Depression

THE NICE GUIDELINE ON THE TREATMENT AND MANAGEMENT OF DEPRESSION IN ADULTS

UPDATED EDITION

This guideline has been partially updated. Sections that have been updated are marked: 'This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.'

NATIONAL COLLABORATING CENTRE FOR MENTAL HEALTH

DEPRESSION

THE TREATMENT AND MANAGEMENT OF DEPRESSION IN ADULTS (UPDATED EDITION)

National Clinical Practice Guideline 90

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1 PREFACE

This guideline was first published in December 2004 (NICE, 2004a; NCCMH, 2004) (referred to as the 'previous guideline'). The present guideline (referred to as the 'update') updates many areas of the previous guideline. There are also new chapters on the experience of depression for people with depression and their carers (Chapter 4), and on the treatment and management of subthreshold depressive symptoms (including dysthymia symptoms) (Chapter 13), which were not part of the scope of the previous guideline. Recommendations categorised as 'good practice points' in the previous guideline were reviewed for their current relevance (including issues around consent and advance directives). Further details of what has been updated and what is left unchanged can be found at the beginning of each evidence chapter. The scope for the update also included updating two National Institute for Health and Clinical Excellence (NICE) technology appraisals (TAs) on the use of electroconvulsive therapy (ECT) (TA59) and on computerised cognitive behaviour therapy (TA51) (NICE, 2003, 2002)[1]. See Appendix 1 for more details on the scope of this update. Sections of the guideline where the evidence has not been updated are marked by asterisks (**_**).

The previous guideline and this update have been developed to advise on the treatment and management of depression. The guideline recommendations in the update have been developed by a multidisciplinary team of healthcare professionals, people with depression, a carer and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for people with depression while also emphasising the importance of the experience of care for them and their carers.

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

1.1 NATIONAL 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 condi-

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

tions' (Mann, 1996). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. Where evidence is lacking, the guidelines incorporate statements and recommendations based upon the consensus statements developed by the Guideline Development Group (GDG).

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

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

1.1.2 Uses and limitations of clinical guidelines

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

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

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

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment

programme including a range of activities, the purpose of which may be to help engage the person and to provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered; otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care in order to support and encourage a good therapeutic relationship is at times as important as the specific treatments offered.

1.1.3 Why develop national guidelines?

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, diminish unacceptable variations in the provision and quality of care across the NHS and ensure that the health service is patient centred. All guidance is developed in a transparent and collaborative manner using the best available evidence and involving all relevant stakeholders.

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

1.1.4 The National Collaborating Centre for Mental Health

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

1.1.5 From national guidelines to local implementation

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, specialist mental health professionals, and people with depression and their carers should undertake the translation of the implementation plan locally, taking into account both the recommendations set out in this guideline and the priorities set in the National Service Framework for Mental Health (Department of Health, 1999) and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take considerable time, especially where substantial training needs are identified.

1.1.6 Auditing the implementation of guidelines

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

1.2 THE NATIONAL DEPRESSION GUIDELINE

1.2.1 Who has developed this guideline?

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included two people with depression and a carer, and professionals from psychiatry, clinical psychology, general practice, nursing and psychiatric pharmacy.

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

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of 14 times throughout the process of guideline development. It met as a whole, but key topics were led by a national expert in the relevant topic. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisers where needed. The group oversaw the production and synthesis of research evidence before presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

1.2.2 For whom is this guideline intended?

This guideline is relevant for adults with depression as the primary diagnosis and covers the care provided by primary, community, secondary, tertiary and other health-care professionals who have direct contact with, and make decisions concerning the care of, adults with depression.

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

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

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

1.2.3 Specific aims of this guideline

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

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

1.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide an introduction to guidelines, the topic of depression and the methods used to update this guideline. Chapters 5 to 13 provide the evidence that underpins the recommendations about the treatment and management of depression, with Chapter 4 providing personal accounts from people with depression and carers that offer an insight into their experience of depression.

Each evidence chapter begins with a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted, and the structure of the chapters varies

accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about the review protocol and studies included in the review. Clinical evidence summaries are used to summarise the data presented. Health economic evidence is then presented (where appropriate), followed by a section (from evidence to recommendations) that draws together the clinical and health economic evidence and provides a rationale for the recommendations. On the CD-ROM, further details are provided about included/excluded studies, the evidence, and the previous guideline methodology (see Table 1 for details).

Table 1: Appendices on CD-ROM

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2 DEPRESSION

This guideline is concerned with the treatment and management of adults with a primary diagnosis of depression in primary and secondary care. The terminology and diagnostic criteria used for this heterogeneous group of related disorders have changed over the years, and the previous guideline related only to those identified by *The ICD–10 Classification of Mental and Behavioural Disorders* (ICD–10) (WHO, 1992) as having a depressive episode (F32 in the ICD–10), recurrent depressive episode (F33) or mixed anxiety and depressive disorder (F41.2). In this guideline update the scope was widened to cover the substantial proportion of people who present with less severe forms of depression. Therefore, this updated guideline covers 'subthreshold depressive symptoms', which fall below the criteria for major depression (and which do not have a coding in ICD–10), and subthreshold depressive symptoms persisting for at least 2 years (dysthymia; F34.1).

It should, however, be noted that much of the research forming the evidence base from which this guideline is drawn has used a different classificatory system – the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, currently in its fourth edition (DSM–IV-TR) (APA, 2000c). The two classificatory systems, while similar, are not identical especially with regard to definitions of severity. After considerable discussion the GDG took the decision to base the guidelines on the DSM–IV-TR (see Section 2.1.5). This covers major depressive disorder single episode (296.2) and recurrent (296.3) together with dysthymic disorder (300.4), and contains research criteria for minor depressive disorder (APA, 2000c). The effect of this change in practice is discussed in Section 2.1.5 (see also Appendix 11). The guideline does not address the management of depression in children and adolescents, depression in bipolar disorder, depression occurring in both antenatal and postnatal periods, or depression associated with chronic physical health problems, all of which are covered by separate guidelines (NICE, 2005, 2006c, 2007e, 2009c). The guideline update does cover psychotic symptoms occurring within the context of an episode of depression (depression with psychotic symptoms), but not depression occurring in a primary psychotic illness, such as schizophrenia or dementia.

2.1 THE DISORDER

2.1.1 Symptoms, presentation and pattern of illness

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Distinguishing the mood changes between clinically significant

degrees of depression (for example, major depression) and those occurring 'normally' remains problematic and it is best to consider the symptoms of depression as occurring on a continuum of severity (Lewinsohn *et al.*, 2000). The identification of major depression is based not only on its severity but also on persistence, the presence of other symptoms, and the degree of functional and social impairment. However, there appears to be no hard-and-fast 'cut-off' between 'clinically significant' and 'normal' degrees of depression; the greater the severity of depression, the greater the morbidity and adverse consequences (Lewinsohn *et al.*, 2000; Kessing, 2007). When taken together with other aspects that need to be considered, such as duration, stage of illness and treatment history, there are considerable problems when attempting to classify depression into categories (see Section 2.1.5).

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. For others, a person's mood may be reactive to positive experiences and events, although these elevations in mood are not sustained, with depressive feelings re-emerging, often quickly (Andrews & Jenkins, 1999).

Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, an exacerbation of pre-existing pains, pains secondary to increased muscle tension (Gerber *et al.*, 1992), a lack of libido, fatigue and diminished activity, although agitation is common and marked anxiety frequent. Typically there is reduced sleep and lowered appetite (sometimes leading to significant weight loss), but for some people it is recognised that sleep and appetite are increased. A loss of interest and enjoyment in everyday life, and feelings of guilt, worthlessness and that one deserves 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 when both are below the threshold for either disorder, dependent upon which constellation of symptoms dominates the clinical picture. In addition, the presentation of depression can vary with age with the young showing more behavioural symptoms and older adults more somatic symptoms and fewer complaints of low mood (Serby & Yu, 2003).

Major depression is generally diagnosed when a persistent low mood and an absence of positive affect are accompanied by a range of symptoms, the number and combination needed to make a diagnosis being operationally defined (ICD–10, WHO, 1992; DSM–IV, APA, 1994).

Some people are recognised as showing an atypical presentation with reactive mood, increased appetite, weight gain and excessive sleepiness together with the personality feature of sensitivity to rejection (Quitkin *et al.*, 1991) and this is classified as major depression with atypical features in DSM–IV (APA, 1994). The definition of atypical depression has changed over time and it is not specifically recognised in ICD–10.

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

People with severe depression 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 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 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). Just as the initial presentation and form of a depressive illness varies considerably, so too does the prodromal period. Some individuals experience a range of symptoms in the months prior to the full illness, including anxiety, phobias, milder depressive symptoms and panic attacks; others may develop a severe major depressive illness fairly rapidly, not uncommonly following a major stressful life event. Sometimes somatic symptoms dominate the clinical picture leading the clinician to investigate possible underlying physical illness until mood changes become more obvious.

Although depression has been thought of as a time-limited disorder, lasting on average 4 to 6 months with complete recovery afterwards, it is now clear that incomplete recovery and relapse are common. The WHO study of mental disorders in 14 centres across the world found that 50% of patients still had a diagnosis of depression 1 year later (Simon *et al.*, 2002) and at least 10% had persistent or chronic depression (Kessler *et al.*, 2003). At least 50% of people, following their first episode of major depression, will go on to have at least one more episode (Kupfer, 1991) and, after the second and third episodes, the risk of further relapse rises to 70 and 90%, respectively (Kupfer, 1991). People with early onset depression (at or before 20 years of age) and depression occurring in old age have a significantly increased vulnerability to relapse (Giles *et al.*, 1989; Mitchell & Subramaniam, 2005). Thus, while the outlook for a first episode is good, the outlook for recurrent episodes over the long term can be poor with many patients experiencing symptoms of depression over many years (Akiskal, 1986).

Sometimes, recurrent episodes of depression will follow a seasonal pattern which has been called ‘seasonal affective disorder’ (SAD; Rosenthal *et al.*, 1984). DSM–IV includes

criteria for a seasonal pattern whereas only provisional criteria are given in the research version of ICD–10. Although a seasonal pattern can apply to both recurrent depression and bipolar disorder it appears most common in the former (70 to 80%, Rodin & Thompson, 1997; Westrin & Lam, 2007), with recurrent winter depression far more common than recurrent summer episodes (Rodin & Thompson, 1997; Magnusson & Partonen, 2005).

Depression with a seasonal pattern refers to depression that occurs repeatedly at the same time of year (not accounted for by psychosocial stress) with remission in between and without a lifetime predominance of non-seasonal depression. Decreased activity is reported as nearly always present and atypical depressive symptoms, particularly increased sleep, weight gain and carbohydrate craving are common (Magnusson & Partonen, 2005). The onset is reported as usually in the third decade and is more common in the young (Rodin & Thompson, 1997; Magnusson & Partonen, 2005). Surveys in the UK have found a surprisingly high prevalence in general practitioner (GP) practice attendees ranging from 3.5% in Aberdeen (Eagles *et al.*, 1999) to 5.6% in southern England (Thompson *et al.*, 2004). However, the validity of 'seasonal affective disorder' has been poorly accepted in Europe and may be an extreme form of a dimensional 'seasonality trait' rather than a specific diagnosis (Kasper *et al.*, 1989). Some patients with non-seasonal mood disorders also report seasonal variation (Bauer & Dunner, 1993) and this also occurs in other disorders such as anxiety and eating disorders (Bauer & Dunner, 1993; Magnusson & Partonen, 2005). After 5 to 11 years' follow-up, approximately half of those with continuing depressive episodes no longer display a seasonal pattern (Magnusson & Partonen, 2005).

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

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

The term 'treatment-resistant depression' was used in the previous guideline to describe depression that has failed to respond to two or more antidepressants at an adequate dose for an adequate duration given sequentially. Although the term is commonly used, and it can be seen as a useful 'short-hand' to refer to difficulties in achieving adequate improvement with treatment, it has problems that led the GDG to a move away from its use in this guideline update. The term implies that there is a natural cut-off between people who respond to one or two antidepressants compared with those who do not, which is not supported by the evidence, and the term may be taken by both doctors and patients as a pejorative label. It is also not helpful as it does not take into account different degrees of improvement or stages of illness (whether occurring in an ongoing episode or relapse in spite of ongoing treatment). It takes no account of psychotherapeutic treatment, and non-antidepressant augmenting agents are not easily incorporated. The limited trial evidence base reflects the lack of a natural distinction and different studies incorporate different degrees of treatment failure. Finally, it fails to take

into account whether psychosocial factors may be preventing recovery (Andrews & Jenkins, 1999). The GDG preferred to approach the problem of inadequate response by considering sequenced treatment options rather than by a category of patient.

2.1.3 Disability and mortality

Depression is the most common mental disorder in community settings and is a major cause of disability across the world. In 1990 it was the fourth most common cause of loss of disability-adjusted life years (DALYs) in the world, and it is projected to become the second most common cause by 2020 (World Bank, 1993). In 1994, it was estimated that about 1.5 million DALYs 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 a review, see Institute of Medicine, 2001). There is a clear dose–response relationship between illness severity and the extent of disability (Ormel & Costa e Silva, 1995) and onsets of depression are associated with onsets of disability, with an approximate doubling of both social and occupational disability (Ormel *et al.*, 1999).

Apart from the subjective experiences of people with depression, the impact on social and occupational functioning, physical health and mortality is substantial. Depressive illness causes a greater decrement in health state than the major chronic physical illnesses: angina, arthritis, asthma and diabetes (Moussavi *et al.*, 2007). Emotional, motivational and cognitive effects substantially reduce a person's ability to work effectively, with losses in personal and family income as well as lost contribution to society in tax revenues and employment skills. Wider social effects include: greater dependence upon welfare and benefits, with loss of self-esteem and self-confidence; social impairments, including reduced ability to communicate and sustain relationships during the illness with knock-on effects after an episode; and longer-term impairment in social functioning, especially for those who have chronic or recurrent disorders. The stigma associated with mental health problems generally (Sartorius, 2002), and the public view that others might view a person with depression as unbalanced, neurotic and irritating (Priest *et al.*, 1996), may partly account for the reluctance of people with depression to seek help (Bridges & Goldberg, 1987).

Depression can also exacerbate the pain, distress and disability associated with physical health problems as well as adversely affecting outcomes. Depression combined with chronic physical health problems incrementally worsens health compared with physical disease alone or even combinations of physical diseases (Moussavi *et al.*, 2007). In addition, for a range of physical health problems, findings suggest an increased risk of death when comorbid depression is present (Cassano & Fava, 2002). In coronary heart disease, for example, depressive disorders are associated with an 80% increased risk, both of its development and of subsequent mortality in established disease, at least partly through common contributory factors (Nicholson *et al.*, 2006). Another guideline on depression in adults with a chronic physical health problem accompanies this guideline update (NCCMH, 2010).

Suicide accounts for nearly 1% of all deaths and nearly two-thirds of this figure occur in people with depression (Sartorius, 2001). Looked at another way, having

depression leads to over a four-times higher risk of suicide compared with the general population, which rises to nearly 20 times in the most severely ill (Bostwick & Pankratz, 2000). Sometimes depression may also lead to acts of violence against others and may even include homicide. Marital and family relationships are frequently negatively affected, and parental depression may lead to neglect of children and significant disturbances in children (Ramachandani & Stein, 2003).

2.1.4 Incidence and prevalence

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

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

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

No significant effect of ethnic status on prevalence rates of a depressive episode or mixed anxiety and depression were found, although numerically there was a higher proportion of South Asians in those with depressive or anxiety disorders than in those without (Singleton *et al.*, 2001). Migration has been high in Europe in the last 2 decades, but data on mental health is scarce and results vary between migrant groups (Lindert *et al.*, 2008).

An illustration of the social origins of depression can be found in a general practice survey in which 7.2% (range 2.4 to 13.7%, depending upon the practice) of consecutive attendees had a depressive disorder. Neighbourhood social deprivation

accounted for 48.3% of the variance among practices and the variables that accounted for most of that variance were: the proportion of the population having no or only one car; and neighbourhood unemployment (Ostler *et al.*, 2001).

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

2.1.5 Diagnosis

In recent years there has been a greater recognition of the need to consider depression that is 'subthreshold'; that is, where the depression does not meet the full criteria for a depressive/major depressive episode. Subthreshold depressive symptoms cause considerable morbidity and human and economic costs, and are more common in those with a history of major depression as well as being a risk factor for future major depression (Rowe & Rapaport, 2006).

There is no accepted classification for subthreshold depression in the current diagnostic systems, with the closest being minor depression (a research diagnosis in DSM–IV). At least two but less than five symptoms are required and it overlaps with ICD–10 mild depressive episode with four symptoms. Given the practical difficulty and inherent uncertainty in deciding thresholds for significant symptom severity and disability, there is no natural discontinuity between subthreshold depressive symptoms and 'mild major' depression in routine clinical practice.

Diagnostic criteria and methods of classification of depressive disorders have changed substantially over the years. Although the advent of operational diagnostic criteria has improved the reliability of diagnosis, this does not circumvent the fundamental problem of attempting to classify a disorder that is heterogeneous and best considered in a number of dimensions (for a fuller discussion, see Appendix 11). DSM–IV and ICD–10, have virtually the same diagnostic features for a 'clinically important' severity of depression (termed a major depressive episode in DSM–IV or a depressive episode in ICD–10). Nevertheless their thresholds differ, with DSM–IV requiring a minimum of five out of nine symptoms (which must include depressed mood and/or anhedonia) and ICD–10 requiring four out of ten symptoms (including at least two of depressed mood, anhedonia and loss of energy). This may mean that more people may be identified as depressed using ICD–10 criteria compared with DSM–IV (Wittchen *et al.*, 2001a), or at least that somewhat different populations are identified (Andrews *et al.*, 2008), related to the need for only one of two key symptoms for DSM–IV but two out of three for ICD–10. These studies emphasise that, although similar, the two systems are not identical and that this is particularly apparent at the threshold taken to indicate clinical importance. The GDG has widened the range of depressive disorders to be considered in this guideline update and emphasises that the diagnostic 'groupings' it uses should be viewed as pragmatic subdivisions of dimensions in the form of vignettes or exemplars rather than firm categories. The GDG considered it important to acknowledge the uncertainty inherent in our current understanding of depression and its classification, and that

assuming a false categorical certainty is likely to be unhelpful and, even worse, damaging.

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

The implication of the change in diagnostic system used in the guideline update, combined with redefining the severity ranges, is that it is likely to raise the thresholds for some specific treatments such as antidepressants. An important motivation has been to provide a strong steer away from only using symptom counting to make the diagnosis of depression and, by extension, to emphasise that symptom severity rating scales should not be used by themselves to make the diagnosis, although they can be an aid in assessing severity and response to treatment. To make a diagnosis of a depression requires assessment of three linked but separate factors: (a) severity, (b) duration and (c) course. Diagnosis requires a minimum of 2 weeks' duration of symptoms that includes at least one key symptom. Individual symptoms should be assessed for severity and impact on function, and be present for most of every day.

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

- subthreshold depressive symptoms: fewer than five symptoms of depression
- mild depression: few, if any, symptoms in excess of the five required to make the diagnosis, and the symptoms result in only minor functional impairment
- moderate depression: symptoms or functional impairment are between 'mild' and 'severe'
- severe depression: most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms.

However, diagnosis using the three factors listed above (severity, duration and course) only provides a partial description of the individual experience of depression. People with depression vary in the pattern of symptoms they experience, their family history, personalities, premorbid difficulties (for example, sexual abuse), psychological mindedness and current relational and social problems – all of which may significantly affect outcomes. It is also common for depressed people to have a comorbid psychiatric diagnosis, such as anxiety, social phobia, panic and various personality disorders (Brown *et al.*, 2001), and physical comorbidity. Gender and socioeconomic factors account for large variations in the population rates of depression and few studies of pharmacological, psychological or indeed other treatments for depression either

control for or examine these variations. This serves to emphasise that choice of treatment is a complex process and involves negotiation and discussion with patients, and, given the current limited knowledge about which factors are associated with better antidepressant or psychotherapy response, most decisions will rely upon clinical judgement and patient preference until there is further research evidence. Trials of treatment in unclear cases may be warranted, but the uncertainty needs to be discussed with the patient and benefits from treatment carefully monitored.

The differential diagnosis of depression can be difficult; of particular concern are patients with bipolar disorder presenting with depression. The issue of differential diagnosis in this area is covered in the NICE guideline on bipolar disorder (NICE, 2006c).

2.2 AETIOLOGY

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

Most people now believe that all of these factors influence a person'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 (Harris, 2000). Nevertheless, the factors identified as likely to increase a person's vulnerability to depression include gender, genetic and family factors, adverse childhood experiences, personality factors and social circumstances. In the stress-vulnerability model (Nuechterlein & Dawson, 1984), vulnerability factors interact with social or physical triggers such as stressful life events or physical illness to result in a depressive episode (for example, Harris, 2000).

A family history of depressive illness accounts for around 39% of the variance of depression in both sexes (Kendler *et al.*, 2001), and early life experiences such as a poor parent–child relationship, marital discord and divorce, neglect, and physical 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 that are directly related to their personality, such as the end of a relationship (Hammen *et al.*, 2000).

The possession of a specific variation in particular genes has also been reported to make individuals more likely to experience depression when faced with life events (for example, Caspi *et al.*, 2003).

The role of current social circumstances in increasing the risk of depression, such as poverty, homelessness, unemployment and chronic physical or mental illness, cannot be doubted even from a brief examination of the epidemiology of depression (see above). In the UK, an influential study found that social vulnerability factors for depression in women in Camberwell, London, included: having three or more children under the age of 14 years living at home; not having a confiding relationship with another person; and having no paid employment outside the home (Brown & Harris, 1978). Lack of a confiding relationship appears to be a strong risk factor for depression (Patten, 1991).

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

In addition to considering the aetiology of the onset of depressive episodes, it is equally important to consider factors that maintain or perpetuate depression because these are potential targets for intervention. Although many studies have reported on factors that predict outcome (including earlier age of onset, greater severity and chronicity, ongoing social stresses, comorbidity with other psychiatric or physical disorders and certain types of personality disorder), there is a lack of understanding about what determines how long a depressive episode lasts, why it varies so much between individuals and why for some it becomes persistent. It is also clinically apparent that depression, especially when it persists, may lead to secondary disability that compounds, and is difficult to distinguish from, the depression itself. Features include loss of self-esteem and independence, feelings of helplessness and hopelessness (which increase the risk of suicide) and loss of engagement in outside activities with social withdrawal. These are aspects that self-help interventions and organisations often target, but about which there is little systematic evidence. These are likely to relate to, and benefit from, the non-specific effects of interventions and the placebo effect (see Section 2.4.3).

2.3 ECONOMIC COSTS OF DEPRESSION

There is now widespread recognition of the significant burden that depression imposes on people and their carers, health services and communities throughout the world. As mentioned previously, by 2020, depression is projected to become the second leading cause of disability with estimates indicating that unipolar depressive disorders account for 4.4% of the global disease burden or the equivalent of 65

million DALYs (Murray & Lopez, 1997b; WHO, 2002). Within the UK setting, the Psychiatric Morbidity Survey of adults aged 16 to 74 years in 2000 reported a prevalence rate for depression of 26 per 1000 people with slightly higher rates for women compared with men (Singleton *et al.*, 2001). Due to its high prevalence and treatment costs, its role as probably the most important risk factor for suicide (Knapp & Illson, 2002), as well as its large impact on workplace productivity, depression places an enormous burden on both the healthcare system and the wider society.

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

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

One of the key findings from the cost-of-illness literature is that the indirect costs of depression far outweigh the health service costs. Thomas and Morris (2003) suggest that the effect on lost employment and productivity is 23 times larger than the costs falling to the health service. Other studies have also supported these findings. Based on UK labour market survey data, Almond and Healey (2003) estimated that respondents with self-reported depression/anxiety were three times more likely to be absent from work (equivalent to 15 days per year) than workers without depression/anxiety. Furthermore, a US-based study suggests that depression is a major cause of reduced productivity while at work, in terms of 'work cut-back days' (Kessler *et al.*, 2001). This reduced workplace productivity is unlikely to be

adequately measured by absenteeism rates and further emphasises the 'hidden costs' of depression (Knapp, 2003). Other intangible costs of depression include the impact on the quality of life of people with depression and their carers.

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

2.4 TREATMENT AND MANAGEMENT IN THE NATIONAL HEALTH SERVICE

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

2.4.1 Detection, recognition and referral in primary care

Of the 130 cases of depression (including mild cases) per 1000, only 80 will consult their GP. The most common reasons given for reluctance to contact the family doctor include: not thinking anyone could help (28%); feeling it was a problem one should be able to cope with (28%); not thinking it was necessary to contact a doctor (17%); thinking the problem would get better by itself (15%); feeling too embarrassed to discuss it with anyone (13%); and being afraid of the consequences (for example, 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 who do consult their GP, 49 are not recognised as depressed, mainly because most of 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 has milder illnesses (Goldberg *et al.*, 1998; Thompson *et al.*, 2001). 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 among individual GPs in their referral rates to mental health services, but those seen by specialist services are a highly selected group – they are skewed towards those who do not respond to antidepressants, people with more severe illnesses, single women and those below 35 years of age (Goldberg & Huxley, 1980).

GPs 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). GPs' communication skills 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 GPs 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, 1988; 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; Kendrick *et al.*, 2001), 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 and colleagues (1990) suggested that the benefits of recognition of common mental disorders could not be attributed entirely to specific mental health treatments. Other factors, such as acknowledgement of distress, reinterpretation of symptoms, and 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 psychoeducation 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.*, 2004). 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 with psychological symptoms, are especially likely to be recognised as depressed while those presenting with somatic symptoms for which no obvious cause can be found are less likely to be recognised. The evidence suggests that these very undesirable circumstances, in which large numbers of people each year experience depression, with all of the attendant negative personal and social consequences, could be changed. With 50% of people with depression never consulting a doctor, 95% never entering secondary mental health services, and many more whose depression goes unrecognised and untreated, this is clearly a problem for primary care.

2.4.2 Assessment and co-ordination of care

Given the low detection and recognition rates, it is essential that primary care and mental health practitioners have the required skills to assess people with depression, their social circumstances and relationships, and the risk they may pose to themselves and 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 [CPA] in secondary care services), is highly likely to improve outcomes and should, therefore, be comprehensive.

