or mixed anxiety/depression	1. BDI, Brief Symptom Inventory, Clinical Interview Schedule, modified Social Adjustment Scale 2. RCT (Friedli *et al.*, 2000)	1. direct health service and non-health care, lost productivity due to morbidity (£, 1995/96) 2. There were no significant differences between the groups on any of the mental health outcomes at three or nine months. In terms of total costs to society, use of a counsellor was significantly more costly after three months than usual care (median difference: £96.2, 95% CI: £29.1 – £174), but there was a trend for the counsellor group to become less expensive compared to usual routine care during the following six months (median difference: –£79, 95% CI: –£235 – £0). Sensitivity analysis made no significant difference to the results. 3. good (23/3/6) 4. no
Guthrie *et al.*, 1999	1. CEA 2. UK 3. secondary care	1. psychodynamic interpersonal therapy (8 sessions) 2. usual psychiatrist care	1. 8 weeks + 6 months 2. patients receiving specialist mental health treatment for more than 6 months (75.5% had depressive illness)	1. SCL-90-R, SF-36, EQ-5D 2. RCT (Guthrie *et al.*, 1999)	1. direct health service and non-health care, lost productivity due to morbidity ($, ?) 2. Six months after the trial there was significant improvement in quality of life (EQ-5D scores) and cost savings, both in direct treatment costs and when direct non-treatment costs and indirect costs were included, for the depressed patients who received psychotherapy in comparison with controls. 3. moderate (19/7/6) 4. no

Kaltenthaler *et al.*, 2002	1. CUA, modelling 2. UK 3. primary care	1. CCBT (BtB) 2. usual care	1. 6 months 2. people with MDD	1. QALYs 2. literature	1. treatment (£, 2000) 2. The incremental cost per QALY gained of BtB over treatment as usual lies between £1210 and £7692 if the data from Bennett *et al.* (2000) are used for the calculation, and between £3000 and £6667 if the data from Revicki and Wood are used. However, these estimates are crude and should be treated with caution. 3. moderate (19/9/4) 4. no
King *et al.*, 2000 **Bower *et al.*, 2000**	1. CEA 2. UK 3. primary care	1. non-directive counselling (max. 12 sessions) 2. CBT (max. 12 sessions) 3. usual GP care	1. 4 + 12 months 2. people with depression or mixed anxiety/depression	1. BDI, EuroQoL 2. RCT (King *et al.*, 2000)	1. direct health service and non-healthcare, lost productivity (£, 1997/1998) 2. Patients in both psychological therapy groups made significantly greater clinical gains in the first four months; however, all groups had equivalent outcomes at 12 months. There were no significant differences in terms of EuroQol. No differences in direct or lost productivity costs between the three treatments were observed at either four months or 12 months. (Caution: the study was not powered for cost!) The additional costs associated with providing practice-based psychological therapy were offset by savings in visits to primary care, psychotropic medication and other specialist mental health treatments. Overall the results implied the observed equivalence of the three options and this result remained in the sensitivity analysis. 3. good (27/0/5) 4. no

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Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Psychological interventions *(continued)*					
Leff *et al.*, 2000	1. CCA 2. UK 3. outpatient care	1. antidepressant therapy	1. 12+12 months 2. people with MDD and living with a partner	1. BDI scores, HRSD scores 2. RCT (Leff *et al.*, 2000)	1. direct health and social services (£, 1995/96) 2. According to the BDI, couple therapy showed a significant advantage. Although the cost of couples therapy was double that of antidepressant treatment over the treatment period, it was almost offset by the difference in other health service use. In the follow-up period, costs were not significantly higher for the medication group. Caution needs to be taken due to highly skewed distribution of service costs. 3. moderate (16/12/4) 4. no
McCrone *et al.*, 2003 (work in progress)	1. CEA, CUA 2. UK 3. primary care	2. couples therapy (12–20 sessions) 1. CCBT (BtB) 2. usual care	1. 6+8 months 2. people with depression, anxiety or mixed depression/anxiety	1. BDI scores, depression-free days, QALYs 2. RCT	1. direct health service and lost productivity (£, 2000/01) 2. The paper could not find any statistically significant cost difference between the two treatment alternatives, although CCBT was non-significantly more expensive when considering only health service costs and non-significantly less expensive when considering all costs. However, CCBT was significantly more effective compared to treatment as usual. The chance of CCBT being cost-effective is more than 99% when one QALY is valued at £15,000. 3. good (23/6/3) 4. yes

Miller *et al.*, 2003	1. CEA 2. UK 3. primary care	1. counselling (6 sessions) 2. routine antidepressant therapy (for at least 4 months after remission)	1. 12 months 2. people with MDD	1. patient with good global outcome 2. RCT (Chivers *et al.*)	1. depression related health service (£, ?) 2. This study found no significant difference between the randomised treatment groups in either outcomes or costs at 12 months; however, the study was not powered for CEA. Sensitivity analyses showed that the counselling group is more likely to be less effective and less costly than the AD group. If decision makers are willing to pay for additional benefits, the antidepressant group becomes more likely to be cost-effective when comparing to the counselling group. 3. good (20/6/6) 4. no
Mynors-Wallis *et al.*, 1997	1. CMA 2. UK 3. primary care	1. problem-solving therapy provided by community nurses 2. usual GP care	1. 26 weeks 2. people with emotional disorders (not clear how many had MDD)	1. clinical interview schedule, GHQ, social adjustment scale, Euroqol scale, patient satisfaction 2. RCT (Mynors-Wallis *et al.*, 1997)	1. direct health service and lost productivity due to morbidity (£, 1995) 2. No difference was shown between the two treatment groups regarding outcomes, but patients may have received less than adequate problem solving treatment. The healthcare cost of problem-solving was £45.50 greater per patient than that of the GP's usual treatment but this was more than offset by savings in the cost of days off work 3. moderate (19/7/6) 4. no

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Study	*1. Design* *2. Country* *3. Setting*	*1. Intervention A* *2. Intervention B* *3. Intervention C* *4. Intervention D*	*1. Analytic time horizon* *2. Patient population*	*1. Outcome(s)* *2. Source of outcome data*	*1. Costs measured (currency, price year)* *2. Results* *3. Internal validity (Yes/No/NA)* *4. Industry support*
Psychological interventions *(continued)*					
Scott & Freeman, 1992	1. CCA 2. UK 3. outpatient care	1. amitriptyline prescribed by a psychiatrist 2. CBT provided by a clinical psychologist 3. usual GP care 4. counselling provided by a social worker	1. 16 weeks 2. people with MDD	1. HRSD scores, recovery (HRSD<7), patient satisfaction 2. RCT (Scott & Freeman, 1992)	1. depression treatment (£, 1986/87) 2. After 16 weeks, only social work counselling was superior to GP care. However, twice as many patients who received usual GP care had an initial score >16 on the HDRS. There were no significant differences in how patients rated their satisfaction, except that social work counselling was evaluated significantly more positively than GP care or antidepressant therapy by a psychiatrist. Usual GP care costs less than half (£55.30) than any of the specialist treatments (amitriptyline: £120.28, CBT: £115, counselling: £121). 3. moderate (17/9/6) 4. no
Scott *et al.*, 2003	1. CEA 2. UK 3. outpatient care	1. antidepressant therapy with clinical management 2. antidepressant therapy and CBT	1. 4+12 months 2. people with residual MDD	1. relapse prevented, relapse-free day 2. RCT (Paykel *et al.*, 1988)	1. direct health and social services (£, 1998/99) 2. The combination of CBT and antidepressant therapy is likely to be cost-effective if a decision maker regards paying about £4500 per additional relapse prevented as value for money. This translates to a cost of about £12.50 per additional relapse-free day. 3. good (27/1/4) 4. no

Simpson et al, 2000	1. CMA 2. UK 3. primary care	1. counselling (6 sessions) 2. usual GP care	1. 12 months 2. people with chronic depression	1. BDI, patient satisfaction 2. RCT (Simpson *et al.*, 2000)	1. direct health and social services and lost productivity (£, 1997/98) 2. No difference was found between the two treatment groups regarding outcomes, and there were no significant differences in the mean total costs, the aggregate costs of services, the costs by service-groups except for primary care. The primary care costs during the intervention period were significantly higher in the counselling than in the usual GP care group and this was directly due to the costs of the psychotherapy. 3. good (22/5/5) 4. no