2.4.3 Aim, and non-specific effects, of treatment and the placebo

The aim of intervention is to restore health through the relief of symptoms and restoration of function and, in the longer term, to prevent relapse. Where possible, the key goal of an intervention should be complete relief of symptoms (remission), which is associated with better functioning and a lower likelihood of relapse (Kennedy & Foy, 2005). It may not always be possible to achieve remission, but it is usually possible to improve symptoms and functioning to an important degree. For this reason the GDG examined a range of outcomes (where available), including response, remission, change in symptoms and relapse. The relative importance of these depends on many factors, including the severity of depression, the degree of impairment to everyday functioning experienced and the patient's psychiatric history. Among those seeking treament for depression, those put on waiting lists do improve steadily with time. Posternak and Miller (2001) studied 221 patients assigned to waiting lists in 19 treatment trials of specific interventions and found that 20% improved within 4 to 8 weeks, and 50% improved within 6 months. They estimated that 60% of responders to placebo and 30% of responders to antidepressants may experience spontaneous resolution of symptoms (if untreated). An earlier study by Coryell and colleagues (1994) followed up 114 patients with untreated depression for 6 months: the mean duration of an episode was 6 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 and colleagues (2000) showed that patients treated by psychiatrists with antidepressants showed greater improvements than untreated patients: the median time to recovery was 3 months, with 26% recovering in 1 month, 63% in 6 months; 85% in 1 year, and 88% in 2 years.

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

and in those with depression that persists over time. However at present it is not possible to clearly identify people with depression who will respond to the specific aspects of a treatment as opposed to the non-specific effects associated with having a treatment.

2.4.4 Pharmacological treatments

The mainstay of the pharmacological treatment of depression for the last 40 or more years has been antidepressants. Tricyclic antidepressants (TCAs) were introduced in the 1950s, the first being imipramine (Kuhn, 1958). The mode of action of this class of drug, 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 monoamine-oxidase inhibitors (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 anticholinergic, histaminergic and other receptor systems reduced their acceptability. Moreover, overdose with TCAs (with the exception of lofepramine) carries a high mortality and morbidity, which is 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: selective 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 57, 2009). 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 57, 2009) and antipsychotics (BNF 57, 2009), 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 10.

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

2.4.5 Psychological treatments

In 1917, Freud published ‘Mourning and melancholia’, which is 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 8 include: cognitive behavioural therapies; behavioural activation; interpersonal therapy (IPT); problem-solving therapy; counselling; short-term psychodynamic psychotherapy; and couples therapy. Psychological treatments have expanded rapidly in recent years and generally have more widespread acceptance from patients (Priest *et al.*, 1996). In the last 15 years in the UK there has been a very significant expansion of psychological treatments in primary care for depression, in particular primary care counselling.

2.4.6 Service-level and other interventions

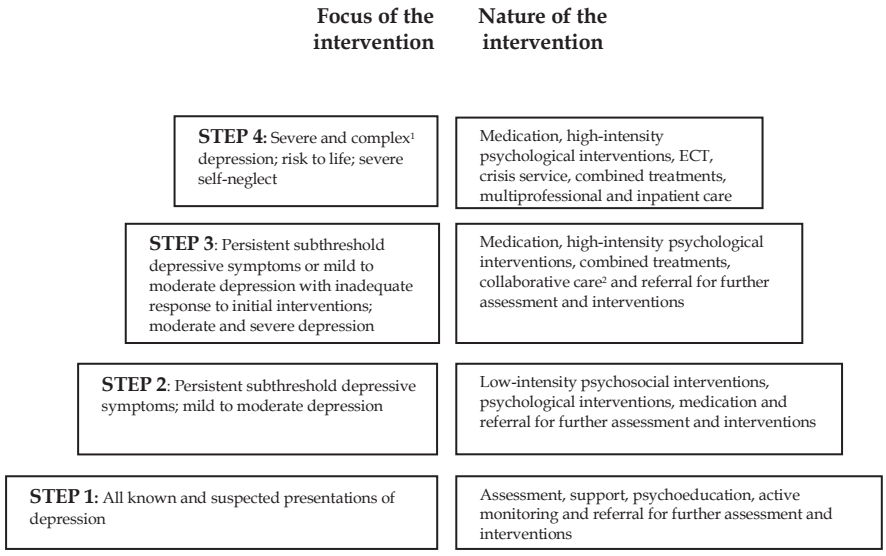
Given the complexity of healthcare organisations, and the variation in the way care is delivered (inpatient, outpatient, day hospital, community teams, and so on), choosing the right service configuration for the delivery of care to specific groups of people has gained increasing interest with regard to both policy (for example, see Department of Health, 1999), and research (for example, 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, non-statutory support and other social supports. Other types of interventions reviewed for this guideline include: physical activity programmes, guided self-help, computerised cognitive behavioural therapy (CCBT) and screening.

2.4.7 Stepped care

In Figure 1, a 'stepped-care' model is developed that 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

Figure 1: The stepped-care model



[1] Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.
[2] Only for depression where the person also has a chronic physical health problem and associated functional impairment (see NICE, 2009c).

provision of services supporting patients, carers and healthcare professionals in identifying and accessing the most effective interventions.

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 depression of only mild severity, many GPs prefer an 'active monitoring' approach, which can be accompanied by general advice on such matters as restoring natural sleep rhythms and getting more structure into the day. However, other people prefer to accept, or indeed require, medical, psychological or social interventions, and these patients are therefore offered more complex interventions. Various interventions are effective, delivered by a range of workers in primary care.

Treatment of depression in primary care, however, often falls short of optimal guideline recommended practice (Donoghue & Tylee, 1996) 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 will need specialist referral.

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

3 METHODS USED TO DEVELOP THIS GUIDELINE[2]

3.1 OVERVIEW

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

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

The update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness. In addition, to ensure a service user and carer focus, the concerns of people with depression and their carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

3.2 THE SCOPE

NICE commissioned the NCCMH to review recent evidence on the management of depression and to update the existing guideline *Depression: Treatment and Management of Depression in Primary and Secondary Care* (NICE, 2004a; NCCMH, 2004). The NCCMH developed a scope for the guideline update (see Appendix 1). The scope for the update also included updating the NICE technology appraisal on the use of ECT (NICE, 2003), which had been incorporated into the previous guideline.

The purpose of the scope is to:

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

[2]The methodology for the previous guideline can be found in Appendix 21.

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

The draft scope was subject to consultation with registered stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from stakeholder organisations and the Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCCMH and NICE reviewed the scope in light of comments received and the revised scope was signed off by the GRP.

3.3 THE GUIDELINE DEVELOPMENT GROUP

The GDG consisted of: professionals in psychiatry, psychiatric pharmacy, clinical psychology, nursing and general practice; academic experts in psychiatry and psychology; and people with depression and a carer. The GDG was recruited according to the specifications set out in the scope and in line with the process set out in the NICE guideline manual (NICE, 2007c). The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline.

3.3.1 Guideline Development Group meetings

Fourteen GDG meetings were held between November 2007 and January 2009. During each day-long GDG meeting, in a plenary session, clinical questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest, and the concerns of people with depression and carers were routinely discussed as part of a standing agenda item.

3.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Three topic groups were formed to cover: (1) pharmacological and physical interventions, (2) psychological and psychosocial interventions and (3) services. These groups were designed to efficiently manage the large volume of evidence needing to be appraised prior to presenting it to

the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the healthcare professionals). Topic groups refined the clinical questions and the clinical definitions of treatment interventions, reviewed and prepared the evidence with the systematic reviewer before presenting it to the GDG as a whole and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting the section of the guideline relevant to the work of each topic group. A group was also convened comprising the service user and carer representatives and members of the NCCMH review team to develop the chapter on experience of care (Chapter 4). The service user and carer representatives jointly ran the group and presented their findings at GDG meetings.

3.3.3 People with depression and carers

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included three people with depression, one of whom was also a carer. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guideline's introduction and Chapter 4 and identified recommendations from the service user and carer perspective.

3.3.4 Special advisers

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

3.3.5 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies to ensure that up-to-date evidence was included in the development of the guideline. They informed the group about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment, and trial data if the GDG could be provided with full access to the complete trial report. Appendix 6 lists the researchers who were contacted.

3.4 CLINICAL QUESTIONS

Clinical questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. The draft clinical questions were discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the questions were refined once the evidence had been searched and, where necessary, subquestions were generated. Questions submitted by stakeholders were also discussed by the GDG and included where appropriate. For the purposes of the systematic review of clinical evidence, the questions were categorised as primary or secondary. The review focused on providing evidence to answer the primary questions. The final list of clinical questions can be found in Appendix 7.

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

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

Table 2: Features of a well-formulated question on effectiveness intervention – the PICO guide

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

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

Type of question	Best primary study design
Effectiveness or other impact of an intervention	RCT; other studies that may be considered in the absence of an RCT are the following: internally/externally controlled before and after trial, interrupted time-series
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in a randomised trial or inception cohort study
Rates (of disease, patient experience, rare side effects)	Cohort, registry, cross-sectional study
Costs	Naturalistic prospective cost study

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of clinical question of relevance to NICE guidelines. These are listed in Table 3. For each type of question the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

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

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

3.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature (updating the existing evidence-base where appropriate) to answer the specific clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence-based where possible and, if evidence is not available, informal consensus methods are used (see Section 3.5.11) and the need for future research is specified.

3.5.1 Methodology

A step-wise hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed this process based on methods set out in *The*

Guidelines Manual (NICE, 2007c) and after considering recommendations from a range of other sources. These included:

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

3.5.2 The review process

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

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

Searches for evidence were updated between 6 and 8 weeks before the guideline consultation. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

3.5.3 The search process for questions concerning interventions

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

The search was exhaustive, using several databases and other sources. For RCTs the search consisted of terms relating to the clinical condition (that is, depression) and study design only, thereby yielding the largest number of relevant papers that might otherwise be missed by more specific searches, formed around additional elements of the question, including interventions and the outcomes of interest. The GDG did not limit the search to any particular therapeutic modality. Standard mental health related bibliographic databases (that is, CINAHL, Cochrane Library, EMBASE, MEDLINE and PsycINFO) were used for the initial search for all studies potentially relevant to the guideline update. Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 10 for quality criteria used to assess systematic reviews). However, in some circumstances existing datasets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

After the initial search, results were scanned liberally to exclude irrelevant papers, the review team used a purpose-built 'study information' database to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). Double checking of all excluded studies was not done routinely, but a selection of abstracts was checked to ensure reliability of the sifting. For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to (a) repeat the search using subject-specific databases (for example, AMED, ERIC, OpenSIGLE or Sociological Abstracts), (b) conduct a new search for lower levels of evidence or (c) adopt a consensus process (see Section 3.5.11).

In addition, searches were made of the reference lists of all eligible systematic reviews and included studies. Known experts in the field, based both on the references identified in early steps and on advice from GDG members, were sent letters requesting relevant studies that were in the process of being published (see Appendix 6)[3]. In addition, the tables of contents of appropriate journals were periodically checked for relevant studies.

3.5.4 Search filters

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

[3]Unpublished full trial reports were also accepted where sufficient information was available to judge eligibility and quality (see Section 3.5.6).

3.5.5 Study selection

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

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

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

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

3.5.6 Unpublished evidence

The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the research; second, where evidence was submitted directly to the GDG, it must have been done so with the understanding that details would be published in the full guideline. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

3.5.7 Data extraction

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

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

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

Where necessary, standard deviations were calculated from standard errors (SEs), confidence intervals (CIs) or p-values according to standard formulae (see the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.1; Higgins & Green, 2008). Data were summarised using the generic inverse variance method using Review Manager.

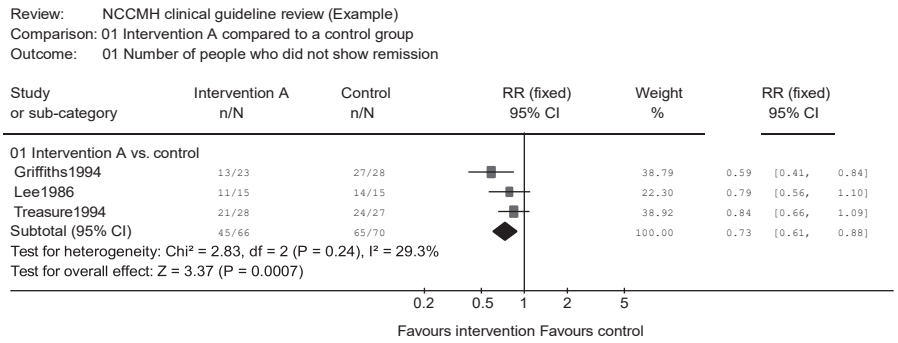
Consultation with another reviewer or members of the GDG was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, data extracted by one reviewer was checked by a second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad *et al.*, 1996; Berlin, 1997).

3.5.8 Synthesising the evidence

Where possible, meta-analysis was used to synthesise the evidence using Review Manager. If necessary, re-analyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews. Studies have been given a 'study ID' to make them easier to identify in the text, tables and appendices of this guideline. Study IDs are composed of the first author's surname followed by the year of publication. Studies that were included in the previous guideline (NCCMH, 2004) have a study ID in title case (for example, Smith1999); studies that were found and included in this guideline update only are labelled in capital letters (for example, JONES2005). References to included and excluded studies can be found in Appendix 17.

Dichotomous outcomes were analysed as relative risks (RR) with the associated 95% CI (for an example, see Figure 2). A 'relative risk' (also called a 'risk ratio') is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control. In Figure 2, the overall RR of 0.73

Figure 2: Example of a forest plot displaying dichotomous data



indicates that the event rate (that is, non-remission rate) associated with intervention A is about three quarters of that with the control intervention or, in other words, the RR reduction is 27%.

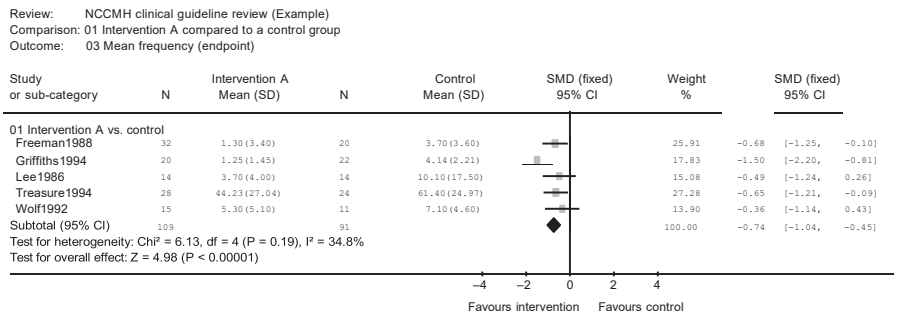
The CI shows with 95% certainty the range within which the true treatment effect should lie and can be used to determine statistical significance. If the CI does not cross the 'line of no effect', the effect is statistically significant.

Continuous outcomes were analysed as weighted mean differences (WMD), or as a standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect (for an example, see Figure 3). If provided, intention-to-treat data, using a method such as 'last observation carried forward', were preferred over data from completers.

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

- >50%: notable heterogeneity (an attempt was made to explain the variation by conducting sub-analyses to examine potential moderators. In addition, studies with effect sizes greater than two standard deviations from the mean of the

Figure 3: Example of a forest plot displaying continuous data



remaining studies were excluded using sensitivity analyses. If studies with heterogeneous results were found to be comparable with regard to study and participant characteristics, a random-effects model was used to summarise the results [DerSimonian & Laird, 1986]. In the random-effects analysis, heterogeneity is accounted for 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).

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

3.5.9 Presenting the data to the GDG

Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the GDG to prepare a GRADE evidence profile table for each review and to develop recommendations.

Evidence profile tables

A GRADE evidence profile was used to summarise, with the exception of diagnostic studies (methods for these studies are at present not sufficiently developed), both the quality of the evidence and the results of the evidence synthesis (see Table 4 for an example of an evidence profile). For each outcome, quality may be reduced depending on the following factors:

- study design (randomised trial, observational study, or any other evidence)
- limitations (based on the quality of individual studies; see Appendix 10 for the quality checklists)
- inconsistency (see Section 3.5.8 for how consistency was measured)
- indirectness (that is, how closely the outcome measures, interventions and participants match those of interest)
- imprecision (based on the CI around the effect size).

For observational studies, the quality may be increased if there is a large effect, if plausible confounding would have changed the effect, or if there is evidence of a dose–response gradient (details would be provided under the other considerations column). Each evidence profile also included a summary of the findings: the number of patients included in each group, an estimate of the magnitude of the effect and the overall quality of the evidence for each outcome.

The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness and any other considerations) and graded using the following definitions:

- High = further research is very unlikely to change our confidence in the estimate of the effect
- Moderate = further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate

Table 4: Example of GRADE evidence profile

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other consider-ations	Intervention	Control	Relative (95% CI)	Absolute	Quality
Outcome 1											
6	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	8/191	7/150	RR 0.94 (0.39 to 2.23)	0 fewer per 100 (from 3 fewer to 6 more)	EBEBEB MODERATE
Outcome 2											
6	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	55/236	63/196	RR 0.44 (0.21 to 0.94)[3]	18 fewer per 100 (from 2 fewer to 25 fewer)	EBEBEB MODERATE
Outcome 3											
3	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	83	81	–	MD –1.51 (–3.81 to 0.8)	EBEBEB MODERATE
Outcome 4											
3	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	88	93	–	SMD –0.26 (–0.56 to 0.03)	EBEBEB MODERATE
Outcome 5											
4	Randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Serious[4]	None	109	114	–	SMD –0.13 (–0.6 to 0.34)	EBEBEB MODERATE

[1]The upper confidence limit includes an effect that, if it were real, would represent a benefit that, given the downsides, would still be worth it.
[2]The lower confidence limit crosses a threshold below which, given the downsides of the intervention, one would not recommend the intervention.
[3]Random-effects model.
[4]95% CI crosses the minimal importance difference threshold.

- Low = further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate
- Very low = any estimate of effect is very uncertain.

For further information about the process and the rationale of producing an evidence profile table, see GRADE (2004).

3.5.10 Forming the clinical summaries and recommendations

Once the GRADE profile tables relating to a particular clinical question were completed, summary tables incorporating important information from the GRADE profiles were developed (these tables are presented in the evidence chapters).

The systematic reviewer in conjunction with the topic group lead produced a clinical evidence summary. Once the GRADE profiles and clinical summaries were finalised and agreed by the GDG and the evidence from depression in the general populations was taken into account, the associated recommendations were drafted, taking into account the trade-off between the benefits and downsides of treatment as well as other important factors. These included economic considerations, the values of the GDG and society, and the GDG's awareness of practical issues (Eccles *et al.*, 1998). The confidence surrounding the evidence in the depression guideline also influenced the GDG's decision to extrapolate.

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

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

Informal consensus

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

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

- A description of what is known about the issues concerning the clinical question was written by one of the topic group members.
- Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question.

- Based on the feedback from the GDG, additional information was sought and added to the information collected. This may have included studies that did not directly address the clinical question but were thought to contain relevant data.
- If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was done.
- At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question were developed.
- Following this, on occasions and as deemed appropriate by the GDG, the report was then sent to appointed experts outside the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.
- Recommendations were then developed and could also be sent for further external peer review.
- After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.6 HEALTH ECONOMICS METHODS

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

- a systematic literature review of existing economic evidence
- economic modelling, where economic evidence was lacking or was considered inadequate to inform decisions; areas for further economic analysis were prioritised based on anticipated resource implications of the respective recommendations as well as on the quality and availability of respective clinical data.

Systematic search of the economic literature was undertaken on all areas that were updated since the previous guideline. Moreover, literature on health-related quality of life of people with depression was systematically searched to identify studies reporting appropriate utility weights that could be utilised in a cost-utility analysis.

In addition to the systematic review of economic literature, the following economic issues were identified by the GDG in collaboration with the health economist as key priorities for further economic analysis (either costing of interventions or full economic modelling) in the guideline update:

- a cost analysis of low-intensity psychological interventions
- cost-utility of pharmacological interventions
- cost-utility of pharmacological therapy versus combined psychological and pharmacological therapy.

These topics were selected after considering potential resource implications of the respective recommendations.

The rest of this section describes the methods adopted in the systematic literature review of economic studies undertaken for this guideline update. Methods employed

in *de novo* economic modelling carried out for this guideline update are described in the respective sections of the guideline.

3.6.1 Search strategy

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

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

The systematic search of the literature identified approximately 35,000 references (stage 1). Publications that were clearly not relevant were excluded (stage 2). The abstracts of all potentially relevant publications were then assessed against a set of selection criteria by the health economist (stage 3). Full texts of the studies potentially meeting the selection criteria (including those for which eligibility was not clear from the abstract) were obtained (stage 4). Studies that did not meet the inclusion criteria, were duplicates, were secondary publications to a previous study, or had been updated in more recent publications were subsequently excluded (stage 5). Finally, all papers eligible for inclusion were assessed for internal validity and critically appraised (stage 6). The quality assessment was based on the checklists used by the *British Medical Journal* to assist referees in appraising full and partial economic analyses (Drummond & Jefferson, 1996) (see Appendix 13).

3.6.2 Selection criteria

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

- Only papers published in English language were considered.
- Studies published from 1998 onwards were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.

- Only economic evaluations conducted in the UK were selected so as to reflect healthcare resource use and unit costs directly relevant to the UK context. This criterion was in line with selection criteria from the previous guideline. However, this criterion was not applied to studies reporting utility weights that could be potentially used in cost-utility analysis.
- Selection criteria based on types of clinical conditions and patients were identical to the clinical literature review.
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable. Poster presentations and abstracts were excluded from the review.
- Full economic evaluations that compared two or more relevant options and considered both costs and consequences (that is, cost–consequence analysis, cost-effectiveness analysis, cost–utility analysis or cost–benefit analysis) were included in the review.
- Studies were included if they used clinical effectiveness data from an RCT, a prospective cohort study, or a systematic review and meta-analysis of clinical studies. Studies were excluded if they had a mirror-image or other retrospective design, or if they utilised efficacy data that were based mainly on assumptions.

3.6.3 Data extraction

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

3.6.4 Presentation of economic evidence

The economic evidence identified by the health economist is summarised in the respective chapters of the guideline, following presentation of the clinical evidence. The references to included studies at stage 5 of the review, as well as the evidence tables with the characteristics and results of economic studies included in the review, are provided in Appendix 15. Methods and results of economic modelling are reported in the economic sections of the respective evidence chapters.

3.7 METHODS FOR REVIEWING EXPERIENCE OF CARE

3.7.1 Introduction

The chapter on experience of care (Chapter 4) presents three different types of evidence: personal accounts that were collected by the service user and carer members of the GDG; interviews from the Healthtalkonline website (www.healthtalkonline.org); and review of the qualitative literature.

3.7.2 Personal accounts

The authors of the personal accounts were contacted primarily through the service user and carer representatives on the GDG, and through various agencies with access to people with depression. In approaching these individuals, the GDG attempted to assemble a range of individual experience that reflected what the GDG considered to be important aspects of the care and treatment of people with depression. All individuals who were approached to write the accounts were asked to consider a number of questions (see Chapter 4) prepared by a service user and carer topic group[4] which oversaw this aspect of the guideline work. Each individual signed a consent form giving permission for their account to be reproduced in this guideline. All personal accounts were read by the members of the service user and carer topic group, and the review team; if necessary, the authors of the accounts were contacted again if parts of their account were unclear or ambiguous, or where it was thought that further information would be helpful. Any changes made for clarity were approved by the authors of the accounts. The full text of the accounts is reproduced in this guideline. The personal accounts were read again by the service user and carer topic group, and the review team, and themes were identified. These themes were developed and reviewed by the topic group and then incorporated in a combined summary with the evidence from the other two sources below.

3.7.3 Interviews from Healthtalkonline

Using the interviews of people with depression available from healthtalkonline.org, the review team analysed the available data and identified emergent themes. Each transcript was read and re-read, and sections of the text were collected under different headings using a qualitative software program (NVivo). Two reviewers independently coded the data and all themes were discussed to generate a list of the main themes. The evidence is presented in the form of these themes, with selected quotations from the interviews. The methods used to synthesise the qualitative data are in line with good practice (Braun & Clarke, 2006).

3.7.4 Review of the qualitative literature

A systematic search for published reviews of relevant qualitative studies of people with depression was undertaken using standard NCCMH procedures as described in the other evidence chapters. Reviews were sought of qualitative studies that used relevant first-hand experiences of people with depression and their families or carers. The GDG did not specify a particular outcome. Instead, the review was concerned with

[4]The topic group comprised three service user and carer members of the GDG and two members of the NCCMH review team.

any narrative data that highlighted the experience of care. The evidence is presented in the form of themes, which were again developed and reviewed by the topic group.

3.7.5 From evidence to recommendations

The themes emerging from the personal accounts, the qualitative analysis of the Healthtalkonline transcripts and the literature review were reviewed by the topic group. They are summarised in Chapter 4 and this summary provides the evidence for the recommendations that appear in that chapter.

3.8 STAKEHOLDER CONTRIBUTIONS

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

- people with depression/carer stakeholders: the national organisations for people with depression and carers that represent people whose care is described in this guideline
- professional stakeholders: the national organisations that represent healthcare professionals who are providing services to people with depression
- commercial stakeholders: the companies that manufacture medicines used in the treatment of depression
- Primary Care Trusts
- Department of Health and Welsh Assembly Government.

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

- commenting on the initial scope of the guideline and attending a briefing meeting held by NICE
- contributing possible clinical questions and lists of evidence to the GDG
- commenting on the draft of the guideline (see Appendices 4 and 5).

3.9 VALIDATION OF THE GUIDELINE

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. Following the consultation, all comments from stakeholders and others were responded to, and the guideline updated as appropriate. The GRP also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE. NICE then formally approved the guideline and issued its guidance to the NHS in England and Wales.

4 EXPERIENCE OF CARE

4.1 INTRODUCTION

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

4.2 PERSONAL ACCOUNTS – PEOPLE WITH DEPRESSION

4.2.1 Introduction

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

- When were you diagnosed with depression and how old were you?
- How did you feel about the diagnosis? How has your diagnosis affected you in terms of stigma and within your community?
- Do you think that any life experiences led to the onset of the condition? If so, please describe if you feel able to do so.
- When did you seek help from the NHS and whom did you contact? (Please describe this first contact.) What helped or did not help you gain access to services? If you did not personally seek help, please explain how you gained access to services.
- What possible treatments were discussed with you?
- Do you have any language support needs, including needing help with reading or speaking English? If so, did this have an impact on your receiving or understanding a diagnosis of depression or receiving treatment?
- What treatment(s) did you receive? Please describe both drug treatment and psychological therapy.
- Was the treatment(s) helpful? (Please describe what worked for you and what didn't work for you.)

- How would you describe your relationship with your practitioner(s)? (GP/community psychiatric nurse/psychiatrist, and so on.)
- Did you use any other approaches to help your depression in addition to those provided by NHS services, for example private treatment? If so please describe what was helpful and not helpful.
- Did you attend a support group and was this helpful? Did any people close to you help and support you?
- How has the nature of the condition changed over time?
- How do you feel now?
- If your condition has improved, do you use any strategies to help you to stay well? If so, please describe these strategies.
- In what ways has depression affected your everyday life (such as schooling, employment and making relationships) and the lives of those close to you?