Service-level interventions

Goldberg *et al.*, 1996	1. CEA 2. UK 3. outpatient care	1. community-based service 2. hospital-based service	1. 6 months 2. patients with anxiety or depressive illness	1. clinical outcomes, social outcome, quality of care 2. controlled observational data	1. direct health and social services, lost productivity due to morbidity (£, 1990/91) 2. There was no significant difference between the groups in terms of clinical outcome, but the quality comparison favoured the community service. The community-based service was also shown to incur very much lower direct health and social services costs than the hospital-based treatment. The difference was for inpatient care, as index patients were less likely to be admitted. Correcting for outliers, lost productivity costs seemed to be similar for the two groups. 3. poor (11/17/4) 4. no

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12 Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AD	Antidepressant
AGREE	Appraisal of Guidelines Research and Evaluation
AMED	Allied and Complementary Medicine Database
APA	American Psychiatric Association
AV	Atrioventricular
BABCP	British Association of Behavioural & Cognitive Psychotherapies
BACP	British Association for Counselling and Psychotherapy
BDI	Beck Depression Inventory
BNF	*British National Formulary*
BT	Behaviour therapy
CBA	Cost-benefit analysis
CBT	Cognitive behavioural therapies
CCA	Cost-consequences analysis
CCBT	Computerised cognitive behavioural therapy
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CEBMH	University of Oxford Centre for Evidence Based Mental Health
CER	Control group event rate
CHAI	Commission for Healthcare, Audit and Improvement
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CM	Case management
CMA	Cost-minimisation analysis
CMHT	Community Mental Health Team
COMB	Combination treatment
CORE	Centre for Outcomes Research and Effectiveness, British Psychological Society
CRHTT	Crisis resolution and home treatment team
CRU	College Research Unit, Royal College of Psychiatrists
CUA	Cost-utility analysis
DA	Dopamine
DARE	Database of Abstracts of Reviews of Effects
DSM	*Diagnostic and Statistical Manual* of the American Psychiatric Association
ECG	Electrocardiograph
ECT	Electroconvulsive therapy
EIS	Early intervention service
EMBASE	Excerpta Medica Database
ES	Effect sizes

FDA	(US) Food and Drugs Administration
FI	Family interventions
GDG	Guideline Development Group
GDS	Geriatric Depression Scale
GHQ	General Health Questionnaire
GI	Gastrointestinal
GP	General practitioner
GPP	Good practice point
5HT	5-hydroxytryptymine
HADS	Hospital Anxiety and Depression Scale
HMO	Health Maintenance Organisation
HRSD	Hamilton Rating Scale for Depression
HTA	Health Technology Appraisal or Health Technology Assessment
ICD	International Classification of Disease
ICERs	Incremental cost-effectiveness ratios
IHD	Ischaemic heart disease
IoP	Institute of Psychiatry
IPT	Interpersonal Psychotherapy
IR	Immediate Release
MADRS	Montgomery Asberg Depression Rating Scale
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MI	Myocardial Infarction
NA	Noradrenaline
NaSSA	Noradrenaline and specific serotonin antidepressant
NCCMH	National Collaborating Centre for Mental Health
NCES	National Center for Education Statistics
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NIMH	National Institute of Mental Health (US)
NIMHE	National Institute of Mental Health in England
NNH	Number needed to harm
NNT	Number needed to treat
NSF	National Service Framework (for mental health)
OECD	Organisation for Economic Cooperation and Development
OHE HEED	Office of Health Economics Health Economics Evaluation Database
PC	Primary Care
PCT	Primary Care Trust
PSE	Present State Examination
QALY	Quality-adjusted life year
QWB	Quality of Well-Being scale

RCT	Randomised controlled trial
RDC	Research diagnostic criteria
RIMA	Reversible inhibitor of monoamine oxidase
RR	Relative risk (risk ratio)
SCID	Structured Clinical Interview for DSM
SD	Standard deviation
SE	Standard error
SFS	Social Functioning Schedule
SMD	Standardised mean difference
SPC	Summary of product characteristics
SSRIs	Selective serotonin reuptake inhibitors
T3	Triiodothyronine
T4	Thyroxine
TAU	Treatment as usual
TCA	Tricyclic antidepressant
TRD	Treatment Resistant Depression
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organisation
WMD	Weighted mean difference
XR	Extended Release

13 Glossary of terms

Acute day hospital: A unit that provides diagnostic and treatment services during daytime hours for acutely ill patients who would otherwise be treated in psychiatric inpatient units.