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

4.2.2 Personal account A

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

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

For the next few years I used therapy to deal with my depression, low self-esteem and my underlying childhood issues, each year becoming more confident. During my childhood I had had to deal constantly with my mother's tempers, mood swings and cruelty, so I had to learn in therapy how to deal with my own emotions from scratch. Initially I had 3 years of gestalt therapy with a wonderful therapist who came recommended by a friend. I then had psychodynamic psychotherapy for 4 years (while I

also ran a self-help group for women). I found this psychotherapist from the UKCP list. During this period I also worked with teenagers and I found hard work to be a great help in having something to focus on and enhance my self-esteem.

In my 30s, however, I had a major depressive episode and I booked myself into hospital which I now see as a big mistake as it was not therapeutic by any means, but my understanding of what hospital offered was not known to me. I had been having some housing problems, family life was difficult and I had been working very long hours at work to solve all of these problems. I knew that I was at danger point. I was given antidepressants, an antipsychotic, a mood stabiliser and benzodiazepines. I was offered no therapeutic help and I found the system of nursing within the ward very damaging – they just observed the patients and didn't talk to us. So I was just left with my depressed thoughts for 11 weeks. I came out and went back to work.

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

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

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

I also had a wonderful GP in 2002 to 2003, who took it upon himself to (in his words) 'have a go at' at my consultant psychiatrist for half an hour on the phone about the cocktail of drugs I was taking. Being on a level of medication that was unnecessary and toxic, I had put on seven and a half stone since 2005 and I was threatened with high blood pressure and impaired glucose syndrome. My GP helped me get off this cocktail of unnecessary medication.

Not being drugged up freed me and enabled me to function at work, as I had previously done, and it 'woke' me up. The threatened 'relapse' has never happened. My self-esteem issues over my depression and weight had left me anxious though, and after an 18-month battle involving Mind and my psychiatrist, I got cognitive behavioural therapy (CBT) in 2004. This was even more wonderful in aiding my recovery and I had one session per week for a year working on my anxiety phobias. The psychologist was a wonderful professional who had faith in me and together we worked very hard overcoming the deep beliefs that I had held and which prevented me leading a full, well life.

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

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

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

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

4.2.3 Personal account B

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

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

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

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

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

Eventually I began a method of self-counselling: occasionally speaking aloud to myself in a deliberate effort to calm myself down since I knew that depression can be a result of over-stimulation.

Fortunately, in the summer of 2006, I was able to change my GP. The new GP provided much more help but unfortunately the initial medication (citalopram), which I took for 4 months, made no difference to me at all.

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

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

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

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

Prior to my mental health team assessment interview in May 2007 (the GP registrar I saw in February had written again to the team to ask for an early appointment) I was in a very foggy state and was particularly vulnerable. However, I think that I expressed the issues quite clearly in the limited time. The interviewer described himself as a nurse, said he was trying to clarify why I was there and at one point told me I looked 'alright', which was frustratingly puzzling to me and based on no knowledge of me whatsoever. I quickly lost confidence in my interviewer. He said, 'Yes, I've had bereavements too' and 'I don't know why you have been referred', which was very unhelpful. He also told me I had to 'negotiate' if the counselling is not right. How can someone who is seriously depressed negotiate?

I was also given the Aaron Beck tick box-type diagnostic tool which I found confusing. (For example 'loss of appetite' is difficult to answer; a lot of people who are depressed have 'abnormal appetite'.) I find these tools very simplistic.

I left this appointment and began crying immediately – again I could not drive home for an hour. I took extra medication to try and cope. I called the mental health

team and was told that I was bound to get upset 'as I was talking about upsetting things'. Again, the problem is presented as being because of the vulnerability of the patient rather than the competence of the interviewer.

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

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

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

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

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

Up until 6 or 7 months ago I was feeling as if in a parallel universe, and at one point as if I was living under water. I could not 'wake up' from dreams, and very unusually for me I could not get up until 10 am on some days. I felt profound grief.

I now have far less faith in getting help so I do not know what I would do if things become worse. I was helped by seeing the consultant psychiatrist and I felt much better having been taken seriously. One problem was being not being able to work.

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

4.2.4 Personal account C

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

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

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

In 1992 I attended a college for the blind for training in the hope that I would be able to get a job. Unfortunately this didn't happen because I was so unprepared, was having emotional breakdowns, and had too much to cope with at college. I was sent to a local hospital by a doctor from the college and was diagnosed with problematic depression and was given more practical help than previously: I had some psychotherapy, relaxation

classes and exercise for my neck. At the end of the college year I was advised to take a break of a few months. This was a very hard time and a struggle for me – both the college and the job centre rejected me by saying they couldn't help me until I was stable.

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

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

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

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

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

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

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

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

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

4.2.5 Personal account D

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

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

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

I was first prescribed diazepam, which made me feel good because I was out of it. I was prescribed one tablet a day but I took three or four. I couldn't work but at least it was a lift and that is what I felt I needed. I was on diazepam for about 6 to 9 months and then I came off it. I tried to look for a job but my feelings of inadequacy and paranoia returned: I felt as if people were looking at me and talking about me. I found it difficult to go outside and became agoraphobic.

Nothing else was offered to treat me so I treated myself by using cannabis, speed and barbiturates. Eventually I found a job I liked and when I was 18 years old I started having serious relationships. I was still living at home then and stayed to protect my mother as my father was still beating her, and I didn't want to take anyone home as I was ashamed of my father.

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

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

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

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

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

Shortly after this I was diagnosed with asthma, which was considered by my doctors to be my major illness rather than depression. The asthma hit me hard as I was my wife's carer and I looked after the children. I also began to have panic attacks. Although I was convincing my wife that I was coping, this was just a mask. I felt as

if I had become invisible, that my purpose was to make someone else become well. I did not see that there was something wrong with me. Then one day I was pushing a trolley around the supermarket and I thought 'I don't want to die in a supermarket; I don't want to die in between the bleach and the biscuits.' This happened several times around this period. I didn't go to doctors as I thought they would think I was nuts.

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

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

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

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

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

4.2.6 Personal account E

I was 27 years old when I was first diagnosed with depression, 14 years ago. I think I started to get depressed 6 years prior to diagnosis, I just didn't know it at the time.

At first, I was relieved at the diagnosis. I had gone to the doctors knowing something was wrong, but not knowing what it was. I was offered counselling and/or medication. I knew that I had to have medication, as it would make me feel better more quickly. I had already withdrawn from my friends and community (due to the depression) so in terms of stigma, there was none, though I didn't tell family, because they wouldn't have understood.

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

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

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

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

As well as the treatments listed above, while I was having counselling I was told that I should attend a women's group, run by my counsellor through the NHS. I attended and it helped much more than I realised at the time in that I formed friendships that were very supportive. However, in terms of therapeutic input it did nothing – people would talk about their week and how awful life was, but I couldn't do that. How could I tell people that I had spent the week trying not to kill myself, when that was all I wanted to do? It was not that I wanted to die, but I could see no other way of stopping the pain. Depression filled every second of every minute of every day, and it was unbearable. I was fortunate in that I was able to sleep a lot (up to 15 hours a day), though time still went slowly. Reading books about depression and self-help gave me an understanding of what was happening to me.

On one occasion I went to a voluntary agency support group, but I couldn't accept at that time that depression would be part of my life forever: I found it difficult to listen to others about how they were managing their lives living with depression. I thought I was going to get better and it would never come back again – how naïve was I?

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

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

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

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

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

I have had to build my life around periods of depression, for which I am resentful. I often feel that my life is hanging by a thread – that at any moment, my life, that I have worked so hard to build up, could be taken away from me. It is on this basis that I choose not to engage in a long-term relationship. I am currently seeing someone, but because of his commitments, I do not see him often. This suits me as it means I am under no obligations or pressure from him.

I feel frustrated that there are no services available to me now. On the surface, I function very well; no one would ever believe that I have depression as I am a good actress. But when it is severe, it would be helpful to be able to access services

immediately from a team that knows me and can support me without me having to go through a series of assessments and then being told 'well you can go on the waiting list for this service, but you can only have this service for a particular length of time'. I also feel that long-term psychodynamic therapy should be available, on the NHS, which can get to the root of the issues that cause depression. I now know that I will have depression until I can resolve my childhood issues.

4.2.7 Personal account F

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

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

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

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

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

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

4.2.8 Personal account G

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

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

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

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

As my condition improved I started to research my illness online and also made online contact with others from across the world suffering from mental illness. I have found the internet very useful for getting information about my condition and when I was very ill and needed to talk, I could usually find someone somewhere in the world

to talk to 24 hours a day. The other advantage was that when I didn't feel like talking, I didn't have to. Over the years I have formed an online network of fellow sufferers and we keep each other up to date on anything of interest happening in the various countries regarding mental illness and its treatment.

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

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

4.3 PERSONAL ACCOUNTS – CARERS

4.3.1 Introduction

The methods used for obtaining the carers' accounts was the same as outlined in Section 4.2.1, but for carers of people with depression, the questions included:

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

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

4.3.2 Personal account H

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

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

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

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

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

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

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

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

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

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

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

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

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

4.3.3 Personal account I

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

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

Mostly she's well but now and again she gets depression. I know the signs. Then she goes quiet and stops going out and seeing her friends and I try and cheer her up and make things better for her. I wish she was like other Mums sometimes, and, well, all the time. But I wouldn't be without her or want to leave her on her own – she's my Mum!

I try and be positive and jokey, behave myself and be there for her, and make sure she sees her therapist even when she doesn't want to go out and sometimes get her friends around for a surprise to make time pass for her. I hope she gets better soon. I go to my room when I feel cross and sometimes talk to my friends. I go out and do usual things too so that she doesn't worry about me. I do well in school.

My Mum takes tablets and sees her therapist but I think seeing people really helps her. When her friends come round and take her mind off it for a while, she laughs.

Don't forget your friends when they are depressed, I say. And chocolate sometimes helps too!

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

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

4.4 QUALITATIVE ANALYSIS

4.4.1 Introduction

The following section consists of a qualitative analysis of personal accounts of people with depression using Healthtalkonline (www.healthtalkonline.org). Healthtalkonline provides interviews with people with both physical illnesses and mental health problems. The review team undertook their own content analysis of the interviews to explore themes that could be used to inform recommendations for the provision of care for people with depression.

The same transcripts were also reviewed by Ridge and Ziebland (2006), which is included in the review of the qualitative literature below. The review team decided to undertake their own analysis to cover a wider range of themes than those focused upon by Ridge and Ziebland.

4.4.2 Methods

Using the interviews available from Healthtalkonline, the review team analysed the experience of 38 patients from across the UK. The methods adopted by Healthtalkonline to collect interviews were two fold. First, the participants were typically asked to describe everything that had happened to them since they first suspected a problem. The researchers tried not to interrupt the interviewees, to obtain a relatively unstructured, narrative dataset. Second, a semi-structured interview was conducted in which the researcher asked about particular issues that were not mentioned in the unstructured narrative but were of interest to the research team.

From the interviews, the review team for this guideline identified emergent themes relevant to the experience of people with depression that could inform the guideline. Each transcript was read and re-read, and sections of the text were collected under different headings using a qualitative software program (NVivo). Two reviewers independently coded the data and all themes were discussed to generate a list of the main themes. The anticipated headings included: 'the experience of depression,

'psychosocial interventions', 'pharmacological interventions' and 'healthcare professionals'. The headings that emerged from the data were: 'coping mechanisms', 'accessing help and getting a diagnosis of depression', 'stigma and telling people about depression' and 'electroconvulsive therapy'.

There are some limitations to the qualitative analysis of people's experience of depression and its management undertaken for this guideline. As the review team relied on transcripts collected by other researchers with their own aims and purposes, information on issues that are particularly pertinent for people with depression that could be used to inform recommendations may not have been collected. Moreover, the review team did not have access to the full interview transcripts and therefore had a selective snapshot of people's experience. However, using Healthtalkonline did highlight issues regarding depression that can be reflected upon for the purpose of this guideline.

4.4.3 Experience of depression

In recounting their experience of depression, some people described life events which they felt had caused the disorder. Some of these events were childhood experiences including both problems in the family and at school. Some people commented that stressful situations at work contributed to the onset of their depression. Many people described the death of a family member or friend as a trigger of their depression. One service user summed up various life events that she believed were associated with her current state of depression:

> *All these experiences from earlier on in life, my Mum dying, being bullied … being neglected and isolated and being treated different academically. I think they all combined with my lack of social skills, which I'd not had a chance to develop until that point when I got to university … within a few months … I was just feeling very low and very lonely, needy … I think, probably about 4 or 5 months after starting my first year, I did become very depressed.*

Some people used metaphor and allusion to illuminate their experience of having depression. For example, one person described having a 'racing' mind that was 'zooming into miserable places'. Others used analogies such as depression being like a 'brick wall' or 'being inside a balloon' to describe how depression can act as a barrier from experiencing the world:

> *I couldn't feel anything. I couldn't feel anything for [husband's name]. I couldn't feel anything for the children. It [depression] was like being inside a very, very thick balloon and no matter how hard I pushed out, the momentum of the skin of the balloon would just push me back in.*

Other people listed the symptoms they were experiencing: lack of pleasurable experiences, body aches, tearfulness and sleep problems; they also described feelings of loneliness, isolation and feeling withdrawn.

Experience of care

A prevalent theme in the interviews was the presence of negative thoughts. These thoughts were described by people with depression as irrational and often caused them to jump to conclusions. One person explains how she experienced negative thoughts:

> *I call, what I've got in my head my chatter box. Basically it is my mind, seeing things a particular way. And with depression you see it really negatively. You see everything negatively, you'll always pull out the negative over the positive if you ever see a positive, you'll . . . if for one positive you'll give ten negatives.*

People also described feelings of suicidal ideation and some disclosed their experiences of attempting suicide. Some of the suicidal thoughts relating to suicide were: the 'world would be a better place without me', 'life wasn't worth going on', and 'life was completely out of my control'. One person described a suicide attempt:

> *I can remember being almost unconscious, and with a doctor and nurses around the bed. And the doctor said to one of the nurses, 'Go and get so and so . . . we've got about 10 minutes or he'll be gone'. And I could hear him, and I just thought, 'I wish you'd leave me alone. I'm warm and comfortable. I don't want this.'*

However many people also identified positive aspects of having experienced depression, for example, having become more confident, positive, understanding of others, able to support others and able to do 'something positive and . . . creative'. They also said that they had become more aware of themselves and their feelings and more able to cope with stressful events.

Another common theme was that people felt that they appreciated life in a different way after having been depressed. For example, one person said:

> *I can listen to music and appreciate it in a different way . . . it can move me now. Something on the TV can move me now, and I have, I feel things and things affect me.*

Many people also felt that experiencing depression had made them re-evaluate their lifestyle and that this had led them to make some important positive life changes. One person described having had a breakdown as a 'breakthrough'. Another person described the positive effects of having had depression:

> *I think it's [depression has] sort of made me question what I thought was good about my life because I was in a very busy and hard-working career, and whilst the depression wasn't the main, or the only reason, that I left, there was a re-organisation at my work, I do think, oh, thank God I left there when I was 36 rather than 56. You know, I understand that I need sort of time for me now, and*

that I'm a person in my own right, and I'm important and I have, you know, the right to have some quality time for me.

4.4.4 Accessing help and getting a diagnosis of depression

Some people detailed how a particular event or problem prompted them to access help, such as sleep deprivation and lack of concentration:

I was putting my eldest daughter to bed and trying to read her a child's story, and I actually found . . . I no longer had the concentration to read . . . I couldn't follow the sentences to actually read it out loud. And that was a point where it was clear that . . . I had to seek help. And so I made an appointment with the doctor the next day.

Once people with depression accessed help, they described their experience of receiving a diagnosis of depression. Some described how there is not enough recognition of depression and how often when they presented with sleep problems or loss of interest in sexual activities to their GP, these symptoms were not initially recognised as symptoms of depression:

I went to the doctor and I said . . . 'I sleep but I always feel tired . . . I've tried . . . everything.' And he just said, 'Try getting more sleep.' [laughing] I was like, yes, I could have thought of that, I've tried that, it didn't work . . . my feeling is that really he should have asked a few questions and could possibly have diagnosed that I was depressed.

4.4.5 Stigma and telling people about depression

Some people described the stigma of having a diagnosis of depression. The majority felt that stigma still existed while a minority thought it was less prevalent than it used to be. There was also stigma around receiving treatment for depression for both psychological and pharmacological interventions:

It took a hell of a lot for me to go to therapy. You know A: nutters go to therapy, B: therapy makes you a nutter. These were the kind of things that I grew up with. And it doesn't help. You know, so hostile kind of lower middle class sort of feeling about that sort of thing.

Conversely one person said it was quite 'fashionable' to be taking medication:

Prozac is quite a fashionable antidepressant. And it was OK to say you were on Prozac, it's like a happy pill isn't it. I'm OK I'm taking Prozac and then of course I knew quite a few people who were taking it as well, so it was like ok like join the club.

Experience of care

Due to the stigma surrounding depression, some people found it difficult to talk to other people about their condition:

> *I can't talk to my family about it. They don't know about the therapy. I think it's the stigma thing . . . my perception is that I would be seen as weak and not coping, so it's easier for me not to admit to that weakness.*

However, some people encouraged others to speak openly about their condition:

> *You should tell someone now, it doesn't have to be the doctor or a therapist, it can be a friend you know. The older I've got, the more I've found that it's acceptable to say to people, 'I'm depressed at the moment'.*

Some described their experiences of telling friends and neighbours and stating that it helped them; one person made a joke to ease the situation:

> *I was just really outright, and I just said, 'Ok, I was in a psychiatric hospital for a month and then outpatients for a further month and now I'm at work part-time to try and get back into the swing of things slowly.' And he just looked at me . . . I said, 'It's ok though,' I said, 'I'm not loopy' and he just started laughing, because I'd just turned it into a joke.*

4.4.6 Psychosocial interventions

People with depression discussed their positive attitudes towards psychological treatments:

> *Sometimes you do need to talk to somebody who you don't know, who understands, instead of chatting to the brick wall. And instead of it going round in your head and trying to sort it out. Or you need somebody to talk to you and push the right buttons to help sort yourself out.*

People with depression expressed the need for psychosocial interventions when the cause of depression was deemed to be psychological rather than a 'chemical imbalance'. In addition they explained how they thought psychosocial interventions, rather than medication, were needed to resolve the maladaptive behaviour and distorted thoughts that contributed to their depression:

> *These tablets helped me . . . but after a while, I realised it sorted out my brain chemistry, but you have learnt all these negative ways of looking at things, and doing things . . . and that is why I believe I need long term therapy as well. I felt better [with medication], but I still didn't have ways of dealing with things.*

The benefit of psychosocial interventions to tackle negative thoughts was a prevalent theme. People described how they learnt to change their thoughts to be more constructive and positive:

> *There are things that keep me in a place of being depressed, and . . . that's what the therapy really helps . . . me understand how I perpetuate the depression . . . I think for me it's about blaming myself . . . thinking that I'm a bad person, and I can expend huge amounts of energy on the mental processes that go into making me responsible for everything that goes wrong in the world.*

In the following sections, experiences of different psychosocial interventions are described by people with depression. The psychosocial interventions that were briefly touched upon were counselling, cognitive therapy, self-help material, relaxation therapy and support groups.

Counselling

Overall people who discussed having counselling were positive about their experiences:

> *The main sort of release point was the counselling, which to me was crucial. If I hadn't have had the counselling, I'd probably still be severely ill and wouldn't be, you know, happily now saying that at last I'm enjoying life to a greater extent.*

Some of the outcomes that people achieved from counselling were: an increase in self-esteem, being able to return to work, dealing with bereavement issues, learning more about oneself and helping to deal with thoughts and feelings. Counselling was a positive experience for many because it provided a safe environment in which to talk about their concerns:

> *It was a big relief to have someone who I could tell anything I wanted, anything that was bothering me, and not worry about what they might think about it or how it might affect our relationship. And you know, it also helped to feel that I was doing something about my problems as well.*

Cognitive therapy

People who had cognitive therapy were positive about it, describing it as enabling because it was practical, focused on the real world and allowed them to begin to help themselves:

> *I could change my thinking and I could thereby change my feeling . . . A particular example was he [therapist] said, when you go lie down to go to sleep, he said, 'You tend to look back on your day and think of all the failures' . . . 'why don't you just think of everything that's been successful?' So . . . I started doing that . . . So just things like that, a few things like that with cognitive therapy. You know I think they helped quite a bit.*

Experience of care

Self-help

Two people described using self-help books to cope with their depression. One read David Burns' *Feeling Good*, which is based on cognitive and behavioural principles:

> *I sat and read this book, and you know it's quite a hefty one. But it's a really good one . . . It's very difficult to sort of . . . stop yourself, and realise that just because you have an opinion or you express yourself a certain way, it's not right or wrong, to you know, to act that way . . . it's really difficult, 'cos it's everything in the book ties up with other things and you know cognitive therapy for me, is my chatter box and arguing with it.*

Another read Dorothy Rowe's *Depression: The Way out of Your Prison:*

> *Some of it is relevant, some of it is not at all relevant . . . It's really good because it's all about . . . looking after you and some of the things just make me laugh. You know because it's so like . . . 'That's me. I'm in there. That's what I do'.*

Relaxation therapy

Two service users described their experience of relaxation therapy:

> *Relaxation therapy . . . when you're depressed is mighty hard to get started. Once you've started and got the grasp of it, then it's quite good, but to actually get relaxed when you're really depressed is damn nigh impossible you know.*

Support groups

People who had attended support groups were positive about their experiences. They described these groups as therapeutic because they were able to meet people with similar problems and share their experiences in an environment where there was no stigma. In addition, people with depression felt relieved to know they were not alone:

> *It was a great source of comfort . . . And to find that in fact you weren't the only person to feel like that was actually a great relief. It was also a great relief to find . . . people who were non-judgemental.*

> *A self-help group isn't group therapy but it is very therapeutic . . . people meeting with a shared interest . . . There are people there who, they won't say, 'Pull yourself together, pull your socks up, what have you got to be depressed about?' There is none of that. The mutual support is just unbelievable.*

One described a suicide support group that provided some source of comfort but also had harmful effects:

> *It's a discussion group of people talking . . . of essentially extremely depressed people talking about suicide. And talking about suicidal feelings and suicidal*

methods and yeah, from time to time people die on it. But in a weird perverse way it's a source of strength and a source of comfort.

4.4.7 Pharmacological interventions

People with depression had mixed views regarding pharmacological interventions. Some people were concerned about taking tablets; they did not think pills solved the problem or they had a cynical view of drug companies. Others who tried medication who did not have positive experiences said they felt that it 'robbed' them of feelings. One person described why a pharmacological intervention was not the right treatment for him:

I've been prescribed antidepressants in the past but I've always felt reluctant and apprehensive about taking it, largely because a) I feel that the effects are probably short-term, they're not going to actually resolve the depression, b) because they do have side-effects and, c) I didn't feel comfortable, myself, with taking some tablets.

However, the majority had positive experiences regarding medication. For those who benefited from a pharmacological intervention, they described taking medication as a turning point in their lives. People said that they felt more in control and had greater awareness of the world around them (this was in contrast to other people's experience of medication):

It was exactly 7 weeks to the day that I took . . . the first tablet . . . I knew that morning when I woke up that I feel differently, things are different. And that was the turning point. It was this lifting again, this lifting of overall and just . . . contentedness

It [medication] gave me a feeling that I've got some control now of this thing [depression]. And I was having some experiences like increased sensitivity to things like noise and colours and feelings.

One person advised that if someone was not benefiting from their current medication, that they should persevere until they found a drug that works for them:

It isn't a one size fits all . . . I would say to folk if you feel like you're not getting any better . . . on the particular medication . . . go back to your doctor and ask your doctor to change, to consider changing your medication.

Many people with depression reported side effects from taking medication, notably dry mouth, hair loss, increased sweating, weight gain and problems ejaculating. A minority also reported experiencing suicidal thoughts as a consequence of their medication:

For many years I hadn't had any suicide thoughts at all, and I had certainly never thought of cutting myself, but while I was on Seroxat, I did start to get sudden images in my head of you know, cutting long gashes in myself.

Despite this, some people with depression said that the benefits of medication outweighed the potential side effects:

> *You're given a sheet which tells you what to expect, and I looked it up on the internet as well. I'm very against taking medicine for a long time, but after my experience with the depression I decided I would be prepared to take it . . . for the rest of my life if I don't get it again, the depression again, if it stops that.*

When some people stopped their medication, they described experiencing discontinuation symptoms, the most prevalent symptom of which was nausea:

> *Being stupidly pig-headed, just stopped it [Efexor] . . . I was just completely off my head with depression . . . the symptoms were so acute it was very frightening. You feel sick, nausea, the nausea was awful. And just panic, really.*

4.4.8 Electroconvulsive therapy

Four service users recounted their experience of ECT; the majority had negative experiences because of the frightening nature of the intervention and loss of memory post-treatment:

> *They'd get you to lie down on the bed, and give you an anaesthetic in your hand, which would basically make you go unconscious. But just that 2 minutes when you might have gone into the room and been waiting, I was just so frightened. And then they give you ECT . . . that is quite a confusing experience. I did find that it affected my memory a fair bit.*

> *I have massive blanks, short-term and long-term . . . I get angry with the professionals that this wasn't explained that this could happen . . . I've tried to talk about it with the doctors at the hospital and they say, 'Give me an example' and I give them an example and they say, 'Oh that's normal, that's just normal, that's not the ECT . . . that's normal'.*

Only one person reported a positive experience regarding ECT:

> *It all sounds very scary, but you really don't . . . you don't see anything because you are anaesthetised, so you are asleep. And you wake up, and I . . . you have a slight headache, but apart from that, I had no side-effects . . . my mood improved instantly, and I was talking and laughing.*

4.4.9 Healthcare professionals

This section covers people's experience of healthcare professionals, including GPs, nurses and psychiatrists.

GPs

As described in Section 4.4.4, people were critical of their GPs because they felt that their depression went undetected. However some people had positive experiences of getting a diagnosis of depression and of how their depression was initially managed:

> *I was very low physically and clearly very low mentally, and the GP … and I'll be forever thankful for him, actually said, 'I don't think I am helping with the right kind of medication for the right reasons, and if you agree I'd like to refer you on to somebody'. And it was like an immense relief … somebody's actually going to treat me as somebody who has a problem here.*

People who had positive experiences of their GPs described them as being sympathetic, warm, tender, kind, helpful and supportive. These people felt that they were listened to and responded to:

> *She's [the GP is] good because she is human. She listens and she responds to me as a human being, not as a professional. She gives me time, as much time as I want sometimes. She cares and she's shown me she cares because she has rung me up before at home and said, 'How are you? Will you come and see me tomorrow?' because she knows I'm not going to ring and make an appointment because I … I mean I'm in isolating mode and things are going wrong.*

Those with negative experiences described how their GP was lacking in the above characteristics:

> *You just didn't get listened to, you didn't get, you know, it was as though what they [GPs] were saying was, 'Well, it's just in your head, you know you don't really understand, I know better.' And I know that they're really busy and I know that they don't have a lot of time, but I really felt that I got no help at all most of the time.*

Nurses

People said that they did not feel that nurses understood the sensitive nature of their depression, that nurses in the NHS were too busy to talk to their patients and that their attitudes may be because of inadequate training:

> *There's an awful lot there who … you felt as though it was people saying to you, 'Oh, for goodness sake pull yourself out of it', and, 'Get yourself together', which you don't want, it's the last thing at the end of the day. I just don't think that there is enough, in regards to, against private and NHS, there is just not enough funding to be able to … I don't know, train the nurses in a certain way.*

Psychiatrists

People had mixed experience of psychiatrists. Some did not like how psychiatrists tried to illicit information about their childhood experiences, describing the method

as a 'text book' approach that instantly created a barrier. Others did not like to discuss feelings in general:

> *I felt my psychiatrist was a very .... oh ... wet individual. Again, I think because I'd been quite a numerate, factual, organised person, to have someone to talking about feelings and what about this and what about that? And it was ... nothing could ever be pin-pointed or ... I just found it annoying.*

People also had mixed opinions about how their psychiatrist dealt with their medication. The majority had positive experiences: one person described how their psychiatrist was able to change their medication to one with fewer side effects; another described how the psychiatrist prescribed a proper therapeutic dose of anti-depressants. However, one person felt that she was not listened to when she explained to her psychiatrist that her current medication was not working:

> *He'd [psychiatrist] say something like, 'Oh well, continue with the paroxetine.' And if I said, 'Look, this isn't helping me. I've been on this for eight months, it's not making me better.' 'It takes time, you have to have patience.' You know, 'You are better really' I was told by one doctor. 'You're not depressed, you're just a very sad lady.'*

4.4.10 Services

The experiences of mental health services were described by people with depression. Issues regarding referral, waiting lists and getting into NHS services were raised. Some people said that that they waited too long to be referred to a psychiatrist or receive psychotherapy. One person said that while she was on a waiting list she was unable to cope with her depression:

> *I was referred to the psychiatric hospital for assessment. Although I think it probably took about two months I believe between the initial sort of GP's referring letter and getting an appointment. Which again in retrospect was, was way, way too long, way too long. I was really, really ill and barely coping.*

Another person described how she felt that she had to be violent in her GP's surgery in order to be referred to NHS services:

> *It's very difficult to get a hospital bed for quite severe mental illness. You've got to be suicidal ... I was feeling suicidal. I was also quite violent at times. I mean in my own doctor's surgery, I swept all the things off his desk you know ... there was a part of me, kind of watching what I was doing ... saying, 'Right, well make it really dramatic.' I wasn't pretending exactly, but I knew I had to make a song and dance to get heard.*

Once in mental health services, people described a mixture of positive and negative experiences. One person said that a psychiatric intensive care unit was 'a place of safety'. Others described a mental health service as a place where they had no responsibilities, where they could 'hand yourself over' to the care of the service. Accompanying this, however, was the feeling of being institutionalised:

> *In eight weeks, I very quickly became institutionalised myself. I was scared to come out because I was in this enclosed world where I knew what was going to happen. There were routines, mealtimes, getting up times, medication times, OT [occupational therapy] times. There were routines and I had no responsibilities . . . I was in a place where I didn't have to think about anything, and nobody could touch me.*

People also had negative experiences of mental health services provided by the NHS, including not feeling cared for. Those who had had private treatment had more favourable accounts, and compared and contrasted the two experiences:

> *The private hospital was, there was a lot of love, a lot of care in there, sincere care. And I won't knock the NHS because they are obviously very limited to money in a way, but there was no care . . . In the private hospital you felt like you were being treated as a human being . . . You felt that yes, you could get well here because they cared.*

4.4.11 Families and carers

People with depression described the impact that their condition had on families and carers. Some stated that it was harder for the family and carers than it was for the person who had depression. Others described the impact that it had on the partner, often resulting in a change in roles. For example, people described how their partners had to take a more active role in daily chores:

> *I found it difficult to relate on the day-to-day things, which is where she [his wife] was so good. She took over those things.*

Some felt that their depression had an impact on their children:

> *My sons were very good, but they missed a lot because of how I was. And they would have to make allowances, which isn't really what you should have to do when you're growing up.*

Some people said that without their family and carers they would not have been able to cope with their depression:

> *My partner has played a key role in my recovery – he was very supportive during my depression periods – I do not know how I would have coped without him . . . Many times he has forced me to do things and helped me out of the house*

in times when I did not feel like doing anything. I believe having a loving and caring partner has helped me get over the most horrible periods of my depression.

4.4.12 Coping strategies

People with depression described coping strategies that they used to overcome their condition. These strategies were those other than pharmacological and psychological interventions employed by people to manage their depression.

Distraction was a common coping strategy. One of the ways in which people distracted themselves from their mental health problem was by having or acquiring a hobby, which ranged from physical activities such as swimming and going to the gym, to those of a more creative nature such as poetry:

Having hobbies, and that … that gets depressed people through because the thing that you can't think of, you know, two things at once.

I wanted to do something physical … So I started to garden, I've never been in the garden before. And it was crap at first, but gradually it was alright, you know you start to think, 'Yeah, this is kind of distracting me a bit.'

For other people, voluntary work was a coping strategy because the process of helping others allowed them to help themselves. In addition, people described how voluntary work helped them to increase their confidence and build up their self-esteem:

At the beginning I used to get anxiety attacks and some days I could just phone up and say, 'Look I'm not feeling well.' If you are doing it voluntarily … I felt I wasn't letting them down … the same pressure is not there. So … voluntary work I would definitely advocate because it gives you a sense of … it helps build your confidence, self-esteem.

Another coping strategy was completing small, manageable tasks:

When I'm depressed … I wasn't able to do anything about it, really. I just felt overwhelmed by it … And with my depression, when I was feeling very low, I would, I did decide to just concentrate on small things; going for a walk, baking some bread, you know pottering around in the garden. Just trying to get through day to day, I think, was how I came out of the suicide attempt.

4.5 REVIEW OF THE QUALITATIVE LITERATURE

4.5.1 Introduction

A systematic search for published reviews of relevant qualitative studies of people with depression was undertaken. The aim of the review was to explore the experience

Table 5: Databases searched and inclusion/exclusion criteria for clinical evidence

Electronic databases	CINAHL, EMBASE, MEDLINE, PsycINFO, HMIC, PsycEXTRA, PsycBOOKS
Date searched	Database inception to February 2009
Study design	Systematic reviews of qualitative studies, surveys, observational studies
Population	People with depression and families/carers
Outcomes	None specified

of care for people with depression and their families and carers in terms of the broad topics of receiving the diagnosis, accessing services and having treatment.

4.5.2 Databases searched and inclusion/exclusion criteria

Reviews were sought of qualitative studies that used relevant first-hand experiences of people with depression and families/carers. The GDG did not specify a particular outcome. Instead, the review was concerned with any narrative data that highlighted the experience of care. For more information about the databases searched see Table 5. Details of the search strings used are in Appendix 8.

4.5.3 Studies considered

The search found one systematic review that explored the experience of care for people with depression that met the inclusion/exclusion criteria (Khan *et al.*, 2007). The review team then looked at primary qualitative studies identified by the search and a further two primary studies (Ridge & Ziebland, 2006; Saver *et al.*, 2007) were included in the review that were not already reviewed by Khan and colleagues (2007). A further seven studies were considered for the review but they did not meet the inclusion criteria (Cooper-Patrick *et al.*, 1997; Rogers *et al.*, 2001; Chew-Graham *et al.*, 2002; Van Schaik *et al.*, 2004; MaGPIe, 2005b; Elgie, 2006; Johnston *et al.*, 2007); the most common reasons for exclusion were the studies did not report qualitative data or the population did not meet criteria for depression.

4.5.4 Themes emerging from the studies

Experiencing depression

Khan and colleagues (2007), in their meta-synthesis of qualitative research in guided self-help in primary care mental health services, found that family conflict, problems at work, chronic physical health problems, childhood events, financial

hardship and racism were the most frequent reasons given for causes for depression. People taking part in the studies spoke about their depression in terms of the effect on functioning and ability to cope rather than feelings or symptoms. The most common means of expressing their feelings was through metaphor: being 'on edge', 'boxed in', 'a volcano bursting', 'broken in half', 'prisoner in my own home', and so on.

Accessing help and stigma

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

Saver and colleagues (2007) described four barriers to accessing help by people with depression. These were characterised as: (1) a lack of motivation because of their depression; (2) stigma associated with depression and/or denial of their diagnosis; (3) healthcare professionals seeming unresponsive; and (4) a mismatch between how information is offered and how people with depression prefer to seek information, for example:

> *I would never sit down and read something about medicine. It has never interested me. I learned more from watching that commercial on television.*

Getting a diagnosis of depression

For people with depression, Saver and colleagues (2007) found that the majority of people received their initial diagnosis from a mental healthcare professional and a minority reported receiving their diagnosis from a GP. In addition, people said that their GP missed opportunities to diagnose their depression. Some people described their own inability or unwillingness to raise the issue of depression with their GP, while others stated that their GP focused solely on their somatic complaints, seemed uninterested in mental health issues or were purely dismissive of depression when it was suggested.

Experience of treatment

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

of guilt, of letting themselves and others down, and concerns about long-term changes to their personality were also expressed.

Saver and colleagues (2007) found that less than half of the people with depression reported receiving information about psychological interventions. One participant commented that the only 'option' was a pharmacological treatment:

> *They just handed me a drug and said go on it right now . . . I felt rushed along, given a prescription, told this will fix it.*

None remembered receiving information about the different treatment options such as CBT, problem-solving therapy or IPT. Only a minority reported that they had some choice in their treatment options.

Ridge and Ziebland (2006) in their analysis of interview transcripts collected by Health talkonline found that people with deep-seated and complex problems needed longer-term psychological therapy.

Self-help and other coping strategies

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

Recovery

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

4.6 FROM EVIDENCE TO RECOMMENDATIONS

This section is a combined summary of themes from the personal accounts, the qualitative analysis and the literature review. It should be noted that most of the

personal accounts received were from people who either have or have had severe and/or chronic depression. Therefore, it is acknowledged that the themes that run through the personal accounts may not be applicable to people who have other forms of depression. Despite these limitations, a number of themes were identified that were present in all three sources of evidence.

4.6.1 Understanding depression

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

4.6.2 Accessing help and getting a diagnosis of depression

Accessing help was also a prevalent theme in the personal accounts, the qualitative analysis and the literature, whether it was during the initial stages of being diagnosed or after years of having treatment. Two people in the personal accounts (B and E) found it difficult to access support when needed, despite having had depression for some years. It was felt that an emergency number to call would be a lifeline for people who live alone and have no carer support. Such means of support would be particularly helpful for people with long-term, severe depression.

The literature also revealed that accessing help may be a problem for some people first experiencing symptoms because of stigma associated with having a mental health problem (see Section 4.6.3), which may leave them unmotivated to raise the issue of depression with their GP.

4.6.3 Stigma

Stigma was frequently discussed in the personal accounts, the qualitative analysis and in the literature. This was experienced both externally and internally. External stigma was felt from employers and colleagues; but many also felt internal stigma and kept their depression concealed from friends, family and work associates. Feelings of

shame were expressed and also an anxiety that asking for help would lead to being offered interventions that they did not want, such as medication (the person in account D said that the idea of taking tablets accentuated the feeling of being mentally unwell).

4.6.4 Recognising depression

Recognition of depression and the severity of symptoms was also a prominent theme in the three forms of evidence. In the literature and qualitative analysis, people spoke about how depression is often not recognised and that physical problems may mask the depressive symptoms or may not be seen as part of the depressive symptomatology. In the personal accounts, two people (B and G) commented that they felt that the severity of their depression was not properly recognised within primary care. One person (B) felt that her diagnosis should have been made by a qualified and experienced professional.

4.6.5 Relationships with healthcare professionals

The relationship with the GP was a prevalent theme in the personal accounts, the qualitative analysis and the literature. In the personal accounts, most found their GPs helpful and understanding. The main area of criticism concerned the quality of contact with the GP (see Khan *et al.*, 2007) – a short appointment when a person is distressed is not long enough and people with depression are unlikely to ask for a longer appointment. In the qualitative analysis and the literature, the relationship with the GP was seen negatively if the GP failed to recognise depressive symptoms or focused solely on the person's somatic symptoms. People who had positive experiences highlighted the sympathetic, supportive and helpful qualities of the GP.

The relationship with nurses was not as positive in both the personal accounts (see B) and the qualitative analysis, with lack of understanding about depression being cited as a common complaint.

In the qualitative analysis there were mixed views about psychiatrists, particularly in the way that they prescribed medication. Some people felt that their psychiatrist was able to work with them to find the right medication and the correct dose; another said her psychiatrist did not listen when she said her medication was not working. In the personal accounts, some people had neutral views about their psychiatrist while three people (C, F and G) expressed negative views, such as the psychiatrist being unsupportive and cursory in their attention.

Most of the personal accounts spoke of the importance of a relationship with professionals that was non-judgemental and supportive. But as one person (B) pointed out, sometimes being well-meaning and supportive is not enough. She felt that while her primary care practitioners and counsellors were pleasant and accommodating, her self-report was not listened to closely enough and the severity of her depression was underestimated. A number of people commented that the relationship

between patient and therapist is of prime importance, and that ideally there should be some choice in terms of the gender of the therapist and their therapeutic approach. Two people (A and B) commented that it is often seen as the patient's 'fault' if they do not benefit from psychological treatment, when the counsellor or therapist should take some responsibility for a lack of therapeutic effect.

4.6.6 Experience of services

Both the personal accounts and the qualitative analysis described experiences of mental health services. Many people said that they waited too long to be referred to a psychiatrist or receive psychological treatment. Once in mental health services, views were mixed. In both sources of evidence, those who had private treatment had, on the whole, more positive experiences.

4.6.7 Experience of depression and its possible causes

In both the personal accounts and the qualitative analysis, people with depression described some of the negative thoughts that they had experienced and some described suicidal thoughts and behaviour; they also used metaphor and allusion to explain their symptoms. In the qualitative analysis some people said that they were able to experience life differently since being depressed which, for some, was a positive outcome.

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

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

emotionally vulnerable to setbacks and upsets. For those who feel hopeless and helpless, depression is often the psychological result.

4.6.8 Experiences of treatments

Psychological therapy

There was a strong feeling within the service user and carer topic group that the excerpt from Howe (1995) in the section above highlights the reasons why many people opt for private therapy; that is, that psychological treatment offered by the NHS in the form of CBT does not go far enough in addressing the trauma experienced in childhood. The study by Ridge and Ziebland (2006) confirms the opinions of the topic group and the testimony from the personal accounts that people with 'deep and complex problems felt the need for longer term therapy'. Those that have had long-term psychodynamic therapy report that it has been helpful in their understanding of themselves and their depression and that until they have worked through and repaired the damage experienced in childhood, depression will be a major factor in the person's life. The service user and carer topic group do acknowledge, however, that as there has been little research into the efficacy of long-term psychodynamic therapy, it cannot be recommended as a course of treatment in this guideline (see Chapter 8).

The study by Saver and colleagues (2007) points to the fact that few people received information about psychological therapy and the different treatments, such as CBT and IPT.

Psychosocial interventions

This was a theme of both the personal accounts and the qualitative analysis. In the qualitative analysis, people expressed a need for psychosocial interventions when they attributed the cause of their depression to psychological processes rather than a 'chemical imbalance' and to help them cope with negative thoughts.

Overall, people in the qualitative analysis were positive about counselling, as were people in the personal accounts, although concerns were raised by two people (B and E). One found counselling inadequate for her needs because it did not get to the 'root' of her depression and indeed did not stop her depression from becoming more severe. Another felt that the counselling she received was unsatisfactory: she was asked inappropriate questions, incorrect assumptions were made about her life, and she felt that she did not talk enough during the sessions. She felt that for counselling to be effective, the counsellor needed to both listen and question skilfully.

In the qualitative analysis, people were generally positive about cognitive therapy, self-help books and support groups, but less positive about relaxation therapy because people with severe depression find it difficult to relax. The view of relaxation therapy is borne out in personal account B. The personal accounts express mixed views about support groups: one person (D) was very positive about them, but another (E) said that, while it was good to meet other people, she gained no therapeutic value from attending.

Experience of care

Khan and colleagues (2007) synthesised qualitative studies of patient experiences of depression management in primary care to develop a framework for a guided self-help intervention.

Medication
There were mixed reports regarding medication. Some people did not find antidepressants helpful, particularly in the form of a 'drug cocktail'; others were concerned about taking tablets. In the literature, it emerged that taking medication could lead to ambivalent feelings: on the one hand, people felt relief because medication helped them cope with difficulties in their day-to-day life; on the other, they felt a lack of control. In the personal accounts, one person (A) commented on the weight gain associated with the medication leading to self-esteem issues and feeling more depressed. Others benefited from it; one person (B) felt strongly that getting the appropriate medication promptly is vital and that there should be intense support before the antidepressive effects are experienced. The majority of people in the qualitative analysis said that antidepressants were beneficial, despite some experiencing side effects.

Electroconvulsive therapy
This theme was only present in the qualitative analysis. The majority of people who had ECT had negative experiences, including loss of memory after treatment. Only one person had a positive experience with no side effects.

4.6.9 Coping strategies

It is evident from the personal accounts and the literature review that people who have had depression for a long time develop positive coping mechanisms that enable them to manage their illness. These mechanisms range from exercise (A) or personal faith (C), to readjusting one's life to be able to manage depression. The qualitative analysis also identified a number of coping strategies such as distraction, having a hobby, activities and voluntary work.

4.6.10 Employment

The theme of employment was only present in the personal accounts. To contextualise this theme, some of the literature regarding this topic that was not identified in the systematic search is briefly described below.

From the personal accounts there are issues for those with long-standing depression when it comes to accessing and remaining in employment. Several personal accounts spoke of difficulties in getting paid employment: one person (C) stated that both their college and job centre could not help until their condition was stable, and another (B) was self-employed when she became ill, was unable to work and had no income. In personal account G, the person had only worked in paid employment

for 8 months in the 8 years he had had depression, but was doing voluntary work with mental health and disability organisations.

Other personal accounts spoke of experiences in work. One person (A) spoke of colleagues not being keen for her to return to work, and instead of returning to her normal activities she was marginalised from external meetings and confined to certain tasks. Another person (E) expressed the fear of getting too ill to work, but with the help of her GP did not have to say that the occasional day or week off with illness was because of depression. However, she also had the support of her manager in whom she confided and who helped with work pressures. In the qualitative analysis, some people commented that stressful situations at work contributed to the onset of their depression.

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

Clinical research and government reports suggest that employment plays a part both in exacerbating stress leading to depression, but also, conversely, that it can be crucial component in aiding the recovery process. The Health and Safety Executive (2008) reported that in 2006/07, an estimated 530,000 people in the UK reported they were experiencing stress, depression or anxiety that was caused or exacerbated by their current or past employment. It was estimated that 13.8 million working days (full-day equivalent) were lost in 2006/07 through work-related stress, depression or anxiety. The Sainsbury Centre for Mental Health (2007) also identified the loss in productivity that occurs when employees come to work but function at less than full capacity because of ill health (termed 'presenteeism'). Fearing possible stigma or discrimination, people with mental health problems may turn up for work even if they are feeling unwell rather than be labelled as mentally ill by their employers and co-workers.

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

A report by the Royal College of Psychiatrists (2008) found two studies that analysed employment schemes in people with mental health problems. In a systematic review of 11 RCTs comparing prevocational training or supported employment for people with severe mental illness with each other or with standard community care, Crowther and colleagues (2001) found that participants who received supported employment were more likely to be in competitive employment than those who received prevocational training (34% compared with 12% at 12 months). Rinaldi and colleagues (2008) examined a supported employment scheme run by South West London and St George's Mental Health NHS Trust. The results showed that, following

the integration of employment specialists into CMHTs, there was a significant increase in the number of clients with various diagnoses (31% with depression – unspecified severity) engaged in mainstream work or educational activity at both 6 and 12 months. The conclusion drawn supports the use of individual placement specialists in clinical practice in CMHTs.

4.6.11 Recovery

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

4.6.12 Families and carers

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

The needs of young carers should be recognised and addressed and recent publications from the Social Care Institute for Excellence and the Department of Health (Department of Health *et al.*, 2008; Greene *et al.*, 2008; Roberts *et al.*, 2008; Department of Health *et al.*, 2009) provide guidance on how this can be achieved. It should be recognised that young carers might marginalise themselves from their peer group and experience other social and educational disadvantage. The report by

Roberts and colleagues (2008) suggests that the needs of young carers could be more effectively addressed by respecting their anxieties and acknowledging their input and skills. It is also recommended that young carers should be included in their family member's care planning.

The impact of depression on families and carers was a prolific theme in both the personal accounts and the qualitative analysis, with some people stating that depression was harder for family members and carers than for themselves. Some people remarked on the change of roles that occurred as a result of one person having depression. Many people also commented on the supportive nature of family members and carers, although some people had to cope with their depression alone.

4.7 RECOMMENDATIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5 CASE IDENTIFICATION AND SERVICE DELIVERY

5.1 INTRODUCTION[10]

The starting point for providing effective treatment for depression is the recognition of the problem and the first point of access is usually primary care, with the majority of people continuing to be managed in primary care. There is evidence, however, that many cases go unrecognised (Del Piccolo *et al.*, 1998; Raine *et al.*, 2000). Where depression is recognised, care often falls short of optimal recommended practice (Katon *et al.*, 1992; Donoghue & Tylee, 1996) and outcomes are correspondingly below what is possible (Rost *et al.*, 1994). This is a cause of considerable concern. More recent studies, however, suggest that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient–doctor relationship and it is milder forms, which are more likely to recover spontaneously, that go undetected and untreated (Thompson *et al.*, 2001; Kessler *et al.*, 2003).

In addition to efforts to improve recognition of depression, a number of responses have been developed over the past 20 or so years to address the problem of suboptimal treatment. These responses have included developments in the treatment of depression in primary and secondary care; the organisational and professional structures of primary and secondary care mental health services; and the development and adaptation of models for the management of chronic medical conditions, for example diabetes (Von Korff *et al.*, 1997; Von Korff & Goldberg, 2001). Since the publication of the previous guideline in 2004, in the UK these developments have included the introduction of graduate mental health workers (Department of Health, 2003), which has contributed to increased access to low-intensity psychosocial interventions, including computerised CBT (NICE, 2002; NICE, 2005). The concept of 'stepped care' advocated in the previous guideline has been embraced by many commissioners and providers in the NHS and is now being taken forward by the Improving Access to Psychological Therapies (IAPT) programme (Department of Health, 2007; IAPT, 2009). It is this later development, with £340 million of funding over 6 years along with 3,400 new psychological therapists, that will bring about the single biggest change in the provision of effective treatments for depression in primary and secondary care.

[10]For this guideline update, all sections of the 'Service-level and other interventions' chapter in the previous guideline were reviewed. The sections from the previous guideline on screening (now re-named case identification), organisational developments such as collaborative care, stepped care, enhanced care and integrated care (now re-named enhanced care), non-statutory support and crisis resolution and home treatment teams remain in this chapter. The updated reviews for guided self-help, computerised CBT and exercise (now termed physical activity programmes) have been moved to Chapter 7, and the updated review for ECT can be found in Chapter 12.

This chapter focuses on two main issues: the identification of depression in primary and secondary care and the range of different service delivery mechanisms that have emerged in recent years. These approaches to service delivery fall into three main groups, including systematic approaches for organising care and making available appropriate treatment choices, the development of new and existing staff roles in primary care and the introduction of mental health specialists into primary care.

5.2 THE IDENTIFICATION OF DEPRESSION IN PRIMARY CARE AND COMMUNITY SETTINGS

5.2.1 Introduction

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

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

5.2.2 Identifying depression – a primary care perspective

For over 40 years, it has been suggested that GPs fail to accurately diagnose depression (Goldberg & Huxley, 1992; Kessler *et al.*, 2002). As stated above, some studies suggest that clinically important depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient–doctor relationship and that its milder forms, which may recover spontaneously, go undetected and untreated (Thompson *et al.*, 2000; Kessler *et al.*, 2002). However, even this suggests that non-clinically important depression may go undetected initially. More recent studies suggest that the probability of prescribing antidepressants in primary care is associated with the severity of the depression, although almost half of the people prescribed antidepressants were not depressed (Kendrick *et al.*, 2005). Other authors draw attention to the dangers of the erroneous diagnosis of depression in patients with a slight psychological malaise and few functional consequences that can lead to the risk of unnecessary and potentially dangerous medicalisation of distress

(Aragones *et al.*, 2006). Given the modest prevalence of depression in most primary care settings the number of false positive errors (people who are incorrectly identified as being at risk of depression) is larger than the number of false negatives (those falsely identified as not being at risk of developing depression). Further work is clearly needed to examine the subsequent outcome of those false positive and false negative diagnoses, and also to clarify the accuracy of GPs in diagnosing anxiety disorders, adjustment disorders and broadly defined distress.

Reasons for lack of recognition fall into four themes: factors related to the person with depression, and practitioner, organisational and societal factors.

5.2.3 Factors related to the person with depression

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

A number of other factors may also influence the identification of depression. Older adults, in particular, may complain less of depressed mood and instead somatise their depressive symptoms (Rabins, 1996). Physical comorbidity can also make the interpretation of depressive symptoms difficult. People may have beliefs that prevent them from seeking help for depression such as a fear of stigmatisation, or that antidepressant medication is addictive or they may misattribute symptoms of depression for 'old age', ill health or grief. Although depression is more frequent in women, differential reporting of symptoms may lead to depression being under-diagnosed in men. From the perspective of the person with depression, it has been suggested that contact with primary care may be of little significance when set against the magnitude of their other problems (Rogers *et al.*, 2001).

5.2.4 Practitioner factors

The construction of 'depression' as a clinical condition is contested amongst GPs (Chew-Graham *et al.*, 2000; May *et al.*, 2004; Pilgrim & Dowrick, 2006). They may be wary of opening a 'Pandora's box' in time-limited consultations and instead collude with the person with depression in what has been called 'therapeutic nihilism' (Burroughs *et al.*, 2006). In deprived areas, primary care physicians have been shown

to view depression as a normal response to difficult circumstances, illnesses or life events (May *et al.*, 2004), and depression may be under-diagnosed because of dissatisfaction with the types of treatment that can be offered, especially a lack of availability of psychological interventions. Primary care practitioners may also lack the necessary consultation skills or confidence to correctly diagnose late-life depression.