Adherence: The behaviour of taking medicine according to treatment dosage and schedule as intended by the prescriber. In this guideline, the term adherence is used in preference to the term compliance, but is not synonymous with concordance, which has a number of different uses/meanings.

Advance directives: Written instructions agreed between a patient and healthcare professional in which the patient specifies their preferred treatments and identifies the treatments he or she does not wish to receive in advance of treatment. These are used to guide clinicians in the event that the patient becomes unable to make decisions for him or herself. Advance directives allow a patient, for instance, to state in advance treatment preferences as well as treatment that he or she would not want to receive (e.g. ECT, or a drug they know gives them bad side effects). The patient should understand the nature of the condition for which treatment may be required, the need for treatment, the expected benefits of the proposed treatment, and the possible adverse consequences. Advance directives cannot be used to refuse treatment altogether when a person is subject to the Mental Health Act.

Akathisia: A condition of motor restlessness in which there is a feeling of muscular quivering, an urge to move about constantly and an inability to sit still, a common extrapyramidal side effect of neuroleptic drugs, and, more rarely, of SSRIs.

Anticholinergic side effects: Side effects such as dry mouth, blurred vision, constipation, urinary retention, and sweating, which may occur with a number of drugs including tricyclic antidepressants.

Atypical depression: A sub-type of major depressive disorder in which patients have reactive mood and at least two of the following four symptoms: hyperphagia, hypersomnia, leaden paralysis, or a lifetime history of interpersonal sensitivity to rejection, resulting in functional impairment.

Augmentation: Increasing the effectiveness or speed of response of one treatment by adding another, for example, adding lithium to an antidepressant.

Beck Depression Inventory (BDI): Rating scale for assessing depression that is completed by the patient.

Befriending: A community-based intervention in which a trained volunteer meets and talks with a patient with depression for a minimum of one hour each week and acts as a friend.

Behaviour therapy (BT): A discrete, time limited, structured psychological intervention, derived from the behavioural model of affective disorders in which the therapist and patient work collaboratively to identify the effects of behaviours on current symptoms, feelings states and/or problem areas. They seek to reduce symptoms and problematic

behaviours through behavioural tasks related to reducing avoidance, graded exposure, activity scheduling, behavioural activation and increasing positive behaviours.

Chronic depression: A form of depression, which is marked by a course of illness lasting two years or more.

Clinical management: A form of treatment and management of depression which often accompanies drug treatments in clinical trials and involves greater access to psychiatric personnel and crisis support than would be the case in the routine treatment of depression.

Clinical significance: Where the effect of a treatment is large enough to be of real benefit to a patient, for example in terms of reduced symptoms or improved quality of life.

Cognitive behavioural therapies (CBT): Discrete, time limited, structured psychological interventions, derived from the cognitive-behavioural model of affective disorders in which the patient: (1) works collaboratively with a therapist to identify the types and effects of thoughts, beliefs and interpretations on current symptoms, feelings states and/or problem areas; (2) develops skills to identify, monitor and then counteract problematic thoughts, beliefs and interpretations related to the target symptoms/problems; and (3) learns a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas.

Cohort study (also known as follow-up, incidence, longitudinal, or prospective study): An observational study in which a defined group of people (the cohort) is followed over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Comorbidity: Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

Computerised cognitive behavioural therapy (CCBT): A form of CBT, which is delivered using a computer (including CD-ROM and the internet). It can be used as the primary treatment intervention, with minimal therapist involvement or as augmentation to a therapist delivered programme where the introduction of CCBT supplements the work of the therapist. It offers patients the potential benefits of CBT with less therapist involvement.