5.2.5 Organisational factors

The trend in the UK for mental health services to be separate from mainstream medical services may disadvantage people with depression who may have difficulties in attending different sites and/or services for mental and physical disorders.

Organisational factors that inhibit the identification and disclosure of symptoms and problems, together with limited access to mental health services, add to professionals' reluctance to encourage patients to disclose their distress (Popay *et al.*, 2007; Chew-Graham *et al.*, 2008).

5.2.6 Societal factors

The barriers described are likely to be particularly difficult for the economically poor and minority populations who tend to have more health problems and are more disabled. The oft-described barrier of stigma has to be set against the arguments that depression is a social construction within which chronic distress or unhappiness are medicalised (Ellis, 1996; Pilgrim & Bentall, 1999) and the suggestion that chronic unhappiness is not 'treatable' in the normal curative or therapeutic sense. It is therefore important that the healthcare professional recognises and accepts their own reaction to people presenting with depression so that they can acknowledge and go on to diagnose depression, and then discuss a range of possible interventions.

5.2.7 Shifting the emphasis from screening to identification

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

identified as not being at risk of developing a condition (false negatives) will also suffer by not being given the further investigation they need.

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

Within the NHS, case identification of depression in people with some chronic conditions (for example, diabetes) is now part of routine clinical work for GPs as stipulated by the GMS Contract (Ellis, 1996). Evidence, however, suggests that such ultra-short screening instruments may fail to detect depression (Mallen & Peat, 2008). It has been suggested that using an additional question ('is this something with which you would like help?' [Arroll *et al.*, 2005]) may improve the specificity of the screening questions. Others, however, caution that the use of such screening instruments may encourage practitioners to take a reductionist, biomedical approach, diverting them from a broader bio-psychosocial approach to both diagnosing and managing depression (Dowrick, 2004).

5.2.8 Case identification

Introduction

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

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

The following sections review available case identification instruments.

Definition

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

Summary statistics used to evaluate identification instruments

Sensitivity, specificity, positive predictive validity and negative predictive validity

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

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

The specificity of an instrument refers to the proportion of those who do not have the condition and test negative. This is important so that healthy people are not offered treatments they do not need. As the specificity of an instrument increases, the number of false positives will decrease.

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

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

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

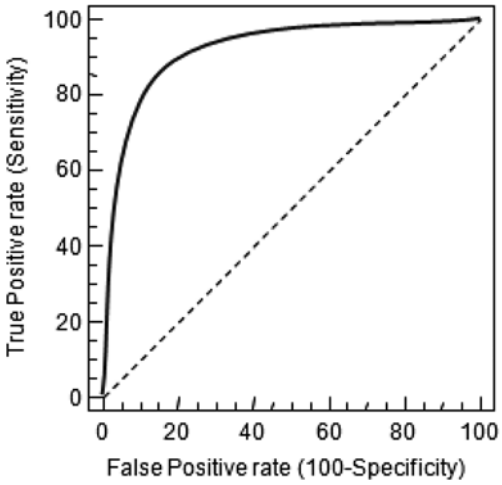
When describing the sensitivity and specificity of the different instruments, the GDG defined values above 0.9 as ‘excellent’, 0.8 to 0.9 as ‘good’, 0.5 to 0.7 as ‘moderate’, 0.3 to 0.5 as ‘low’, and less than 0.3 as ‘poor’.

Receiver operator characteristic curves

The qualities of a particular tool are summarised in a receiver operator characteristic (ROC) curve, which plots sensitivity (expressed as a per cent) against (100-specificity) (Figure 4).

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

Figure 4: Receiver operator characteristic curve



Negative and positive likelihood ratios

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

Diagnostic odds ratios

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

Databases searched and inclusion/exclusion criteria

The review team conducted a new systematic search for cross-sectional studies to assess tools for identifying depression. This was undertaken as a joint review for this guideline and the guideline for depression in adults with a chronic physical health problem (NICE, 2009c). Information about the databases searched and the inclusion/exclusion criteria used can be found in Table 6. Details of the search strings used are in Appendix 8.

Studies considered

A total of 126 studies met the eligibility criteria of the review; 54 studies were conducted in consultation samples, 45 were on people with chronic physical health problems[11] and 50 were on older people (over 65 years of age). Of these studies, 16

[11]Data for the population with chronic physical health problems and information about the included studies is presented in the related guideline, *Depression in Adults with a Chronic Physical Health Problem* (NCCMH, 2010).

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

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library
Date searched	Database inception to February 2009
Study design	Cross-sectional studies
Patient population	People in primary care, community, and general hospital settings
Instruments	BDI, PHQ, GHQ, CES-D, GDS, HADS, Zung Self Rated Depression Scale, and any one- or two-item measures of depression
Outcomes	Sensitivity, specificity, AUC, diagnostic odds ratio, positive likelihood, negative likelihood

were on the PHQ-9, five on the PHQ-2, six on the 'Whooley questions', 19 on the BDI, nine on the BDI – short form, two on the GHQ-28, 12 on the GHQ-12, 17 on the CES-D, 20 on the GDS, 11 on the GDS-15, 16 on HADS-D, five on HADS-total and seven on one-item measures (see Appendix 20 for further details).

In addition, 251 studies were excluded from the analysis. The most common reason for exclusion was a lack of a gold standard (DSM/ICD) comparator (see Appendix 20 for further details).

Evaluating identification tools for depression

A bivariate diagnostic accuracy meta-analysis was conducted using Stata 10 with the Module for Meta-analytical Integration of Diagnostic Test Accuracy Studies (MIDAS) (Dwamena, 2007) commands in order to obtain pooled estimates of sensitivity, specificity, likelihood ratios and diagnostic odds ratio (for further details, see Chapter 3). To maximise the available data, the most consistently reported and recommended cut-off points for each of the scales were extracted (see Table 7).

Heterogeneity is usually much greater in meta-analyses of diagnostic accuracy studies compared with RCTs (Gilbody *et al.*, 2007; Cochrane Collaboration, 2008). Therefore, a higher threshold for acceptable heterogeneity in such meta-analyses is required. However when pooling studies resulted in $I^2 > 90\%$, meta-analyses were not conducted.

Table 8 summarises the results of the meta-analysis in terms of pooled sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, and diagnostic odds ratios. Additional subgroup analyses were conducted for older adults.

Patient Health Questionnaire

The PHQ developed out of the more detailed Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer *et al.*, 1994). There are three main instruments that

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

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

have been developed from this scale; the PHQ-9 (Spitzer *et al.*, 1999), PHQ-2 (Kroenke *et al.*, 2003) and the 'Whooley questions' (Whooley *et al.*, 1997).

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

For the PHQ-9 in consultation samples (people in primary care or general medical settings) there was relatively high heterogeneity (although of a similar level to most other scales) ($I^2 = 74.04\%$). The PHQ-9 was found to have good sensitivity (0.82, 95% CI, 0.77, 0.86) and specificity (0.83, 95% CI, 0.76, 0.88).

The PHQ-2 could not be meta-analysed as there was very high heterogeneity. The Whooley questions analysis included studies both on consultation and chronic physically ill samples as there were too few studies to break down by population. This scale was found to have high sensitivity (0.95, 95% CI, 0.91, 0.97) but lower specificity (0.66, 95% CI, 0.55, 0.76). A single study by Arroll and colleagues

Table 8: Evidence summary of depression identification instruments in primary care, people with a chronic physical health problem, and older populations

Population and instrument	Sensitivity	Specificity	Likelihood ratio+	Likelihood ratio-	Diagnostic odds ratio	AUC
PHQ-9 Consultation samples: 11 studies	0.82 (0.77, 0.86)	0.83 (0.76, 0.88)	4.70 (3.29, 6.72)	0.22 (0.17, 0.29)	21.38 (11.87, 38.52)	0.88 (0.85, 0.91)
Whooley*: All populations: 7 studies	0.95 (0.91, 0.97)	0.66 (0.55, 0.76)	2.82 (2.01, 3.96)	0.08 (0.04, 0.15)	36.25 (14.89, 88.24)	0.94 (0.92, 0.96)
BDI Consultation samples: 4 studies	0.85 (0.79, 0.90)	0.83 (0.70, 0.91)	5.14 (2.83, 9.32)	0.18 (0.12, 0.24)	29.29 (15.10, 56.79)	0.90 (0.87, 0.92)
BDI-non somatic items Consultation sample: 5 studies	0.82 (0.57, 0.94)	0.73 (0.61, 0.83)	3.02 (1.87, 4.90)	0.25 (0.09, 0.69)	11.92 (3.02, 47.04)	0.83 (0.79, 0.86)
CES-D Consultation sample: 8 studies	0.84 (0.78, 0.89)	0.74 (0.65, 0.81)	3.19 (2.41, 4.22)	0.21 (0.15, 0.29)	15.02 (9.38, 24.05)	0.87 (0.84, 0.90)
Older adults: 5 studies	0.81 (0.74, 0.87)	0.79 (0.67, 0.88)	3.82 (2.35, 6.22)	0.24 (0.17, 0.33)	15.95 (8.05, 31.60)	0.83 (0.80, 0.86)
GDS-15 Consultation sample: 11 studies	0.87 (0.80, 0.91)	0.75 (0.69, 0.80)	3.40 (2.73, 4.24)	0.18 (0.12, 0.27)	18.98 (10.85, 33.20)	0.86 (0.83, 0.89)
1-item Consultation sample: 6 studies	0.84 (0.78, 0.89)	0.65 (0.55, 0.73)	2.38 (1.81, 3.13)	0.25 (0.17, 0.36)	9.67 (5.35, 17.46)	0.85 (0.82, 0.88)

*It was not possible to conduct separate subgroup analyses for consultation and chronic physical illness samples due to lack of studies for the Zung and Whooley questions.

(2005) added a further question to the two in the PHQ-2, asking the patient if they wanted help with their depression. This increased specificity and the GDG considered the findings of the study and the adoption of the third question, but as there was only a single study showing the effect of this approach the GDG decided not to adopt it.

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

Beck Depression Inventory

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

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

For the 21-item BDI there was high heterogeneity for consultation samples (I^2 = 88.61%). The BDI appeared to perform relatively well in terms of sensitivity (0.85, 95% CI, 0.79, 0.90) and specificity (0.83, 95% CI, 0.70, 0.91). This was also consistent with the diagnostic odds ratio (29.29, 95% CI, 15.103, 56.79). However, this is based on only four studies so it is difficult to draw firm conclusions. Subgroup analyses on older adults were also not possible as there were only two studies for this population.

Beck Depression Inventory – non-somatic items

Data from BDI fast-screen (Beck *et al.*, 2000) and BDI short-form (Beck *et al.*, 1974, 1996) were combined to assess the impact of removing somatic items as data from both scales were relatively sparse. There was sufficient, although relatively low, consistency between studies to assess these scales (BDI: non-somatic) in consultation (I^2 = 75.71%) populations. There was high sensitivity (0.82, 95% CI, 0.57, 0.94) but lower specificity (0.73, 95% CI, 0.61, 0.83). A meta-analysis was not possible for older adults as there were only two studies.

General Health Questionnaire

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

There were only two trials of the GHQ-28, therefore meta-analysis was not conducted. In addition, while there were more studies on the GHQ-12 there was very high heterogeneity (I^2 > 90%) for studies on consultation populations, therefore these studies were also not meta-analysed. Moreover, a meta-analysis specifically for older adults was not possible due to there being only two studies.

Hospital Anxiety and Depression Scale

The HADS (Zigmond & Snaith, 1983) is a measure of depression and anxiety developed for people with physical health problems. The depression subscale has seven items and the cut-off is 8 to 10 points.

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

Center for Epidemiological Studies Depression Scale

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

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

For consultation samples sensitivity was high (0.84, 95% CI, 0.78, 0.89) but specificity was lower (0.74, 95% CI, 0.65, 0.81). For older adults, there was relatively low sensitivity (0.81, 95% CI, 0.74, 0.87) and higher specificity (0.79, 95% CI, 0.67, 0.87).

Geriatric Depression Scale

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

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

In the consultation population there was higher sensitivity (0.87, 95% CI, 0.80, 0.91) but specificity was relatively low (0.75, 95% CI, 0.69, 0.80). The diagnostic odds ratio was just below 20 (18.98, 95% CI, 10.85, 33.20). Heterogeneity was relatively acceptable ($I^2 = 70.96\%$).

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

Zung Self-Rating Depression Scale

The self-rating depression scale was developed by Zung (Zung, 1965) and has been revised (Guy, 1976). This has 20 items where a cut-off of 50 is typically used. It is sometimes used as an outcome measure as well. There were insufficient studies to conduct a meta-analysis.

One-item measures

Five studies were found to assess a one-item measure in consultation samples. There was a relatively good sensitivity (0.84, 95% CI, 0.78, 0.89) but very low specificity (0.65, 95% CI, 0.55, 0.73). The diagnostic odds ratio indicated a lack of accuracy

(9.67, 95% CI, 5.35, 17.46). It was not possible to conduct a subgroup analysis of older adults as there were only two studies.

Comparing validity coefficients for case identification tools in older adults

The impact of old age and residing in a nursing home on the validity coefficients of the case identification tools reviewed above were assessed through meta-regression (see Table 9). Because of a lack of data the PHQ-2, Whooley, Zung, and one-item measures were not included in the analysis.

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

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

Population and instrument	Beta-coefficient	I^2(%)	p-value
PHQ-9 Comparing over 65s with under 65s	Sensitivity = 1.23 Specificity = 1.84	Joint $I^2 = 0$	0.65 0.73 0.83
BDI Comparing over 65s with under 65s	Sensitivity = 1.58 Specificity = 0.74	Joint $I^2 = 0$	0.34 0.79 0.65
BDI-non somatic items Comparing over 65s with under 65s	Sensitivity = 1.58 Specificity = 2.12	Joint $I^2 = 58.64$	0.80 0.02 0.09
CES-D Comparing over 65s with under 65s	Sensitivity = 1.23 Specificity = 1.61	Joint $I^2 = 43.30$	0.09 0.18 0.17
GDS Comparing nursing home with non-nursing home	Sensitivity = 1.54 Specificity = 1.13	Joint $I^2 = 0$	0.85 0.65 0.80
GDS-15 Comparing nursing home with non-nursing home	Sensitivity = 2.14 Specificity = 0.91	Joint $I^2 = 0$	0.36 0.34 0.44
GHQ-12 Comparing over 65s with under 65s	Sensitivity = 0.43 Specificity = 1.45	Joint $I^2 = 11.28$	0.14 0.33 0.32

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

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

5.2.9 Case identification in black and minority ethnic populations

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

There is an increasing evidence base to suggest that the reduced identification of depression in different ethnic and cultural groups may be one barrier to receiving appropriate treatment, including both psychological and pharmacological interventions. For example, research has suggested that across mental disorders, particular ethnic groups are often under-represented in primary care services (Bhui *et al.*, 2003; Department of Health, 2008b), whereas a Healthcare Commission survey highlighted how both Asian and black/black British people were less likely to be offered 'talking therapies' (Department of Health, 2008b).

Case identification and service delivery

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

Definition and aim of topic of review

The review considered any ethnic-specific case identification instruments aimed at detecting depression in black and minority ethnic populations. This included new identification tools designed for different cultural and ethnic groups, and also existing scales modified and tailored towards the specific needs of particular black and minority ethnic groups. Although the GDG was aware of papers from outside the UK (most notably from the US), the decision was made to only include UK studies. As discussed above, the presentation and subjective experience of depression is known to be influenced by cultural and ethnic factors; therefore, it was felt that findings from non-UK ethnic minority populations would not be generalisable because of the ethnic and cultural differences among the populations studied. The review also assessed the validity of established depression case identification tools for different black and minority ethnic populations within the UK[12].

Databases searched and inclusion/exclusion criteria

The review team conducted a new systematic search for cross-sectional studies aiming to assess tools for identifying depression. This was undertaken as a joint review for this guideline and the guideline for depression in adults with a chronic physical health problem (NCCMH, 2010). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 10. Details of the search strings used are in Appendix 8.

Studies considered

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

[12]Papers assessing the validity of established scales in UK black and minority ethnic populations were required to have a 'gold standard' diagnosis defined as DSM–IV or ICD–10 diagnosis of depression.

Table 10: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological interventions

Electronic databases	MEDLINE, EMBASE, PsycINFO, Cochrane Library
Date searched	Database inception to February 2009
Study design	Cross-sectional studies
Patient population	People in primary care, community, and general hospital settings from black and minority ethnic groups
Instruments	1. Any ethnic-specific depression case identification instrument 2. Any cultural or ethnically adapted version of the following validated case identification instruments: BDI, PHQ, GHQ, CES-D, GDS, HADS, Zung Self Rated Depression Scale, and any one- or two-item measures of depression 3. Any of the above validated identification tools, assessed in a UK black and minority ethnic population
Outcomes	Sensitivity, specificity, AUC, diagnostic odds ratio, positive likelihood, negative likelihood

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

Evaluating identification tools for depression in black and minority ethnic populations
Because of both the paucity of data on ethnic specific scales in the UK and differences in the populations and instruments investigated, it was not possible to conduct a meta-analysis of the included studies. Instead the findings from the included studies are summarised in a narrative review below.

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

Using the ADI and the GHQ-12, Bhui and colleagues (2000) screened both Punjabi and white English attendees of five primary care practices in South London. Throughout the study, a cultural screen assessing self-affirmed cultural origin was

applied to detect both Punjabi and white English participants. To overcome any additional barriers because of language, the screening tools were administered in English, Punjabi or a combination of the two, depending on the preference of the participant. A two-phase screening protocol was applied in which all 'probable cases', for example, those scoring >2 on the GHQ or >5 on the ADI, and one third of 'probable non-cases' proceeded to a second interview in which the Clinical Interview Schedule-Revised (CIS-R) was administered by a bilingual psychiatrist.

Results of the validity coefficients and ROC curve analysis using the standard CIS-R thresholds for depression indicated that while the GHQ-12 performed well across both groups, culture had an impact on the validity coefficient of the ADI. In particular, although performing in line with the GHQ-12 for the white English participants, the ADI performed worse in detecting depression in the Punjabi participants. Results indicated that the ADI was no better than chance in identifying cases of depression, particularly for Punjabis who had been resident in the UK for more than 30 years. One additional finding of interest was that the optimal cut-off for the ADI was higher for the Punjabi participants compared with their white English counterparts, although this finding was not sustained for the GHQ-12 in which the same cut-off was optimal for both groups. Analysis of the individual items of both the GHQ-12 and the ADI failed to indicate any specific items that were strongly predictive of depression caseness in either cultural group.

Caribbean Culture-Specific Screen for emotional distress

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

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

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

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

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

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

Personal Health Questionnaire

Husain and colleagues (2007) assessed the validity of the Personal Health Questionnaire in Pakistani people who were resident in the UK. The authors noted that, unlike many screening instruments, the Personal Health Questionnaire contains no 'difficult culture specific idioms', thus making translations into other languages possible. In the present study, the Personal Health Questionnaire was translated and back-translated into Urdu, the main language of immigrants from Pakistan, with group discussion utilised to reach a single consensus.

Case identification and service delivery

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

Results of the ROC curve analysis indicated that the recommended cut off score of >7 produced a sensitivity of 70.4% and a specificity of 89.3%, with a positive predictive value of 82.6 and a negative predictive value of 80.6. The high sensitivity and specificity at the recommended cut-off suggested that the Personal Health Questionnaire is able to detect depression in people of Pakistani family origin when administered in either English or Urdu. Furthermore, the authors noted that participants in this study and in a study conducted in Pakistan (Husain *et al.*, 2000) did not experience any difficulties in understanding and answering the screening questions.

Limitations with the evidence base

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

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

5.2.10 Clinical summary for both reviews

There was very high heterogeneity found for almost all identification tools, which is an important limitation of the reviews. Scales varied a great deal in terms of targeted populations, number of items and scoring systems. When compared with the Whooley

questions, other scales such as the PHQ-9 and GDS-15 had better specificity but not as much sensitivity (although they still met the criteria for high sensitivity).

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

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

5.2.11 Health economic evidence and considerations

No evidence on the cost effectiveness of case identification tools for depression in primary care and community settings was identified by the systematic search of the economic literature. Details on the methods used for the systematic search of the economic literature are described in Chapter 3, Section 3.6.1.

5.2.12 From evidence to recommendations

The GDG noted the different nature of the scales contained in the review and their psychometric properties, as well as the possible benefit of a two-stage process of identification and diagnosis.

The first stage of case identification would require using a highly sensitive instrument that could be used in routine clinical practice with limited training and implementation difficulties. The data supported the use of the Whooley questions and, given that this measure is already in current use in primary care, the GDG concluded that in the first stage of case identification the Whooley questions remained an appropriate tool for depression. However, given the lack of specificity found with the Whooley questions it was the view of the GDG that people with a positive response would benefit from a more detailed clinical assessment, which may include a more detailed instrument possessing better overall psychometric properties. The data on case-finding instruments in black and minority ethnic groups did not identify any specific measures that in the opinion of the GDG improved upon the results obtained

with the Whooley questions, and therefore no specific black and minority ethnic recommendations on case finding tools are made. However, the need for cultural competence of staff in assessments was noted in the review of case-finding instruments in black and minority ethnic groups, and this is reflected in the recommendations. In addition, in performing a more comprehensive mental health assessment, as recommended in the previous guideline, the need to move beyond simple symptom counts was noted, so the recommendation from the previous guideline has been amended. This guideline update also makes recommendations for people with depression and learning disabilities or acquired cognitive impairments because it is likely that depression, which is 'relatively common' (Prasher, 1999) in this population, will be under-diagnosed, particularly if they have autism, a learning disability, established aggressive, self-harming or over-active behaviours or comorbid physical health problems such as epilepsy, diabetes or heart disease (Prasher, 1999; Mind, 2007). Other recommendations from the previous guideline remain essentially the same.

5.2.13 Recommendations

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.3 SERVICE DELIVERY SYSTEMS IN THE TREATMENT AND MANAGEMENT OF DEPRESSION

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.4 STEPPED CARE

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.4 COLLABORATIVE CARE

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.6 CRISIS RESOLUTION AND HOME TREATMENT TEAMS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.7 ACUTE DAY HOSPITAL CARE

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.8 NON-ACUTE DAY HOSPITAL CARE

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.9 NON-STATUTORY SUPPORT

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

5.10 RESEARCH RECOMMENDATION

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

6 INTRODUCTION TO PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

7 LOW-INTENSITY PSYCHOSOCIAL INTERVENTIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

8 HIGH-INTENSITY PSYCHOLOGICAL INTERVENTIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

9 INTRODUCTION TO PHARMACOLOGICAL AND PHYSICAL INTERVENTIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

10 PHARMACOLOGICAL INTERVENTIONS

This section was updated and replaced in 2022, with the exception of St John's Wort (see below). Please see the NICE website for the updated guideline.

10.1 ST JOHN'S WORT

The following sections on St John's wort marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

10.1.1 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 ten constituents or groups of components that may contribute to its pharmacological effects (Linde & Mulrow, 2004), 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.*, 2004). 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 important drug interactions have been reported (Committee on Safety of Medicines, 2000). St John's wort may also cause photosensitivity.

10.1.2 Studies considered[135,136]

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 (Bergmann93, Philipp99, Wheatley97, Woelk2000); one for a comparison with

[135]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[136]Study IDs in title case refer to studies included in the previous guideline. References for these studies are in Appendix 18.

TCA-related antidepressants (Harrer94); and six studies for a comparison with SSRIs (Behnke2002, Brenner00, Davidson02, Harrer99, Schrader00, VanGurp02)[137]. Data from up to 1520 participants were available from studies comparing St John's wort with placebo, and data from up to 1629 participants were available from comparison with antidepressants.

All included studies were published between 1993 and 2002 and were between 4 and 12 weeks' long (mean = 6.47 weeks). 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 study (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) at 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 to 0.28% hypericin
- 3 X 350 mg (1050 mg) STEI 300: 0.2 to 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) at 0.3% hypericum
- 3 X 300 mg (900 mg) LI 160 = 720 to 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.

10.1.3 Clinical evidence statements for St John's wort compared with placebo[138]

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically important difference favouring St John's wort over placebo on increasing the likelihood of achieving a 50% reduction in symptoms of depression as measured by the HRSD in:

- the dataset as a whole (K = 6[139]; N = 995; RR = 0.79; 95% CI, 0.71 to 0.88)

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[137]Davidson02 and Philipp99 are 3-arm trials.

[138]The forest plots can be found in Appendix 19c.

[139]Three studies (Davidson02, Hangsen1996, Schrader98) were removed from the meta-analysis to remove heterogeneity from the dataset.

- moderate depression (K = 1; N = 162; RR = 0.64; 95% CI, 0.51 to 0.79)
- severe depression (K = 5[140]; N = 898; RR = 0.81; 95% CI, 0.72 to 0.9).

There is insufficient evidence to determine if there is a clinically important 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 (K = 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 symptoms of depression by the end of treatment as measured by the HRSD, but the size of this difference is unlikely to be of clinical importance in:

- the dataset as a whole (K = 6[141]; N = 1031; SMD = –0.35; 95% CI, –0.47 to –0.22)
- severe depression (K = 5[142]; 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 important difference favouring St John's wort over placebo on reducing symptoms of depression by the end of treatment as measured by the HRSD (K = 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 important difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early for any reason (K = 8; N = 1472; RR = 0.96; 95% CI, 0.74 to 1.25).

There is insufficient evidence to determine if there is a clinically important difference between St John's wort and placebo on reducing the likelihood of patients leaving treatment early due to adverse effects (K = 5; N = 1127; RR = 0.88; 95% CI, 0.32 to 2.41).

There is evidence suggesting that there is no clinically important difference between St John's wort and placebo on reducing the likelihood of patients reporting adverse effects (K = 7; N = 1106; RR = 0.89; 95% CI, 0.72 to 1.1).

10.1.4 Clinical evidence statements for St John's wort compared with antidepressants[143]

Effect of treatment on efficacy outcomes

There is evidence suggesting that there is no clinically important difference between St John's wort and antidepressants on:

- increasing the likelihood of achieving a 50% reduction in symptoms of depression as measured by the HRSD (K = 10; N = 1612; Random effects RR = 1.03; 95% CI, 0.87 to 1.22)

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[140]Two studies (Davidson02, Hangsen1996) were removed from the meta-analysis to remove heterogeneity from the dataset.

[141]Three studies (Davidson02, Hangsen1996, Schrader98) were taken out of the meta-analysis to remove heterogeneity from the dataset.

[142]Ibid.

[143]The forest plots can be found in Appendix 19c.

- increasing the likelihood of achieving remission by the end of treatment as measured by the HRSD (K = 1; N = 224; RR = 1.01; 95% CI, 0.87 to 1.17)
- reducing symptoms of depression by the end of treatment as measured by the HRSD (K = 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 important difference favouring St John's wort over antidepressants on increasing the likelihood of achieving a 50% reduction in symptoms of depression as measured by the HRSD (K = 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 important difference favouring low-dose antidepressants over St John's wort on increasing the likelihood of achieving a 50% reduction in symptoms of depression as measured by the HRSD (K = 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 important difference favouring St John's wort over antidepressants given at therapeutic doses (K = 5; N = 1011; RR = 0.69; 95% CI, 0.47 to 1).

There is strong evidence suggesting that there is a clinically important difference favouring St John's wort over antidepressants on:

- reducing the likelihood of patients leaving treatment early due to side effects (K = 10; N = 1629; RR = 0.39; 95% CI, 0.26 to 0.6)
- reducing the likelihood of patients reporting adverse effects (K = 8; N = 1358; RR = 0.65; 95% CI, 0.57 to 0.75).

10.1.5 Clinical summary

St John's wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing symptoms of depression 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.

11 FACTORS INFLUENCING CHOICE OF ANTIDEPRESSANTS

11.1 INTRODUCTION

While the previous chapter reviewed the relative efficacy of different antidepressants, this chapter looks at factors that may affect the choice of antidepressant, including:

- the pharmacological management of depression in older adults (Section 11.2)
- the effect of sex on antidepressant choice (Section 11.3)
- the pharmacological management of depression with psychotic symptoms (Section 11.4)
- the pharmacological management of atypical depression (Section 11.5)
- the physical and pharmacological management of depression with a seasonal pattern (Section 11.6)
- dosage issues for tricyclic antidepressants (Section 11.7)
- antidepressant discontinuation symptoms (Section 11.8)
- the cardiotoxicity of antidepressants (Section 11.9)
- depression, antidepressants and suicide (Section 11.10).

This chapter updates the reviews on the effect of sex on antidepressant choice, antidepressant discontinuation symptoms, cardiotoxicity of antidepressants, and antidepressants and suicide. It includes a new review of treatments for depression with a seasonal pattern because this diagnosis was added to the scope of the updated guideline.

The review of the pharmacological management of depression in older adults was not updated because there were little new data in older adults to indicate that the existing recommendations should be amended. In addition, since the previous guideline, a separate guideline has been developed specifically for depression in adults with a chronic physical health problem, which covers many issues relevant to older people with depression (NICE, 2009c; NCCMH, 2010).

The section on depression with psychotic sypmtoms was not updated and the recommendations were left unchanged. The review of atypical depression was also not updated. However, the GDG felt that the previous recommendations should be removed since there was no reason why treatment for people whose depression had atypical features should not follow that for those with major depression. The review of low-dose versus high-dose TCAs was not updated.

11.2 THE PHARMACOLOGICAL MANAGEMENT OF DEPRESSION IN OLDER ADULTS

The following sections on the pharmacological management of depression in older adults marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

11.2.1 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 among 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 (Plummer *et al.*, 1997) 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, it is not reviewed
- augmentation of an antidepressant with lithium
- strategies for relapse prevention.

11.2.2 Use of individual antidepressants in the treatment of depression in older adults

Studies considered[153,154]

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

[153]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[154]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 (unless a study is in press or only submitted for publication, when first author only is used). Study IDs in title case refer to studies included in the previous guideline and study IDs in capital letters refer to studies found and included in this guideline update. References for studies from the previous guideline are in Appendix 18 and references for studies for the update are in Appendix 17c.

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, Mahapatra1997, Pelicier1993, Phanjoo1991, Rahman1991, Schatzberg02, Smeraldi1998). 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 1,083 patients, and tolerability data from up to 1,620 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 5 to 8 weeks long.

Clinical evidence statements[155]

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically important difference on reducing symptoms of depression in older adults:

- between amitriptyline and paroxetine (K = 2; N = 126; SMD = –0.1; 95% CI, –0.46 to 0.27)
- between SSRIs and alternative antidepressants (K = 8; N = 602; SMD = –0.01; 95% CI, –0.17 to 0.15)
- between venlafaxine and TCAs (K = 2; N = 202; SMD = 0.02; 95% CI, –0.26 to 0.29)
- between alternative antidepressants and TCAs (K = 6, N = 443; SMD = 0.00; 95% CI, –0.19 to 0.19)
- between St John's wort and fluoxetine (K = 1; N = 149; SMD = –0.04; 95% CI, –0.36 to 0.28)
- between mirtazapine and paroxetine (K = 1, N = 254; SMD = –0.12; 95% CI, –0.37 to 0.13).

There is insufficient evidence to determine if there is a clinically important difference in older adults on increasing the likelihood of achieving a 50% reduction in symptoms of depression between:

- amitriptyline and paroxetine
- venlafaxine and TCAs
- alternative antidepressants and TCAs
- St John's wort and fluoxetine
- mirtazapine and paroxetine.

[155]The forest plots can be found in Appendix 19c.

There is evidence suggesting that there is no clinically important difference between mirtazapine and paroxetine on increasing the likelihood of achieving remission in older adults (K = 1, N = 254; RR = 0.87; 95% CI, 0.73 to 1.03).

There is insufficient evidence to determine if there is a clinically important 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 important difference favouring mirtazapine over paroxetine on reducing the likelihood of older adults leaving treatment early due to side effects (K = 1, N = 254; RR = 0.57; 95% CI, 0.34 to 0.94).

There is evidence suggesting that there is no clinically important difference between alternative antidepressants and TCAs on reducing the likelihood of older adults reporting adverse effects (K = 7, N = 581; RR = 0.89; 95% CI, 0.79 to 1.02).

There is evidence suggesting that there is no clinically important difference on reducing the likelihood of older adults leaving treatment early between:

- amitriptyline and SSRIs (K = 3; N = 422; RR = 0.89; 95% CI, 0.7 to 1.12)
- SSRIs and alternative antidepressants (K = 10; N = 1115; RR = 0.96; 95% CI, 0.82 to 1.13)
- alternative antidepressants and TCAs (K = 10; N = 1058; RR = 0.97; 95% CI, 0.83 to 1.13).

There is evidence suggesting that there is no clinically important difference between SSRIs and alternative antidepressants on reducing the likelihood of older adults leaving treatment early due to side effects (K = 10; N = 1154; RR = 1; 95% CI, 0.81 to 1.23).

There is evidence suggesting that there is no clinically important difference on reducing the likelihood of older adults reporting adverse events between:

- SSRIs and alternative antidepressants (K = 8; N = 717; RR = 0.95; 95% CI, 0.85 to 1.05)
- phenelzine and nortriptyline (K = 1; N = 60; RR = 0.97; 95% CI, 0.87 to 1.09)
- mirtazapine and paroxetine (K = 1, N = 254; RR = 0.97; 95% CI, 0.86 to 1.09).

There is insufficient evidence to determine if there is a clinically important 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 important difference between SSRIs and TCAs on reducing symptoms of depression in older inpatients (K = 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 important difference favouring paroxetine over amitriptyline on reducing the likelihood of older adults in primary care reporting adverse effects (K = 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.

11.2.3 Augmentation of an antidepressant with lithium in older adults

Studies considered[156,157]

In the review of lithium augmentation[158] 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.

Clinical evidence statements[159]

Effect of treatment on efficacy outcomes

There is some evidence suggesting that there is a clinically important difference favouring nortriptyline alone over nortriptyline plus lithium on increasing the likelihood of achieving remission in older adults (K = 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 important difference favouring nortriptyline alone over nortriptyline plus lithium on reducing the likelihood of older adults leaving treatment early (K = 1; N = 44; RR = 5.02; 95% CI, 1.26 to 20.07).

There is insufficient evidence to determine if there is a clinically important difference between nortriptyline plus lithium and nortriptyline alone on reducing the likelihood of older adults leaving treatment early due to side effects (K = 1; N = 44; RR = 5.48; 95% CI, 0.72 to 41.82).

11.2.4 Relapse prevention in older adults

Studies considered[160,161]

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,

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[156]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[157]Study IDs in title case refer to studies included in the previous guideline. References for these studies guideline are in Appendix 18.

[158]See Chapter 12, Section 12.3.5.

[159]The forest plots can be found in Appendix 19c.

[160]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[161]Study IDs in title case refer to studies included in the previous guideline. References for these studies are in Appendix 18.

Klysner2002, Wilson2003), one in patients in primary care (Wilson2003) and four in outpatients (Alexopoulos00, Cook1986, Georgotas1989, Klysner2002).

Clinical evidence statements[162]

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 important difference favouring continuing treatment with antidepressants over discontinuing antidepressants on reducing the likelihood of relapse in elderly patients (K = 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.

11.2.5 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.**

11.2.6 From evidence to recommendations

The review of pharmacological treatments for older adults was not updated because there were little new data, and the overall conclusions in the previous guideline were that management of older adults should follow general principles. These were based on the fact that older people tend to metabolise drugs more slowly and are more likely to be taking concomitant medication and to be in poorer physical health than younger people. These recommendations are unchanged. However, they have been amended to bring them up to date with current NICE style. Since the publication of the previous guideline, a guideline on the management of dementia has been published

[162]The forest plots can be found in Appendix 19c.

(NICE, 2006b). This covers the management of depression comorbid with dementia and, therefore, recommendations relating to this topic have been removed.

11.2.7 Recommendation

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.3 THE EFFECT OF SEX ON ANTIDEPRESSANT CHOICE

11.3.1 Review of the evidence

Although the female preponderance in the prevalence of unipolar depression has been well established (Weissman *et al.*, 1993), relatively little attention has been paid to gender differences in treatment response to antidepressant medication. A meta-analysis of 35 studies published between 1957 and 1991 that reported imipramine response rates separately by sex reported that men responded more favourably to imipramine than women (Hamilton *et al.*, 1996). Some studies since then have suggested that younger women may respond preferentially to SSRIs over noradrenaline reuptake inhibitors (TCAs, maprotiline, reboxetine) with predominantly no difference found for men (Kornstein *et al.*, 2000; Martenyi *et al.*, 2001; Joyce *et al.*, 2002; Baca *et al.*, 2004; Berlanga & Flores-Ramos, 2006). This may be accounted for by a poorer tolerability of TCAs in younger women (Kornstein *et al.*, 2000; Joyce *et al.*, 2002; Baca *et al.*, 2004). Results are inconsistent as to whether men respond better than women to TCAs (Quitkin *et al.*, 2001). A study comparing TCAs and MAOIs found that in patients with atypical depression and associated panic attacks, women showed a more favourable response to MAOIs and men to TCAs (Davidson & Pelton, 1986).

However, the data are not consistent, and several studies have failed to show any significant effect of sex on antidepressant response, for example, when SSRIs were compared with clomipramine in inpatients (Hildebrandt *et al.*, 2003), and no effect of sex has been found with venlafaxine (Hildebrandt *et al.*, 2003), duloxetine (Kornstein *et al.*, 2006), and amfebutamone (bupropion) (Papakostas *et al.*, 2007). A large observational study of sertraline treatment in over 5,000 patients failed to find a clinically relevant effect of sex on response to treatment (Thiels *et al.*, 2005).

Taken as a whole, no convincing data showing differential benefits for antidepressants based on sex have accrued since the previous guideline; the GDG considered that the previous recommendations should be removed from the guideline update. However, recommendations from the guideline *Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance* (NICE, 2007e) should be considered when treating women of childbearing age who have depression.

11.3.2 Recommendation

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.4 THE PHARMACOLOGICAL MANAGEMENT OF DEPRESSION WITH PSYCHOTIC SYMPTOMS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.5 THE PHARMACOLOGICAL MANAGEMENT OF ATYPICAL DEPRESSION

The following sections on the pharmacological management of atypical depression marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

11.5.1 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,

[168]The evidence for this recommendation has not been updated since the previous NICE guideline. Any wording changes have been made for clarification only.

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 MAOIs than TCAs. However, the significance of atypical features remains controversial as does the preferential treatment response to MAOIs. The absence of specific diagnostic criteria has limited the ability to assess the aetiology, prevalence and validity of the condition.

11.5.2 Studies considered[169,170]

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 of atypical depression using drugs not reviewed for this guideline are not included.**

No new studies were found in the update search for the guideline update.

**In all, three studies from other reviews were of atypical depression (Mcgrath00, 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.

11.5.3 Clinical evidence statements[171]

Effect of treatment on efficacy

In people with atypical depression there is some evidence suggesting that there is a clinically important difference favouring phenelzine over other antidepressants (imipramine/ desipramine and fluoxetine) on increasing the likelihood of achieving a 50% decrease in symptoms of depression by the end of treatment as measured by the HRSD (K = 2; N = 232; RR= 0.69; 95% CI, 0.52 to 0.9).

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[169]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[170]Study IDs in title case refer to studies included in the previous guideline. References for these studies are in Appendix 18.

[171]The forest plots can be found in Appendix 19c.

Factors influencing choice of antidepressants

In people with atypical depression there is insufficient evidence to determine if there is a clinically important difference between phenelzine and other antidepressants on:

- increasing the likelihood of patients achieving remission by the end of treatment as measured by the HRSD (K = 2; N = 232; Random effects RR = 0.83; 95% CI, 0.39 to 1.75)
- reducing symptoms of depression as measured by the HRSD (K = 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 important difference favouring phenelzine over TCAs (imipramine/desipramine) on:

- increasing the likelihood of patients achieving a 50% decrease in symptoms of depression by the end of treatment as measured by the HRSD (K = 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 (K = 1; N = 192; RR = 0.65; 95% CI, 0.49 to 0.87)
- reducing symptoms of depression as measured by the HRSD (K = 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 important difference between phenelzine and fluoxetine on reducing symptoms of depression by the end of treatment as measured by the HRSD (K = 1; N = 40; WMD = 0.20; 95% CI, –2.11 to 2.51).

There is insufficient evidence to determine if there is a clinically important 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 important 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.

11.5.4 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.**

11.5.5 From evidence to recommendations

The previous guideline recommended treatment with an SSRI for people with atypical depression. Since this is the treatment of choice for all people with depression, the

guideline group decided to remove the recommendation from the updated guideline. They also considered that the other recommendations for treating atypical depression were adequately covered elsewhere in the guideline (cautions about the use of phenelzine, and referring to a mental health specialist), and that no special management of people with atypical depression could be recommended.

11.5.6 Recommendation

11.5.6.1 See recommendation 11.3.2.1.

11.6 THE PHYSICAL AND PHARMACOLOGICAL MANAGEMENT OF DEPRESSION WITH A SEASONAL PATTERN

11.6.1 Introduction

The term seasonal affective disorder (SAD), introduced by Rosenthal and colleagues (1984) to describe recurrent depressions that have a seasonal pattern and occur annually at the same time each year, includes bipolar depression but most people affected have recurrent unipolar depression (70 to 80%). Winter depression with a seasona pattern is far more common than summer depression with a seasonal pattern. DSM–IV includes criteria for a seasonal pattern for depressive episodes whereas only provisional criteria are given in the research version of ICD–10. The characteristic quality of major depression with a seasonal pattern is that symptoms usually present during the winter and remit in the spring. The symptoms of depression with a seasonal pattern do not clearly delineate it from other types of depression but in reported samples decreased activity was nearly always present and atypical depressive symptoms were common, particularly increased sleep, weight gain and carbohydrate craving.

Depression with a seasonal pattern as a separate diagnosis has been less accepted in Europe than North America, and an alternative view is that major depression with a seasonal pattern is an extreme form of a dimensional 'seasonality trait' rather than a specific diagnosis with so-called 'subsyndromal major depression with a seasonal pattern' appearing to be common. Nevertheless there are some patients with recurrent major depression who experience a seasonal pattern to their illness, at least for a time. There also appear to be people who experience seasonal fluctuations in mood that do not reach criteria for major depression.

The hypothesis that light therapy (that is, increasing the amount or duration of light exposure) might be an effective treatment is based on the presumption that depression with a seasonal pattern is caused by a lack of light in the winter months. There have subsequently been a number of controlled studies and meta-analyses (for example, Golden *et al.*, 2005) that have concluded that light therapy may be effective. There has been little research into other treatments in patients with depression with a seasonal pattern.

11.6.2 Databases searched and the inclusion/exclusion criteria

Information about the databases searched for published trials and the inclusion/exclusion criteria used are presented in Table 91. Details of the search strings used are in Appendix 8.

11.6.3 Light therapy for depression with a seasonal pattern

Depression with a seasonal pattern was not included in the scope of the previous guideline. Light therapy, which has been developed as a treatment specifically for major depression with a seasonal pattern, was therefore not reviewed, but has been included here as an additional review for the guideline update. For this review both published and unpublished RCTs investigating light therapy in patients diagnosed with major or subsyndromal major depression with a seasonal pattern were sought. There are a range of methods for administering light therapy; this review included a range of light treatments such as a light box, light room or visor and dawn simulation. Trials comparing a light treatment with a control condition, another light treatment or light administered at different times of day were included in this review.

A special adviser was consulted regarding a number of issues for this review (see Appendix 3). He advised the GDG that 5,000 lux hours[172] per day is a reasonable

Table 91: Databases searched and inclusion/exclusion criteria for clinical effectiveness of psychological treatments

Electronic databases	MEDLINE, EMBASE, PsycINFO, CINAHL
Date searched	Database inception to January 2008
Update searches	July 2008; January 2009
Study design	RCT
Population	People with a diagnosis of depression with a seasonal pattern according to DSM, ICD or similar criteria, or seasonal affective disorder according to Rosenthal's (1984) criteria or subsyndromal major depression with a seasonal pattern as indicated by score on seasonal depression scale
Treatments	Light therapy, dawn simulation, antidepressants, psychological therapies, other physical treatments

[172]Lux is a standard measure of illuminance; 1 lux is equal to 1 lumen per square metre [lumen is the unit of luminous flux].

minimum dose for light box treatment, but that a minimum effective dose of light administered by a light visor has not yet been established. For the control light condition a placebo light of not more than 300 lux is appropriate. He suggested that a minimum trial duration of a week would be reasonable for evaluating the efficacy of light treatment. His advice was also sought regarding dawn simulation; he suggested that it would be informative to include this type of light treatment in the review and that a simulation of around an hour and a half peaking at 250 lux is an appropriate minimum, with a control condition of a light of less than 2 lux.

Studies considered[173]

In total, 61 trials were found from searches of electronic databases. Of these, 19 were included and 42 were excluded. The most common reasons for exclusion were that papers were not RCTs or participants did not have a diagnosis of depression or subsyndromal depressive symptoms with a seasonal pattern. In addition, studies that used a cross-over design (where participants serve as their own controls by receiving both treatments) were not used unless pre-crossover data were available.

The studies that were found by the search and included in this review varied considerably in methodology. The intensity and duration of light, time of day, mode of administration of light, and the comparison conditions were different across studies. A range of outcomes were reported by the included studies, including the HRSD (termed 'typical' depression rating scale to distinguish it from scales measuring depression with seasonal pattern symptoms), and scales adapted for measuring symptoms in depression with a seasonal pattern. These included the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH) for major depression with a seasonal pattern (Williams *et al.*, 1988), which combines the HRSD with an additional eight items relevant to depression with a seasonal pattern. Some studies report the eight additional items separately. Both typical and atypical symptoms were measured using clinician- and self-rated scales. All data were extracted and can be seen in the full evidence profiles and forest plots (Appendix 16c and Appendix 19c, respectively). Only data for the SIGH for major depression with a seasonal pattern (clinician- and self-rated) are presented here.

Data were available to compare light therapy with a range of control conditions including waitlist, attentional controls and active treatment controls. In addition administration of light in the morning versus evening was compared and dawn simulation was compared with attentional control and with bright light. One study included a combination treatment of light and CBT and one trial reported on light therapy for relapse prevention.

Summary study characteristics of the included studies are presented in Table 92 and Table 93 with full details in Appendix 17c, which also includes details of excluded studies.

[173]Study IDs in capital letters refer to studies found and included in this guideline update.

Table 92: Summary study characteristics of light therapy studies versus control and morning light versus afternoon/evening light

	Light versus waitlist control	Light versus attentional control	Light versus active treatment control	Morning versus afternoon/evening light
No. trials (total participants)	2 RCTs (82)	8 RCTs (401)	4 RCTs (243)	4 RCTs (144)
Study IDs	(1) RASTAD2008 (2) ROHAN2007	(1) DESAN2007 (2) EASTMAN1998 (3) JOFFE1993 (4) LEVITT1996 (5) ROSENTHAL1993 (6) STRONG2008 (7) TERMAN1998† (8) WILEMAN2001	(1) LAM2006F (2) MARTINEZ1994 (3) ROHAN2004 (4) ROHAN2007	(1) AVERY2001A (2) EASTMAN1998 (3) LAFER1994‡ (4) TERMAN1998†
N/% female	(1) 51/80 (2) 31/84	(1) 26/77 (2) 81/88 (3) 67/87 (4) 44/72 (5) 55/84 (6) 30/78 (7) 39/80 (8) 59/88	(1) 96/67 (2) 20/65 (3) 26/92 (4) 61/94	(1) 31/90 (2) 81/85 (3) 32/65 (4) 39/80

Continued

Table 92: (*Continued*)

	Light versus waitlist control	**Light versus attentional control**	**Light versus active treatment control**	**Morning versus afternoon/evening light**
Mean age	(1) 46 (2) 45	(1) 46 (2) 37 (3) 40 (4) 35 (5) 42 (6) 44 (7) 39 (8) 41	(1) 43 (2) 46 (3) 51 (4) 45	(1) 40 (2) 37 (3) 35 (4) 39
Diagnosis	(1)–(2) MDD with seasonal pattern (DSM–IV)	(1) MDD with seasonal pattern (DSM–IV) (2) Major depression with a seasonal pattern (Rosenthal) (3) MDD or bipolar with seasonal pattern (DSM–III-R) or major depression with a seasonal pattern (Rosenthal) (4) MDD with seasonal pattern (DSM–III-R) (5) Major depression with a seasonal pattern (Rosenthal)	(1) MDD or bipolar with seasonal pattern (DSM–IV) (2) MDD with seasonal pattern (DSM–III-R) (3)–(4) MDD with seasonal pattern (DSM–IV)	(1) Subsyndromal major depression with a seasonal pattern (2) Major depression with a seasonal pattern (Rosenthal) (3) Major depressive episode with a seasonal pattern (DSM–III-R) (4) Mood disorder with major depression with a seasonal pattern (DSM–III-R)

		(6) MDD with seasonal pattern (DSM–IV) (7) Mood disorder with major depression with a seasonal pattern (DSM–III-R) (8) MDD with seasonal pattern (DSM–IV)		
Light therapy	(1) Fluorescent light room (2) Fluorescent light box	(1) LED Litebook device (2) Fluorescent light box (3) Light visor (4a) Fluorescent light box (4b) LED visor (5) Light visor (6) Narrow-band blue light panel (7)–(8) Light box	(1) Fluorescent light box + placebo pill (2) Light box + hypericum (3) Light box (4) Fluorescent light box	(1) Light box used between 7 am–12 pm (2) Fluorescent light box used as soon as possible after waking (3) Bright light for 2 hours (4) Light box 10 minutes after waking
Lux hours/day	(1) Varies 1650–8600 (2) 15000 in 1st week, varies after week 1	(1) 675 (2) 9000 (3) Mean 1762 (4a) Mean 3800 (4b) Mean 323 (5) 3000 or 6000 (6) 470 nm 176 lux X 45 minutes (7) 10000	(1) 5000 (2) 3000 (3) 15000 (4) 15000 in 1st week, varies after week 1	(1) 5000 (2) 9000 (3) 2,500 (4) 10000

Continued

Table 92: (*Continued*)

	Light versus waitlist control	Light versus attentional control	Light versus active treatment control	Morning versus afternoon/evening light
		(8) 5000 in 1st week, 7500 in 2nd week, 10000 in last 2 weeks		
Comparator(s)	(1)–(2) Waitlist	(1)–(2) Deactivated negative ion generator (3) Dim 67 lux light visor (4a) Light box producing no light (4b) Visor producing no light (5) Dim 400 lux light visor (6) Red light (7) Low-density negative ions (8) Dim 500 lux red light box	(1) Dim 100 lux light + 20 mg/day fluoxetine (2) Dim light + hypericum (3) Group CBT/light + group CBT (4) Group CBT	(1) Light box used between 12–5 p.m. (2) Fluorescent light box used within 1 hour of bedtime (3) Bright light for 2 hours (4) Light box 2–3 hours before bedtime
Length of treatment (days)	(1) 21 (2) 42	(1)–(2) 28 (3)–(4) 14 (5) 7 (6) 21 (7) 14 (8) 28	(1) 56 (2) 28 (3)–(4) 42	(1) 14 (2) 28 (3) 7 (4) 14

*3-armed trial, †5-armed trial and ‡3-armed trial but 1 arm not used (bright light alternating morning and evening).

Table 93: Summary study characteristics of dawn simulation and relapse prevention studies

	Dawn simulation versus attentional control	Light versus dawn simulation	Relapse prevention
No. trials (total participants)	3 RCTs (139)	2 RCTs (112)	1 RCT (46)
Study IDs	(1) AVERY1993 (2) AVERY2001 (3) TERMAN2006	(1) AVERY2001 (2) TERMAN2006	(1) MEESTERS 1999
N/% female	(1) 27/70 (2) 62/87 (3) 50/79	(1) 64/88 (2) 48	(1) 46/71
Mean age	(1) 35 (2) 41 (3) 40	(1) 41 (2) 40	(1) 40
Diagnosis	(1) Major depression with a seasonal pattern (Rosenthal) (2) MDD or bipolar with seasonal pattern (DSM–IV) (3) MDD with seasonal pattern (DSM–III-R)	(1) MDD or bipolar with seasonal pattern (DSM–IV) (2) MDD with seasonal pattern (DSM–III-R)	(1) MDD with seasonal pattern (DSM–IV)
Light therapy	(1) Gradual dawn simulation over 2 hours (2) Gradual dawn simulation over 1.5 hours (3) Gradual dawn simulation over 3.5 hours	(1)–(2) Light box	(1) Light visor
Lux hours/day	(1)–(3) 250 lux peak intensity	(1) 5000 (2) 10000	(1) 1250
Comparator	(1) Rapid dim 0.2 lux dawn (2) Dim 0.5 lux red dawn (3) Pulse dawn 250 lux 30 minutes	(1) Gradual dawn simulation over 1.5 hours peaking at 250 lux (2) Gradual dawn simulation over 3.5 hours	(1a) No treatment (1b) Dim 0.18 lux infrared light
Length of treatment (days)	(1) 7 (2) 42 (3) 21	(1) 42 (2) 21	(1) 182

Clinical evidence

Bright light versus waitlist or attentional control

Compared with waitlist control, bright light (either light room or light box) shows a strong effect on symptoms in depression with a seasonal pattern although there are few studies. Compared with attentional controls, such as deactivated negative ion generator, dim red light, and sham light boxes, bright light (either via light box or light visor) shows a small effect on symptoms in depression with a seasonal pattern that was not clinically important. Evidence from the important outcomes and overall quality of evidence are presented in Table 94. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Bright light versus active treatment control

There were data to compare light therapy with group CBT, light therapy plus CBT, and dim light plus fluoxetine. There was also a study comparing light therapy plus St John's wort with dim light plus St John's wort.