Confidence interval (CI): The range within which the 'true' values (e.g. size of effect of an intervention) are expected to lie with a given degree of certainty (e.g. 95% or 99%). *(Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)*

Cost-effectiveness analysis: An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio.

Cost-minimisation analysis: An economic study concerned only with the comparative costs of different treatments or policies. It assumes (based on previous research) that the outcomes of the compared treatment or policy alternatives are identical. The aim is to look for the lowest cost alternative.

Costs (direct): The costs of all the goods, services and other resources that are consumed in the provision of a health intervention. They can be medical or non-medical.

Costs (indirect): The lost productivity suffered by the national economy as a result of an employee's absence from the workplace through illness, decreased efficiency or premature death.

Cost-utility analysis: A form of cost-effectiveness analysis, which measures and values the impact of a treatment or policy alternative in terms of changes in health-related quality of life in utility units (e.g. QALY – see below). The result is expressed in the form of a cost-utility ratio. It gives a more generalisable result than a single-outcome cost-effectiveness study.

Counselling: A psychological intervention (regular planned meetings of usually 50 minutes or an hour in length). The intervention may have a facilitative approach often with a strong focus on the therapeutic relationship but may also be structured and at times directive. In the guideline, an intervention was classified as counselling if the intervention(s) offered in the study did not fulfil all the criteria for any other psychological intervention. If a study using counsellors identifies a single approach, such as cognitive behavioural or interpersonal, it has been analysed in that category.

Couple-focused therapies: Time limited, psychological interventions derived from a model of the interactional processes in relationships where: (1) interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems; (2) the aim is to change the nature of the interactions so that they may develop relationships that are more supportive and have less conflict.

Crisis resolution and home treatment teams: Services that provide intensive home-based, crisis-orientated treatment of an acute psychiatric episode by staff with a special remit to deal with such situations during and beyond office hours. The objective is to manage acute episodes in the community rather than in inpatient care.

Detection bias (also termed ascertainment bias): Systematic differences between comparison groups in how outcomes are ascertained, diagnosed or verified.

Discontinuation/withdrawal symptoms: A cluster of somatic and psychological symptoms following the discontinuation of an antidepressant and not attributable to other causes (e.g. concomitant medication, illness). Symptoms can include dizziness, light-headedness, insomnia, fatigue, anxiety/agitation, nausea, headache, and sensory disturbance. Symptoms can last up to three weeks and may be improved by restarting the antidepressant or starting a different antidepressant with a similar pharmacological profile.

Double blind (also termed double masked): A trial in which neither the participants nor the investigators (outcome assessors) are aware of which intervention the participants are given. The purpose of blinding the participants (recipients and providers of care) is to prevent performance bias. The purpose of blinding the investigators (outcome assessors) is to protect against detection bias.

Dropout: A term used to indicate leaving a study before its completion (the phrase 'leaving treatment early' is generally preferred).

Drug half-life: The amount of time it takes for one-half of an administered drug to be lost through biological processes (metabolism and elimination).

Dysthymia: A chronic lowering of mood that does not fulfil the criteria for recurrent depressive disorder, in terms of either severity or duration of individual episodes. There are variable phases of minor depression and comparative normality. Despite tiredness, feeling down and not enjoying very much, people with dysthymia are usually able to cope with everyday life.

Economic evaluation: Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision-making framework.

Effectiveness: The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do. Clinical trials that assess effectiveness are sometimes called management trials.

Effect size: An estimate of the size of the effect that a given treatment has compared with a control treatment (for example, another active treatment, no treatment or 'treatment as usual'). Examples of effect sizes are the relative risk statistic (used for dichotomous outcomes), and the weighted mean difference and standardised mean difference statistics (both used for continuous outcomes).

Efficacy: The extent to which an intervention produces a beneficial result under ideal conditions. Clinical trials that assess efficacy are sometimes called explanatory trials and are restricted to participants who fully cooperate. The randomised controlled trial is the accepted 'gold standard' for evaluating the efficacy of an intervention.

Electroconvulsive therapy (ECT) (also termed convulsive therapy, electroshock therapy or shock therapy): A therapeutic procedure in which an electric current is briefly applied to the brain to produce a seizure. This is used for treatment of severe depression symptoms or to ease depression that is not responding well to other forms of treatment.

Forest plot: A graphical display of results from individual studies on a common scale, allowing visual comparison of trial results and examination of the degree of heterogeneity between studies.

Funnel plot: A scatter plot used to assess publication bias within a set of studies in a meta-analysis. Publication bias can occur when studies finding a favourable result are published in favour of those finding an unfavourable result. It plots estimated treatment effects against a measure of studies' sample sizes. If no publication bias is present, the plot should resemble an inverted funnel with the results of smaller studies being more widely scattered than those of larger studies.

Good practice point (GPP): Recommended good practice based on the clinical experience of the Guideline Development Group.

Guided self-help (GSH): A self-administered intervention designed to treat depression, which makes use of a range of books or a self-help manual that is based on an evidence-based intervention and is designed specifically for the purpose.

Guideline Development Group (GDG): The group of academic experts, clinicians and patients responsible for developing the guideline.

Guideline recommendation: A systematically developed statement that is derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate evidence relating to the specific condition in question.

Hamilton Rating Scale for Depression (HRSD): A 17-item scale for assessing depression symptoms that is completed by a clinician. The scale is also available in 21- and 24-item versions.

Health Technology Appraisal (also known as Health Technology Assessment) (HTA): The process of determining the clinical and cost effectiveness of a health technology in order to develop recommendations on the use of new and existing medicines and other treatments within the NHS in England and Wales.

Hyperphagia: Eating that is beyond normal feeling of hunger and involves eating even when one is full.

Hypersomnia: Sleeping more than usual, without an obvious cause. This is a common characteristic of atypical depression.

Interpersonal psychotherapy (IPT): A discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where: (1) therapist and patient work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems; (2) they seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

Maintenance treatment: Treatment after remission of depressive symptoms in order to prevent relapse or recurrence.

Major depression (also called clinical depression or major depressive disorder): The guideline uses the ICD 10 definition in which 'an individual usually suffers from depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability and diminished activity. Marked tiredness after only slight effort is common. Other symptoms are: (a) reduced concentration and attention; (b) reduced self-esteem and self-confidence; (c) ideas of guilt and unworthiness (even in a mild type of episode); (d) bleak and pessimistic views of the future; (e) ideas or acts of self-harm or suicide; (f) disturbed sleep; (g) diminished appetite.'

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of several independent studies.

Mild depression: The guideline uses the ICD 10 definition of four to six depressive symptoms.

Mindfulness-based CBT: A form of cognitive behavioural therapy that develops a person's ability to be attentive and aware of their negative thoughts but not react to them. The idea is to change a person's relationship with their negative thoughts, rather than the content of their thoughts.

Moderate depression: The guideline uses the ICD 10 definition of seven to nine depressive symptoms.

Monoamine oxidase inhibitors (MAOIs): A class of antidepressants that help brain neurotransmitters remain active longer, which may lead to a reduction in symptoms of depression.

Montgomery Asberg Depression Rating Scale (MADRS): A rating scale completed by a clinician for assessing depression.

Multifaceted care: Any systematic approach to the treatment of depression that combines any standard treatment approach with any of the following approaches to the management of depression (telephone contact, specialist assessment or consultation, professional or paraprofessional role development and guideline implementation).

NICE 2002: In this guideline, the reference used to cite recommendations from NICE technology appraisals.

Non-acute day hospital care: Psychiatric day hospitals that offer continuing care to people with severe mental disorders.

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

Performance bias: Systematic differences in care provided apart from the intervention being evaluated. For example, if study participants know they are in the control group they may be more likely to use other forms of care; people who know they are in the experimental (intervention) group may experience placebo effects, and care providers may treat patients differently according to what group they are in. Blinding of study participants (both the recipients and providers of care) is used to protect against performance bias.

Pharmacotherapy: Treatment of disease with prescription medications.

Placebo: A non-drug, or physically inactive substance, which is given as part of a clinical research trial. It has no specific pharmacological activity against illness.