Compared with group CBT (tailored to depression with a seasonal pattern) bright light therapy was no better in terms of reducing depressive symptoms in depression with a seasonal pattern, although the effect size is not statistically significant and was graded low quality. However, more participants achieved remission with bright light therapy than with group CBT (52% compared with 37.5%), although the result is not clinically important. Similarly, light therapy appeared to be more acceptable than group CBT with fewer people leaving treatment early (8% compared with 16.7%) although the effect size is not statistically significant. Treatment lasted for 6 weeks.

Combination treatment (bright light plus CBT) was more effective than light therapy alone on both the SIGH for major depression with a seasonal pattern and the BDI, although the effect sizes were not statistically significant. Roughly equal numbers of participants left treatment early.

There appeared to be little difference between bright light therapy and fluoxetine (20 mg) on efficacy outcomes (both treatments given with a sham treatment mimicking the other). Treatment lasted for 8 weeks.

There was no evidence for the efficacy of light therapy combined with St John's wort compared with a sham light condition plus St John's wort. There was only a single small 4-week study (n = 20).

Evidence from the important outcomes and overall quality of evidence are presented in Table 95. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Morning light versus afternoon/evening light

Three studies compared light therapy administered in the morning compared with light therapy in the afternoon or evening, one of which was in participants with subsyndromal major depression with a seasonal pattern. There were no significant differences in outcome measures for those given light therapy in the morning compared with those given light therapy in the afternoon or evening. Evidence from the important outcomes and overall quality of evidence are presented in Table 96. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Table 94: Summary evidence profile for bright light versus waitlist or attentional controls

	Bright light versus waitlist control	**Bright light versus attentional control**
Leaving treatment early	RR 0.95 (0.21 to 4.32) (7.1 versus 7.5%)	RR 0.88 (0.50 to 1.54) (13.4 versus 14.5%)
Quality	Low	Low
Number of studies; participants	K = 2; n = 82	K = 6; n = 266
Forest plot number	Pharm SAD 01.01	Pharm SAD 02.01
Reported side effects	Not reported	RR 0.98 (0.73 to 1.32) (55.6 versus 58.3%)
Quality	–	Low
Number of studies; participants	–	K = 2; n = 81
Forest plot number	–	Pharm SAD 02.03
Clinician-rated endpoint (SIGH-SAD)	WMD -10.4 (-15.99 to -4.81)	WMD -3.07 (-6.71 to 0.58)
Quality	Moderate	Low
Number of studies; participants	K = 1; n = 31	K = 8; n = 300
Forest plot number	Pharm SAD 01.04	Pharm SAD 02.04
Self-rated endpoint (SIGH-SAD-SR)	WMD -12.8 (-18.52 to -7.08)	Not reported
Quality	Moderate	–
Number of studies; participants	K = 1; n = 44	–
Forest plot number	Pharm SAD 01.03	–
Non-remission (based on SIGH-SAD-SR)	RR 0.53 (0.38 to 0.74) (47.6 versus 90%)	RR 0.89 (0.66 to 1.2) (56.3 versus 61.3%)
Quality	High	Low
Number of studies; participants	K = 2; n = 82	K = 6; n = 336
Forest plot number	Pharm SAD 01.10	Pharm SAD 02.08
Non-response (based on SIGH-SAD	RR 0.50 (0.34 to 0.73) (50 versus 100%)	RR 0.86 (0.64 to 1.15) (45.4 versus 53.8%)
Quality	Moderate	Low
Number of studies; participants	K = 1; n = 51	K = 7; n = 354
Forest plot number	Pharm SAD 01.11	Pharm SAD 02.09

Table 95: Summary evidence profile for bright light versus active treatment control

	Light box versus group CBT	Light box versus light box + group CBT	Light box + placebo pill versus dim light box + fluoxetine	Light box + St John's wort versus dim light + St John's wort
Leaving treatment early	RR 0.53 (0.12 to 2.31) (8 versus 16.7%)	RR 0.92 (0.17 to 4.91) (8 versus 8.7%)	RR 1.14 (0.45 to 2.90) (16.7 versus 14.6%)	Not reported
Quality	Moderate	Moderate	Moderate	–
Number of studies; participants	K = 2; n = 49	K = 2; n = 48	K = 1; n = 96	–
Forest plot number	Pharm SAD 03.01	Pharm SAD 04.01	Pharm SAD 03.01	–
Reported side effects	Not reported	Not reported	RR 1.03 (0.82 to 1.29) (77.1 versus 75%)	Not reported
Quality	–	–	Moderate	–
Number of studies; participants	–	–	K = 1; n = 96	–
Forest plot number	–	–	Pharm SAD 03.04	–
Clinician-rated mean endpoint	WMD -0.2 (-6.5 to 6.1) (SIGH-SAD)	WMD 4.2 (-0.52 to 8.92) (SIGH-SAD)	WMD -0.00 (-3.88 to 3.88) (SIGH-SAD)	SMD -0.32 (-1.2 to 0.57) (HRSD)
Quality	Low	Moderate	High	Low
Number of studies; participants	K = 1; n = 31	K = 1; n = 31	K = 1; n = 96	K = 1; n = 20
Forest plot number	Pharm SAD 03.05	Pharm SAD 04.03	Pharm SAD 03.05	Pharm SAD 03.06

Self-rated mean endpoint	WMD -0.7 (-7.16 to 5.76) (BDI)	SMD 2.3 (-2.47 to 7.07) (BDI)	WMD -1.6 (-5.68 to 2.48) (BDI)	Not reported
Quality	Low	Low	Low	–
Number of studies; participants	K = 1; n = 31	K = 1; n = 31	K = 1; n = 96	–
Forest plot number	Pharm SAD 03.08	Pharm SAD 04.06	Pharm SAD 03.08	–
Non-remission (based on SIGH-SAD-SR)	RR 0.77 (0.46 to 1.28) (48 versus 62.5%)	RR 2.22 (0.92 to 5.32) (48 versus 21.7%)	RR 1.09 (0.57 to 1.76) (50 versus 45.8%)	Not reported
Quality	High	High	Low	–
Number of studies; participants	K = 2; n = 49	K = 2; n = 48	K = 1; n = 96	–
Forest plot number	Pharm SAD 03.09	Pharm SAD 04.07	Pharm SAD 03.09	–
Non-response (based on SIGH-SAD-SR)	Not reported	Not reported	RR 1 (0.57 to 1.76) (33.3 versus 33.3%)	Not reported
Quality	–	–	Low	–
Number of studies; participants	–	–	K = 1; n = 96	–
Forest plot	–	–	03.10	–

Table 96: Summary evidence profile for morning light versus evening light

	Overall results	**Subsyndromal major depression with a seasonal pattern only**
Leaving treatment early	RR 0.98 (0.41 to 2.35) (12.1 versus 12.5%)	Not reported
Quality	Moderate	–
Number of studies; participants	K = 3; n = 130	–
Forest plot number	Pharm SAD 05.01	–
Reported side effects	RR 0.47 (0.05 to 4.65) (6.3 versus 13.3%)	RR 0.47 (0.05 to 4.65) (6.3 versus 13.3%)
Quality	Low	Low
Number of studies; participants	K = 1; n = 31	K = 1; n = 31
Forest plot number	Pharm SAD 05.03	Pharm SAD 05.03
Clinician-rated mean endpoint	WMD -1.38 (-5.49 to 2.73) (SIGH-SAD)	WMD 0.6 (-3.89 to 5.09) (SIGH-SAD)
Quality	Low	Low
Number of studies; participants	K = 2; n = 68	K = 1; n = 30
Forest plot number	Pharm SAD 05.04	Pharm SAD 05.04
Self-rated mean endpoint	WMD –0.9 (–4.66 to 2.86) (BDI)	Not reported
Quality	Low	–
Number of studies; participants	K = 1; n = 65	–
Forest plot number	Pharm SAD 05.07	–
Non-remission (based on SIGH-SAD-SR)	RR 1.0 (0.69 to 1.45) (54 versus 54.2%)	Not reported
Quality	Low	–
Number of studies; participants	K = 2; n = 98	–
Forest plot number	Pharm SAD 05.08	–
Non-response (based on SIGH-SAD-SR)	RR 1.0 (0.51 to 1.98) (44 versus 42.9%)	RR 0.52 (0.23 to 1.20) (31.3 versus 60%)
Quality	Low	Moderate
Number of studies; participants	K = 3; n = 129	K = 1; n = 31
Forest plot number	Pharm SAD 05.09	Pharm SAD 05.09

Dawn simulation versus attentional control or light therapy

Three studies compared dawn simulation with an attentional control. There was some evidence that dawn simulation improved symptoms of depression but it was not clinically important and was not supported by other outcomes including the major depression with a seasonal pattern subscale. Similarly, there was no evidence of superiority of dawn simulation over regular light therapy. Evidence from the important outcomes and overall quality of evidence are presented in Table 97. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Table 97: Summary evidence profile for dawn simulation studies

	Dawn simulation versus attentional control	**Light therapy versus dawn simulation**
Leaving treatment early	RR 0.27 (0.08 to 0.92) (2.9 versus 14.1%)	RR 3.72 (0.62 to 22.22) (8.9 versus 1.8%)
Quality	Low	Moderate
Number of studies; participants	K = 3; n = 141	K = 2; n = 112
Forest plot number	Pharm SAD 06.01	Pharm SAD 07.01
Reported side effects	RR 5.57 (0.77 to 40.26) (42.9 versus 7.7%)	Not reported
Quality	Low	–
Number of studies; participants	K = 1; n = 27	–
Forest plot number	Pharm SAD 06.04	–
Clinician-rated mean endpoint	SMD -0.53 (-1.62 to 0.15) (HRSD) WMD -2.20 (-7.52 to 3.11) (SAD subscale)	WMD -0.9 (-4 to 2.2) (HRSD) WMD -1.8 (-6.98 to 3.38) (SAD subscale)
Quality	Moderate (HRSD) Very low (SAD subscale)	Very low (HRSD) Low (SAD subscale)
Number of studies; participants	K = 2; n = 73	K = 1; n = 45
Forest plot number	Pharm SAD 06.05/06	Pharm SAD 07.06/07
Self-rated mean endpoint	Not reported	Not reported
Quality	–	–

Continued

Table 97: (*Continued*)

	Dawn simulation versus attentional control	**Light therapy versus dawn simulation**
Number of studies; participants	–	–
Forest plot number	–	–
Non-remission (based on SIGH-SAD)	RR 0.9 (0.46 to 1.78) (44.6 versus 50%)	RR 1.19 (0.70 to 2.00) (53.6 versus 44.6%)
Quality	Low	Very low
Number of studies; participants	K = 2; n = 114	K = 2; n = 112
Forest plot number	Pharm SAD 06.07	Pharm SAD 07.04
Non-response (based on SIGH-SAD)	RR 0.71 (0.34 to 1.48) (25 versus 38%)	RR 1.45 (0.82 to 2.58) (35.7 versus 25%)
Quality	Moderate	Moderate
Number of studies; participants	K = 2; n = 114	K = 2; n = 112
Forest plot number	Pharm SAD 06.08	Pharm SAD 07.05

Prevention of future episodes using light therapy

One study compared bight light therapy with a control treatment and with no treatment as relapse prevention in people who had a history of depression with a seasonal pattern but had not yet developed symptoms. This showed that those receiving light therapy were less likely to develop symptoms of depression compared with those receiving no treatment. However, those using the infrared light visor were less likely to develop symptoms of depression than those using the bright white light visor. Neither finding was clinically important. Evidence from the important outcomes and overall quality of evidence are presented in Table 98. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Clinical summary

Although there are a large number of studies that address the efficacy of light treatment in people with depression that follows a seasonal pattern, these studies are difficult to interpret due to methodological differences. The doses and colours of light, methods of delivery, comparator treatments, and clinical populations included in studies are diverse. While bright light is clearly more effective than waitlist control, it is unclear if this is more than a placebo effect (see discussion on the placebo effect in Chapter 2, Section 2.4.3). Studies that compare bright light with other treatments that are not known to be effective give equivocal results. There are too few data

Table 98: Summary evidence profile for relapse prevention using bright light

	Bright white light visor versus no treatment control	**Bright white light visor versus infrared light visor**
Leaving treatment early	RR 2.22 (0.29 to 17.27) (22.2 versus 10%)	RR 1.33 (0.35 to 5.13) (22.2 versus 16.7%)
Quality	Low	Low
Number of studies; participants	K = 1; n = 28	K = 1; n = 36
Forest plot number	Pharm SAD 08.01	Pharm SAD 08.01
Relapse (BDI >13 for 2 consecutive weeks)	RR 0.63 (0.36 to 1.09) (50 versus 80%)	RR 2.25 (0.84 to 5.99) (50 versus 22.2%)
Quality	Moderate	Moderate
Number of studies; participants	K = 1; n = 28	K = 1; n = 36
Forest plot number	Pharm SAD 08.02	Pharm SAD 08.02

relating to active controls to determine non-inferiority, and few systematic data relating to side effects. In clinical practice, where bright light is used, a minimum daily dose of 5,000 lux administered in the morning during the winter months is the most common treatment strategy. The most common side effect seen is mild agitation.

11.6.4 Other therapies for depression with a seasonal pattern

Studies considered[174]

In total, 14 trials of interventions other than bright light were found, mostly of antidepressants, of which five met inclusion criteria for a review of acute-phase treatment, one for a review of continuation treatment in people who had responded to open-label treatment, and three (published in the same paper) for a review of prevention in people with a history of depression with a seasonal pattern. Summary study characteristics of the included studies are presented in Table 99, with full details in Appendix 17c, which also includes details of excluded studies.

[174]Study IDs in title case refer to studies included in the previous guideline and study IDs in capital letters refer to studies found and included in this guideline update. References for studies from the previous guideline are in Appendix 18.

Table 99: Summary study characteristics for interventions other than bright light for major depression with a seasonal pattern

	Acute phase treatments	Continuation treatment	Prevention treatment
No. trials (total participants)	5 RCTs (346)	1 RCTs (23)	3 RCTs (1061)
Study IDs	(1) LAM1995 (2) LINGJAERDE1993 (3) MOSCOVITCH2004 (4) PARTONEN1996 (5) TERMAN1995	(1) SCHLAGER1994*	(1) MODELL2005 study 1 (2) MODELL2005 study 2 (3) MODELL2005 study 3
N/% female	(1) 68/66 (2) 34/74 (3) 187/78 (4) 32/66 (5) 25/88	(1) 23 (not available)	(1) 277/72 (2) 311/67 (3) 473/68
Mean age	(1) 36 (2) 43 (3) 40 (4) 44 (5) 38	(1) Not given	(1) 42 (2) 42 (3) 41
Diagnosis	(1) Recurrent major depressive episodes with seasonal pattern (2) Mood disorder with seasonal pattern (3) 79% major depression with seasonal pattern; 13%	(1) Responders to initial treatment for recurrent major depressive episodes with seasonal pattern	(1)–(3) History of MDD with seasonal pattern (DSM-IV)

	depression NOS with seasonal pattern; 7% bipolar disorder with seasonal pattern; 2% bipolar disorder NOS with seasonal pattern (4) 100% MDD; 18% mood disorder with seasonal pattern (5) Major depression with a seasonal pattern, MDD with seasonal pattern, or bipolar disorder NOS with seasonal pattern - % not clear		
Treatment	(1) Fluoxetine 20 mg (2) Moclobemide 400 mg (3) Sertraline 50–200 mg (4) Moclobemide 300–450 mg (5) High density negative ions	(1) Propanolol 33 mg	(1) Buspirone 150–300 mg (2)–(3) Bupropion XL 150–300 mg
Comparator	(1)–(3) Placebo (4) Fluoxetine 20–40 mg (5) Low density negative ions	(1) Placebo	(1)–(3) Placebo
Length of treatment (days)	(1) 5 weeks (2) 3 weeks (3) 8 weeks (4) 6 weeks (5) 3 weeks	(1) 2 weeks	(1) 6 months (2)–(3) Unclear

*Continuation trial.

Clinical evidence

Acute-phase treatments

The data for acute-phase treatment comparing antidepressants with placebo were largely inconclusive, although on one outcome (response) there appeared to be little difference. Acceptability and tolerability data were inconclusive. There was no evidence to suggest a difference between moclobemide and fluoxetine, which was the only head-to-head evidence available. There was some evidence to suggest that high ion density was more effective than low ion density, although there was only one study. Evidence from the important outcomes and overall quality of evidence are presented in Table 100. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Table 100: Summary evidence profile for acute-phase treatments (not light therapy) for major depression with a seasonal pattern

	Antidepressants versus placebo	**Antidepressants versus antidepressants**	**High ion density versus low ion density**
Non-response (based on SIGH-SAD)	RR 0.82 (0.63 to 1.05) (44.2 versus 54%)	Not reported	RR 0.49 (0.24 to 1) (41.7 versus 84.6%)
Quality	High	–	Moderate
Number of studies; participants	K = 2; n = 255	–	K = 1; n = 25
Forest plot number	Pharm SAD 09.01	–	Pharm SAD 12.01
Clinician-rated mean endpoint SIGH-SAD	SMD -0.11 (-0.65 to 0.42)	Moclobemide versus fluoxetine: WMD -1.6 (-7.01 to 3.81)	Not reported
Quality	Low	Low	–
Number of studies; participants	K = 2; n = 99	K = 1; n = 29	–
Forest plot number	Pharm SAD 09.02	Pharm SAD 11.01	–
Self-rated mean endpoint BDI	WMD -1.7 (-6.53 to 3.13)	Not reported	Not reported
Quality	Low	–	–
Number of studies; participants	K = 1; n = 68	–	–
Forest plot number	Pharm SAD 09.02	–	–

Continued

Table 100: (*Continued*)

	Antidepressants versus placebo	**Antidepressants versus antidepressants**	**High ion density versus low ion density**
Leaving treatment early	RR 0.7 (0.16 to 3.05) (18.3 versus 20.5%)	Not reported	Not reported
Quality	Very low	–	–
Number of studies; participants	K = 2; n = 221	–	–
Forest plot number	Pharm SAD 10.01	–	
Leaving treatment early due to side effects	RR 1.48 (0.63 to 3.47) (8.3 versus 5.6%)	Not reported	Not reported
Quality	Low	–	–
Number of studies; participants	K = 3; n = 289	–	–
Forest plot number	Pharm SAD 10.02	–	–

Continuation treatment and prevention of future episodes
One small study compared the [3-blocker, propanolol, with placebo for people who had responded to previous open treatment. This showed that symptoms of depression in those continuing treatment remained lower compared with those switched to placebo. Another three trials compared bupropion with placebo to prevent episodes in people with a history of depression. Treatment started before the onset of winter and continued until early spring. There was a clinically important reduction in the number of recurrences among those taking bupropion compared with the rate in those taking placebo. Evidence from the important outcomes and overall quality of evidence are presented in Table 101. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

Clinical summary
There was a lack of evidence for the effectiveness of antidepressants in the treatment of major depression with a seasonal pattern once symptoms have begun but evidence for a prophylactic effect of starting treatment before symptoms start and continuing until early spring.

11.6.5 From evidence to recommendations

The evidence for light therapy for major depression with a seasonal pattern is poorly developed, with many trials comparing different elements of treatment, including

Table 101: Summary evidence profile of continuation treatment and prevention of future episodes for people with major depression with a seasonal pattern

	Continuation treatment: propanolol versus placebo	**Prevention: bupropion versus placebo**
Efficacy outcome	HAMD-21: WMD -7 (-11.24 to -2.76)	Recurrence: RR 0.58 (0.46 to 0.72) (17% versu 29.5%)
Quality	Moderate	High
Number of studies; participants	K = 1; n = 23	K = 3; n = 1061
Forest plot number	Pharm SAD 13.01	Pharm SAD 14.01
Leaving treatment early	RR 2.57 (0.12 to 57.44) (7.7 versus 0%)	Not reported
Quality	Low	–
Number of studies; participants	K = 1; n = 24	–
Forest plot number	Pharm SAD 13.02	–

time of day, level of light and length of treatment. There is little evidence for the efficacy of bright light in the treatment of major depression with a seasonal pattern compared with placebo treatment.

The evidence for other treatments is sparse. Evidence is lacking that antidepressants are effective once symptoms have begun, but they may be worthwhile as prophylactics. For depression with a seasonal pattern practitioners should follow the guidance for depression elsewhere in this guideline.

11.6.6 Recommendations

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.6.7 Research recommendations

11.6.7.1 The efficacy of light therapy compared with antidepressants for mild to moderate depression with a seasonal pattern

How effective is light therapy compared with antidepressants for mild to moderate depression with a seasonal pattern?

Why this is important

Although the status of seasonal depression as a separate entity is not entirely clear, surveys have consistently reported a high prevalence of seasonal (predominantly winter) depression in the UK. This reflects a considerable degree of morbidity, predominantly in the winter months, for people with this condition. Light therapy has been proposed as a specific treatment for winter depression but only small, inconclusive trials have been carried out, from which it is not possible to tell whether either light therapy or antidepressants are effective in its treatment. Clarification of whether, and to what degree, treatments are effective would help to inform the decisions that people with seasonal depression and practitioners have to make about the treatment of winter depression.

This question should be answered using a randomised controlled trial design in which people with mild to moderate depression with a seasonal pattern (seasonal affective disorder) receive light therapy or an SSRI antidepressant in a partially placebo-controlled design. The doses of both light and SSRI should be at accepted or proposed therapeutic levels and there should be an initial phase over a few weeks in which a plausible placebo treatment is administered followed by randomisation to one of the active treatments. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects, and mediators and moderators of response should be investigated.

11.7 DOSAGE ISSUES FOR TRICYCLIC ANTIDEPRESSANTS

The following sections on dosage issues for tricyclic antidepressants marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

11.7.1 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.

11.7.2 Studies considered for review[175,176]

The GDG used an existing review (Furukawa *et al.*, 2002a) as the basis for this review. The Furukawa and colleagues' (2002a) 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 4 and 8 weeks' long (mean = 6 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 the 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).

11.7.3 Clinical evidence statements[177]

Effect of treatment on efficacy

There is evidence suggesting that there is no clinically important difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving remission by the end of treatment (K = 3; N = 222; RR = 0.99; 95% CI, 0.84 to 1.16).

There is insufficient evidence to determine whether there is a clinically important difference between low-dose TCAs and high-dose TCAs on increasing the likelihood of achieving a 50% reduction in symptoms of depression or on reducing symptoms of depression as measured by the HRSD.

There is insufficient evidence to determine whether there is a clinically important 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 symptoms of depression by the end of treatment as measured by the HRSD.

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[175]Details of standard search strings used in all searches are in Appendix 8. Information about each study along with an assessment of methodological quality is in Appendix 17c, which also contains a list of excluded studies with reasons for exclusions.

[176]Study IDs in title case refer to studies included in the previous guideline. References for these studies are in Appendix 18.

[177]The forest plots can be found in Appendix 19c.

Acceptability and tolerability of treatment

There is some evidence suggesting that there is a clinically important difference favouring low-dose TCAs over high-dose TCAs on leaving the study early due to side effects (K = 1; N = 151; RR = 0.35; 95% CI, 0.16 to 0.78).

There is insufficient evidence to determine whether there is a clinically important difference between low-dose TCAs and high-dose TCAs on reducing the likelihood of patients leaving treatment early.

11.7.4 Clinical summary

There is no clinically important 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 TCAs with high-dose TCAs, two reported completer data only. Patients receiving a low-dose TCA were less likely to leave treatment early due to side effects.**

11.7.5 From evidence to recommendations

This review was not updated by the GDG and the recommendation to maintain a low-dose TCA in people whose depression had responded was retained. However, the recommendation to monitor outcomes and increase dose depending on efficacy and side effects was removed since the points made are adequately covered by other recommendations in the guideline.

11.7.6 Recommendation

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.8 ANTIDEPRESSANT DISCONTINUATION SYMPTOMS

The following sections on antidepressant discontinuation symptoms marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

[178]The evidence for this recommendation has not been updated since the previous guideline. Any wording changes have been made for clarification only.

11.8.1 Introduction

There can be confusion over the use of the terms 'addiction', 'psychological dependence' and 'physical dependence' when referring to drugs. This has been associated with concern in the mind of the public about whether antidepressants (and indeed other psychotropic drugs) may be addictive. The DSM–IV (APA, 1994) definition of 'substance dependence' consists of a combination of psychological, physiological and behavioural effects that together comprise what is commonly called addiction. The diagnosis of substance dependence/addiction requires at least three of the following:

(1) tolerance (marked increase in amount; marked decrease in effect)
(2) characteristic 'withdrawal' symptoms or substance taken to relieve withdrawal
(3) substance taken in larger amount and for longer period than intended
(4) persistent desire or repeated unsuccessful attempt to quit
(5) much time/activity taken to obtain, use and recover from the substance
(6) important social, occupational, or recreational activities given up or reduced
(7) use continues despite knowledge of adverse consequences (for example, failure to fulfill role obligation, using when physically hazardous).

Physical dependence refers to the first two features (tolerance to the effect and 'withdrawal' symptoms) and substance dependence/addiction can be with or without physical dependence. There is no evidence that antidepressants cause psychological dependence or adverse behavioural and functional effects in the sense defined by criteria 3 to 7 above, and therefore antidepressants are not 'addictive' in the accepted sense of the word used to describe dependence on drugs like alcohol or opioids. There is also no good evidence to support tolerance to the therapeutic effect of antidepressants (Zimmerman & Thongy, 2007) and therefore the debate about whether or not antidepressants cause physical dependence centres on the symptoms some people experience when stopping antidepressants. It is important to understand the nature of the phenomenon and its implications for people with depression who have antidepressant treatment. In this guideline these are described as 'discontinuation symptoms', which is a term that makes no assumption about their status.