Placebo response (or placebo effect): A phenomenon in which a placebo – a substance like sugar, distilled water, or saline solution – can improve a patient's condition simply because the person has the expectation that it will be helpful. Expectation plays a potent role in the placebo effect.

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

Psychodynamic psychotherapy: Psychological interventions, derived from a psychodynamic/psychoanalytic model in which: (1) therapist and patient explore and

gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference); (2) patients are given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with the technical focus on interpreting and working though conflicts; (3) therapy is non-directive and patients are not taught specific skills such as thought monitoring, re-evaluation or problem-solving.

Psychoeducation: Programmes for individual patients or groups of patients that involve an explicitly described educational interaction between the intervention provider and the patient or carer as the prime focus of the study.

Quality-adjusted life years (QALYs): A form of utility measure. QALYs are calculated by estimating the total life-years gained from a treatment and weighting each year with a quality-of-life score in that year.

Randomisation: A method used to generate a random allocation sequence, such as using tables of random numbers or computer-generated random sequences. The method of randomisation should be distinguished from concealment of allocation, because if the latter is inadequate, selection bias may occur despite the use of randomisation. For instance, a list of random numbers may be used to randomise participants, but if the list were open to the individuals responsible for recruiting and allocating participants, those individuals could influence the allocation process, either knowingly or unknowingly.

Randomised controlled trial (RCT) (also termed randomised clinical trial): An experiment in which investigators randomly allocate eligible people into groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the different groups. Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.

Recurrent depression: The development of a depressive disorder in a person who has previously suffered from depression.

Relapse: The reappearance of disease signs and symptoms after apparent recovery. The definitions of relapse used in this review were those adopted by the individual studies and varied between studies.

Relative risk (RR): Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of one indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

Residual depression: This refers to the symptoms of depression that remain following treatment to which there has been only a partial response. These symptoms often include anxiety, sleep disturbance, fatigue and loss of interest or pleasure in activities.

Screening: Screening is defined by the Guideline Development Group as a simple test performed on a large number of people to identify those who have depression.

Selective serotonin reuptake inhibitors (SSRIs): A class of antidepressant medications

that increase the level of serotonin (a neurotransmitter believed to influence mood) in the brain.

Sleep hygiene: Behavioural practices that promote continuous and effective sleep.

Standard care: The usual care given to those suffering from acute psychiatric episodes in the area concerned.

Standard doses: The recommended dose range listed in the *British National Formulary*; this normally reflects the information contained in the manufacturers' Summary of Product Characteristics (SPC) as well as advice from an external panel of experts.

Statistical significance: An effect size that is statistically significant is one where the probability of achieving the result by chance is less than 5% – i.e. a p-value less than 0.05.

Stepped care: A considered, organised, coordinated approach to screening, assessment, treatment and onward referral by an individual practitioner, team or care provider organisation, within the parameters of defined protocols or pathways. These approaches may or may not be provided within the context of a fixed budget (for example, the Health Maintenance Organisation (HMO) in the US). Primary Care Trusts are required to develop protocols for the treatment of depression in primary care within the National Service Framework for Mental Health.

Stepped care model: A sequence of treatment options to offer simpler and less expensive interventions first and more complex and expensive interventions if the patient has not benefited, based on locally agreed protocols.

Sub-syndromal depression (also termed sub-threshold depression): Depression symptoms that fail to meet criteria for major depressive disorder.

Telephone support: Augmentation of a therapeutic intervention designed to improve the effectiveness of the intervention; it usually consists of a limited number of telephone contacts that have a facilitative and monitoring function.

Treatment-resistant depression: For the purpose of the guideline, treatment resistant depression is defined as failure to respond to more than one course of antidepressants.

Tricyclic antidepressants (TCAs): The original class of antidepressants used to treat depression by increasing levels of the neurotransmitters serotonin and norepinephrine.

Wait list control: A term used in controlled trials when participants are allocated to a 'wait list' condition. Outcome measures are taken from these participants at the end of the waiting period and compared to those from participants who received the treatment. The wait list participants then receive the treatment.

Watchful waiting: An intervention in which no active treatment is offered to the person with depression if in the opinion of the health professional the person may recover without a specific intervention. All such patients should be offered a follow-up appointment.