Discontinuation symptoms can be broadly divided into six groups; affective (for example, irritability), gastrointestinal (for example, nausea), neuromotor (for example, ataxia), vasomotor (for example, sweating), neurosensory (for example, paraesthesia), and other neurological (for example, dreaming; Delgrado, 2006). They may be new or hard to distinguish from some of the original symptoms of the underlying illness. By definition they must not be attributable to other causes. They are experienced by at least a third of patients (Lejoyeux *et al.*, 1996; MHRA, 2004) and are seen to some extent with all antidepressants (Taylor *et al.*, 2006). Of the commonly used antidepressants, the risk of discontinuation symptoms seems to be greatest with paroxetine, venlafaxine and amitriptyline (Taylor *et al.*, 2006). There have been prospective studies, including some RCTs and quasi-randomised trials, which have examined the effect of discontinuation in people taking paroxetine and other antidepressants. These studies suggest an increase in discontinuation symptoms in those

taking paroxetine compared with escitalopram (Baldwin *et al.*, 2006), fluoxetine (Rosenbaum *et al.*, 1998; Bogetto *et al.*, 2002; Hindmarch *et al.*, 2000; Judge *et al.*, 2002; Michelson *et al.*, 2000), sertraline (Hindmarch *et al.*, 2000; Michelson *et al.*, 2000), and citalopram (Hindmarch *et al.*, 2000). In addition two RCTs measuring discontinuation symptoms when stopping antidepressants after 8 weeks of treatment found that these were more common with venlafaxine than escitalopram (Montgomery *et al.*, 2004) and moderate and severe symptoms were more common with venlafaxine compared with sertraline (Sir *et al.*, 2005).

The onset is usually within 5 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 be severe and prolonged, particularly if withdrawal is abrupt. Some symptoms are more likely with individual drugs, for example dizziness and electric shock-like sensations with SSRIs, and sweating and headache with TCAs (Lejoyeux *et al.*, 1996; Haddad, 2001).

11.8.2 Factors affecting the development of discontinuation symptoms

**Although anyone can experience discontinuation symptoms, the risk is increased in those prescribed short half-life drugs (Rosenbaum *et al.*, 1998), such as paroxetine and venlafaxine (Fava *et al.*, 1997; Hindmarch *et al.*, 2000; 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 8 weeks or longer (Haddad, 2001); those who developed anxiety symptoms at the start of antidepressant treatment (particularly with SSRIs); those receiving other centrally acting medications (for example, antihypertensives, antihistamines, antipsychotics); children and adolescents; and those who have experienced discontinuation symptoms before (Lejoyeux & Ades, 1997; Haddad, 2001).

Discontinuation symptoms may also be more common in those who relapse on stopping antidepressants (Zajecka *et al.*, 1998; Markowitz *et al.*, 2000).

11.8.3 Clinical relevance

The symptoms of a discontinuation reaction may be mistaken for a relapse of illness or the emergence of a new physical illness (Haddad, 2001) leading to unnecessary investigations or reintroduction of the antidepressant. Symptoms may be severe enough to interfere with daily functioning. Another point of clinical relevance is that patients who experience discontinuation symptoms may assume that this means that antidepressants are addictive and not wish to accept further treatment. It is very

important to counsel patients before, during and after antidepressant treatment about the nature of this syndrome.**

11.8.4 How to avoid discontinuation symptoms

Although it is generally advised that antidepressants (except fluoxetine) should be discontinued over a period of at least 4 weeks, preliminary data suggest that it may be the half-life of the antidepressant rather than the rate of taper that ultimately influences the risk of discontinuation symptoms (Tint *et al.*, 2008).

When switching from one antidepressant to another with a similar pharmacological profile, the risk of discontinuation symptoms may be reduced by completing the switch as quickly as possible (a few days at most). A different approach may be required at the end of treatment where a slower taper is likely to be beneficial.

The half-life of the drug should be taken into account. The end of the taper may need to be slower as symptoms may not appear until the reduction in the total daily dosage of the antidepressant is substantial. Patients receiving MAOIs may need dosage to be tapered over a longer period. Tranylcypromine may be particularly difficult to stop. It is not clear if the need for slow discontinuation of MAOIs, and particularly tranylcypromine, is due to the discontinuation syndrome or the loss of other neurochemical effects of these drugs. Since it is not possible to disentangle these phenomena, the clinical advice is that patients on MAOIs and those at-risk patients need a slower taper (Haddad, 2001).

Many patients experience discontinuation symptoms despite a slow taper. For these patients, the option of abrupt withdrawal should be discussed. Some may prefer a short period of intense symptoms over a prolonged period of milder symptoms.

11.8.5 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 (Haddad, 2001; Lejoyeux & Ades, 1997).

11.8.6 From evidence to recommendations

Since the previous guideline, the evidence base for discontinuation symptoms with antidepressants is largely unchanged. Practitioners should ensure that they discuss the issue fully with all patients, and consider prescribing antidepressants that are associated with fewer discontinuation symptoms (for example, fluoxetine), particularly for

patients who have had previous experience of these. The previous recommendations are therefore retained, but rewritten to fit the updated NICE style.

11.8.7 Clinical practice recommendations

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.9 THE CARDIOTOXICITY OF ANTIDEPRESSANTS

The following sections on the cardiotoxicity of antidepressants marked by asterisks (**_**) are from the previous guideline and have not been updated except for style and minor clarification.

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[179]Discontinuation symptoms include increased mood change, restlessness, difficulty sleeping, unsteadiness, sweating, abdominal symptoms and altered sensations.

11.9.1 Introduction

**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 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). The antidepressants used in these studies were predominately TCAs. 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).

11.9.2 Tricyclic antidepressants

Sinus tachycardia, postural hypotension and episodic hypertension are side effects frequently observed. Electrocardiogram (ECG) changes are frequent, such as lengthening of the QT, PR and QRS intervals relating to alterations in atrioventricular conduction and repolarisation (Roose & Glassman, 1989). These effects are due to the wide-ranging pharmacological actions of TCAs that are not correlated with recognised mechanisms of antidepressant action. In healthy patients such changes may be asymptomatic or clinically unimportant, but in those with heart disease they may lead to significant morbidity and mortality (Glassman *et al.*, 1993). For example, prolonged increased heart rate (mean 11%, Roose & Glassman, 1989) could have a major impact in terms of cardiac work (Roose, 2003).

In patients with left ventricular impairment on TCAs, orthostatic hypotension is three to seven times more common and potentially clinically harmful (Glassman *et al.*, 1993). The TCA induced prolongation of conduction may be clinically unimportant in healthy patients, but can lead to complications in those with conduction disease, in particular bundle branch block, and these can be severe in 20% of subjects (Roose *et al.*, 1987). TCAs may be regarded as Class I arrhythmic drugs. Evidence suggests that this class of drug is associated with an increase in mortality in post-infarction patients and in patients with a broader range of ischaemic disease,

probably because they turn out to be arrhythmogenic when cardiac tissue becomes anoxic. Overdose of TCAs or elevated plasma levels as a result of interactions with other drugs, liver disease and age is associated with serious hypotension and atrial and ventricular arrhythmias may arise even to the extent of complete atrioventricular 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 (for example, nortriptyline). These drugs, such as nortriptyline, have 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).

11.9.3 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). Sauer and colleagues (2001) compared the rate of myocardial infarction (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 (IHD) 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 gastrointestinal bleed, particularly in the very old (Walraven *et al.*, 2001).

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 (1,789 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 7-week open trial of older adults with cardiac disease, Roose and colleagues (1998b) showed that fluoxetine caused no major cardiovascular change. Strik and colleagues (2000) showed that fluoxetine was safe in 27 patients with recent MI (more than 3 months since the MI) 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
A daily dose of 20 to 30 mg of paroxetine 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 major depressive disorder and IHD (Roose *et al.*, 1998a). Paroxetine was not associated with clinically importantly sustained changes in heart rate, blood pressure or conduction intervals whereas nortriptyline caused 'clinically significant' changes in these measures and 'more serious cardiac events'.

Sertraline
Three hundred and sixty nine patients with either unstable angina (26%) or recent (within 30 days) MI (74%) were randomised to receive either placebo or sertraline (flexible dose, 50 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 symptoms of depression in those taking SSRIs compared with those taking placebo (N = 90; WMD= –3.4, 95% CI, –6.47 to –0.33[180]). However, this study and others in the field are not adequately powered

[180]These data were calculated from data in the paper.

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, while reporting complications with high-dose citalopram overdoses, have not reported deaths (Grundemar *et al.*, 1997; Personne *et al.*, 1997b). The mechanisms of the deaths reported by Ostrom and colleagues (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 (Catalano *et al.*, 2001). However, Boeck and colleagues (1982) did not report cardiotoxicity with high-dose citalopram in the dog, and in the deaths reported by Ostrom and colleagues (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.

11.9.4 Other drugs

Lithium
Lithium has a number of cardiac effects and they can be of clinical importance 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 TCAs (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 (Hla & Boyd, 1987; Haefeli *et al.*, 1991) and, rarely, bradycardia at therapeutic doses (Carcone *et al.*, 1991). Bucknall and colleagues (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 IHD.

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 (for example, 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 cardiovascular events and the use of venlafaxine in individuals with pre-existing cardiovascular disease (MHRA, 2004).**

11.9.5 Recommendation

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

11.10 DEPRESSION, ANTIDEPRESSANTS AND SUICIDE

The following sections on depression, antidepressants and suicide marked by asterisks (**_**) are from the previous guideline and have not been updated except for

style and minor clarification.

11.10.1 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 experiencing depression, and suicide is the main cause of the increased mortality of depression and is commonest in those with comorbid physi- cal and mental illness. Suicidal behaviour also occurs with milder forms of depres- sion. In a meta-analysis of 36 studies the lifetime prevalence of suicide has been reported to be 4% in hospitalised depressed patients, rising to 8.6% if hospitalised for suicidality. In mixed inpatient/outpatient populations the lifetime prevalence is 2.2% compared with less than 0.5% in the non-affectively ill population (Bostwick & Pankratz, 2000). Harris and Barraclough (1997) found a suicide risk of 12 times that expected in a cohort of patients with dysthymia (DSM–III) (APA, 1980). Therefore, the effective recognition and treatment of depression should lead to a fall in the overall suicide rate.

11.10.2 Suicidality and antidepressants

There is evidence for a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment (Jick *et al.*, 2004). However this must be put against recent data showing that the risk of clinically important suicidal behaviour is highest in the month before starting antidepressants and declines thereafter (Simon *et al.*, 2006). The highest rates of suicidal behaviour were seen in patients treated by psychiatrists but the same pattern was also seen with psychological treatments and in primary care (Simon & Savarino, 2007). No temporal pattern of completed suicide was found in the 6 months after starting an antidepressant (Simon *et al.*, 2006). No increase in suicide/suicidal thoughts or attempts was seen with SSRIs compared with other antidepressants (Jick *et al.*, 2004; Simon *et al.*, 2006).

It is therefore not clear from these naturalistic data to what extent suicidal thoughts or behaviour can be attributable to a direct result of taking an antidepressant (the effect was seen with all classes of antidepressant) as opposed to the timing of when help was sought. Two meta-analyses of RCTs (Fergusson *et al.*, 2005; Gunnell *et al.*, 2005) with 702 and 477 studies respectively and a large nested case-control study comparing new prescriptions of SSRIs and TCAs (Martinez *et al.*, 2005) found no evidence of an increase in completed suicide with SSRIs but possible evidence of increased suicidal/self-harming behaviour with SSRIs compared with placebo (NNH 684 and 754 in the two meta-analyses). There was no overall difference between SSRIs and TCAs (Fergusson *et al.*, 2005; Martinez *et al.*, 2005) but Martinez and colleagues (2005) found some evidence for increased self-harming behaviour with SSRIs compared with TCAs in those under 19 years. A review by Möller and colleagues (2008) concluded that all antidepressants carry a small risk of inducing suicidal thoughts and suicide attempts in age groups below 25 years, the risk reducing further at the age of about 30 to 40 years.

There may be a delay in noticeable improvement after starting antidepressants, and, just after initiation of treatment, mood remains low with prominent feelings of guilt and hopelessness, but energy and motivation can increase and may be related to the increased suicidal thoughts. A similar situation can arise with patients who develop akathisia or increased anxiety due to a direct effect of some SSRIs and related drugs and it has been hypothesised that this may increase the propensity to suicidal ideation and suicidal behaviour (Healey, 2003). Careful monitoring is therefore indicated when treatment is initiated with an antidepressant. Patients should be monitored regardless of the apparent severity of their depression.

A meta-analysis of observational studies (Barbui *et al.*, 2009) found that compared with depressed people who did not take antidepressants, adolescents receiving SSRIs had a significantly higher risk of suicide attempts and completed suicide. In contrast adults, especially older adults, had a significantly lower risk of suicide attempts and completed suicide. Ecological data has failed to find any link between SSRI use and higher completed suicide rates (Gibbons *et al.*, 2005; Hall & Lucke, 2006), in fact it has been suggested that the overall reduction in suicide rate may be partly due to more effective treatment of depression with newer antidepressants. In particular, it has been argued that the significant reductions in suicide rates in Sweden, Hungary, the US 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 socioeconomic circumstances, and demonstrating a causal link between increased antidepressant prescription and falling suicide rates is not straightforward and has not been conclusively established (Gunnell & Ashby, 2004).

The use of antidepressants in the treatment of depression is also not without risk not least because of their toxicity in overdose. Antidepressants were involved in 18% of deaths from drug poisoning between 1993 and 2002 (Morgan *et al.*, 2004), with TCAs, which are cardiotoxic in overdose (see Section 8.2.9), accounting for 89% of these. This is equivalent to 30.1 deaths per million prescriptions. Dothiepin/dosulepin alone accounted for 48.5 deaths per million prescriptions (Morgan *et al.*, 2004). 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 (Morgan *et al.*, 2004). Venlafaxine alone accounted for 8.5 deaths per million prescriptions. Morgan and colleagues (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 (Morgan *et al.*, 2004). 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.** The MHRA (2006a and b) concluded that the increased rate seen with venlafaxine was partly, but not wholly, attributable to patient characteristics.

11.10.3 From evidence to recommendations

There is a small risk of inducing suicidal ideation in younger people starting antidepressants. Although the most recent data suggests the cut-off for this is around 25 years old, previous advice from the MHRA suggests the cut-off should be around 30. Practitioners should seek strategies to reduce risk as far as possible for people who are at increased risk of suicide, including prescribing drugs with relatively low toxicity and prescribing small amounts of drugs. They should refer people at high risk to specialist mental health services. The recommendations in this section are unchanged from the previous guideline, but have been reworded to fit current NICE house style and to fit with new recommendations developed for the updated guideline.

11.10.4 Recommendations

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

12 THE PHARMACOLOGICAL AND PHYSICAL MANAGEMENT OF DEPRESSION THAT HAS NOT ADEQUATELY RESPONDED TO TREATMENT, AND RELAPSE PREVENTION

This section was updated and replaced in 2022, with the exception of ECT, TMS and Vagal nerve stimulation (see below). Please see the NICE website for the updated guideline.

12.4 ELECTROCONVULSIVE THERAPY

12.4.1 Introduction

Electroconvulsive therapy (ECT) has been used as a treatment for depression since the 1930s. In its modern form ECT is perceived by many healthcare professionals to be a safe and effective treatment for severe depression that has not responded to other standard treatments (Geddes *et al.*, 2003b). But many others, including many patient groups, consider it to be an outdated and potentially damaging treatment (Rose *et al.*, 2003). During ECT, an electric current is passed briefly through the brain, via electrodes applied to the scalp, to induce generalised seizure activity. The individual receiving treatment is placed under general anaesthetic and muscle relaxants are given to prevent body spasms. The ECT electrodes can be placed on both sides of the head (bilateral placement) or on one side of the head (unilateral placement). Unilateral placement is usually to the non-dominant side of the brain, with the aim of reducing cognitive side effects. The standard bilateral placement is bitemporal/temporofrontal but some studies have used bifrontal placement in the hope of reducing cognitive side effects associated with the standard placement. The number

[205]Aripiprazole, olanzapine, quetiapine and risperidone do not have UK marketing authorisation for the indication in question at the time of publication. Informed consent should be obtained and documented.
[206]Buspirone, carbamazepine, lamotrigine, valproate, pindolol and thyroid hormones do not have UK marketing authorisation for the indication in question at the time of publication. Informed consent should be obtained and documented.

of sessions undertaken during a course of ECT usually ranges from six to twelve, although a substantial minority of patients responds to fewer than six sessions. ECT is usually given twice a week in the UK; less commonly it is given once a fortnight or once a month as continuation or maintenance therapy to prevent the relapse of symptoms. It can be given on either an inpatient or day patient basis.

ECT causes short-term disorientation immediately after treatment and may cause short- or long-term memory impairment for past events (retrograde amnesia) and current events (anterograde amnesia). These effects appear to be dose related and depend on electrode placement, possibly the type of electrical stimulus and patient characteristics (Ingram *et al.*, 2008). However the persistence, severity and precise characterisation of such impairments are still a subject of debate. There is preliminary evidence that prolonged short-term disorientation immediately after treatment predicts retrograde amnesia after the end of a course of treatment (Sobin *et al.*, 1995) but not 2 months after the course. Cognitive impairments have been highlighted as a particular concern by many patients, especially retrograde amnesia for autobiographical events (Rose *et al.*, 2003). There is no simple relationship between subjective cognitive impairment and cognitive test measures, which has contributed to polarising views about the relative risks and benefits of ECT.

At present there is a lack of consensus as to the best method of assessing cognitive function during a course of ECT. The benefit of using only a global measure such as the MMSE in its original or modified form (3MSE) is uncertain given the inconsistent effects of ECT on these measures in trials. And given the evidence that the ability to learn new material (anterograde memory) recovers after the end of ECT treatment, a main concern is in the early detection and minimisation of persistent retrograde memory loss, particularly for important autobiographical memories. Detecting cognitive impairments only at the end of treatment does not give the practitioner the opportunity to alter treatment to attempt to minimise this, although it may lead the practitioner to consider cognitive remediation; there is no evidence, however, to show that this is effective. A battery consisting of a formal mood rating scale (MADRS), the 3MSE, an autobiographical memory task, a word learning task, and tests of digit span forward and backward has been suggested (Porter *et al.*, 2008), but it takes an hour to administer.

In line with NICE policy regarding the relationship of technology appraisals to clinical practice guidelines, this guideline updates the NICE technology appraisal on ECT (TA59) only for depression in adults (the TA covered the use of ECT in the treatment of mania and schizophrenia as well as depression in children and adolescents; NICE, 2003).

Key points to emerge from the reviews underpinning the NICE TA on ECT (NICE, 2003), which concluded that ECT is an effective treatment, include:

- real ECT had greater short-term benefit than sham ECT
- ECT had greater benefit than the use of certain antidepressants
- bilateral ECT was reported to be more effective than unilateral ECT
- the combination of ECT with pharmacotherapy was not shown to have greater short-term benefit than ECT alone
- cognitive impairment does occur but may only be short term

- compared with placebo, continuation pharmacotherapy with tricyclic antidepressants and/or lithium reduced the rate of relapses in people who had responded to ECT
- preliminary studies indicate that ECT is more effective than repetitive transcranial magnetic stimulation.

12.4.2 Databases searched and the inclusion/exclusion criteria

For the updated review double-blind RCTs were sought that compared ECT either with sham ECT or another active treatment in the treatment of people experiencing an acute depressive episode or in relapse prevention following successful treatment (either with ECT or another treatment). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 119. Details of the search strings used are in Appendix 8.

12.4.3 Studies considered[207]

In total, 21 new trials were found from searches of electronic databases. These included: ten trials comparing ECT with transcranial magnetic stimulation (TMS), which the GDG did not review since NICE has produced guidance on TMS (NICE, 2007d); four trials of continuation treatment following successful treatment with ECT (two of which included continuation ECT), which are considered in the section on relapse prevention, and eight comparing bilateral with unilateral ECT, which are considered in the section on next-step treatments. Several studies included populations with a relatively high proportion of participants with bipolar disorder (up to 30%). These were included since ECT is not known to cause switching to mania (and, indeed, is used as a treatment for mania).

Summary study characteristics of the included studies are presented in Table 120, with full details in Appendix 17c, which also includes details of excluded studies.

Table 119: Databases searched and inclusion/exclusion criteria for clinical effectiveness of ECT

Electronic databases	MEDLINE, EMBASE, PsycINFO, CINAHL
Date searched	January 2002 to January 2008
Update searches	July 2008; January 2009
Study design	RCT
Population	People with a diagnosis of depression according to DSM, ICD or similar criteria
Treatments	ECT

[207]Study IDs in capital letters refer to studies found and included in this guideline update.

Table 120: Summary study characteristics of studies of ECT or of treatment following successful ECT published since the systematic reviews underpinning the NICE TA were undertaken

	Relapse prevention studies following remission with ECT	**Next-step treatment studies (bilateral ECT versus unilateral ECT)**
No. trials (Total participants)	4 RCTs (305)	8 RCTs (472)
Study IDs	(1) GRUNHAUS2001 (2) KELLNER2006 (3) NAVARRO2008 (4) VAN den BROEK2006	(1) ESCHWEILER2007 (2) HEIKMAN2002B (3) McCALL2002 (4) RANJKESH2005 (5) SACKEIM2008 (6) SIENAERT2009 (7) STOPPE2006 (8) TEW2002
N/% female	(1) 39/56 (2) 201/68 (3) 38/55 (4) 27/74	(1) 92/58 (2) 24/54 (3) 77/64 (4) 45/60 (5) 90/57 (6) 81/60 (7) 39/56 (8) 24/not reported
Mean age	(1) 60 (2) 57 (3) 70 (4) 51	(1) 54 (2)–(3) 57 (4) 35 (5) 50 (6) 55 (7) 75 (8) 67
Diagnosis	(1) MDD, 17% psychotic features (2) MDD, 39% psychotic features (3) MDD, 100% psychotic features (4) MDD, 33% psychotic features	(1) MDD and failed >= 2 antidepressants courses (2) MDD, 21% psychotic features (3)–(4) MDD (5) MDD, 30% with bipolar disorder

Continued

Table 120: (*Continued*)

	Relapse prevention studies following remission with ECT	**Next-step treatment studies (bilateral ECT versus unilateral ECT)**
		(6) MDD, 20% with bipolar disorder, 27% with psychotic features (7) MDD, 33% psychotic features (8) MDD, some psychotic features (% not reported), insufficient response to 5–8 unilateral ECT (150% above seizure threshold)
Treatments (% above seizure threshold)	(1) Fluoxetine 20 mg – 40 mg + melatonin 5 mg or 10 mg versus fluoxetine 20 mg–40 mg (2) ECT versus nortriptyline + lithium (3) Nortriptyline versus nortriptyline + ECT (4) Imipramine versus placebo	(1) Bilateral 50% versus unilateral 150% (2) Bilateral 0% versus unilateral 400% versus unilateral 150% (3) Bilateral 50% versus unilateral 700% (4) Bilateral 50% versus bilateral 0% versus unilateral 400% (5) Bilateral 150% (separate groups for ultra brief and brief ECT) versus unilateral ECT 500% (separate groups for ultra brief and brief ECT) (6) Bilateral 50% versus unilateral 500% (7) Bilateral 'high' dose versus unilateral 'high' dose (8) Bilateral 150% versus unilateral 450%
Placement	Not examined	(1)–(2) Bifrontal (3) Bitemporal (4)–(6) Bifrontal (7)–(8) Bitemporal

Continued

Table 120: (*Continued*)

	Relapse prevention studies following remission with ECT	**Next-step treatment studies (bilateral ECT versus unilateral ECT)**
Setting	(1) Israel; unclear (2) US; unclear (3) Spain; inpatients + outpatients (4) Holland; inpatients	(1) Germany and Austria; inpatients (2) Finland; inpatients (3) US; unclear (4) Iran; unclear (people referred for ECT) (5) US; inpatients (6) US; unclear (7) Brazil; inpatients (8) US; unclear
Length of treatment	(1) 12 weeks (2) 6 months (3) 24 months (outcomes at 6 months and 24 months) (4) 6 months	(1) 6 treatments (2) Unclear (3) Mean 5.8 sessions (4) >= 8 treatments (5) >= 5 treatments (6) Mean 8 sessions (7) 4–16 treatments (8) >= 3 treatments

0% = just above seizure threshold.

Two older trials on relapse prevention following response to ECT were also discussed narratively (Lauritzen1996, Sackheim2001); see Section 12.4.5.

12.4.4 Clinical evidence for ECT as a next-step treatment

The TA reviews of ECT compared with sham ECT and with pharmacological interventions were not updated because no new studies were found. However, the review comparing bilateral ECT with unilateral ECT, including a sub-analysis by dose, was updated. In addition a narrative review of cognitive impairment related to electrode placement and dose was undertaken.

Bilateral ECT versus unilateral ECT

A review by Geddes and colleagues (2003b) was used as the basis of this review. The effect sizes reported in the published paper were input into CMA (Comprehensive Meta-Analysis) and combined with effect sizes from the eight new studies found (see Table 120 for a summary of these studies). The overall SMD calculated by Geddes

and colleagues (2003b) from 22 studies and 1,137 particpiants was -0.322 (Random effects) (-0.458 to -0.186). With the addition of the relevant new data the SMD effect size was reduced slightly to -0.23 (Random effects) (-0.37, -0.09) (31[208] studies, 1,693 participants; I^2 =39%), thus confirming an overall small to medium effect favouring bilateral ECT (see Figure 10).

Bilateral ECT versus unilateral ECT – the effect of dose and electrode placement on efficacy

For this guideline update, a sub-analysis by dose was also undertaken on efficacy related to electrode placement. This topic was also included in the review by Geddes and colleagues (2003b), which included seven studies comparing different doses of unilateral ECT and different doses of bilateral ECT, as well as five that specifically compared bilateral ECT with unilateral ECT at doses related to seizure threshold. These five studies were included in the sub-analysis (SACKHEIM1993, SACKHEIM2000; Malitz *et al.*, 1986; Sackeim *et al.*, 1987; Letemendia *et al.*, 1993).

Dose was classified based on percentage above seizure threshold (one new study described doses as 'high' [STOPPE2006]). Doses described as 'just above seizure threshold' were classified 0%. The doses given in the studies available for the sub-analysis are in Table 121.

Low-dose unilateral ECT was defined as doses up to 150% above seizure threshold (that is, including low and standard doses used clinically) and high-dose unilateral ECT was defined as doses over 150% above seizure threshold. There was insufficient evidence to show a difference between low-dose bilateral ECT and low-dose unilateral ECT from the available studies in this subset, although the direction of effect was similar to that in the full set (see Table 122). On one outcome measure (non-remission) high-dose unilateral ECT tended to be more effective than low-dose bilateral ECT but this was not clinically important and no differential benefit was suggested with the other outcome measures. Evidence from the important outcomes and overall quality of evidence are presented in Table 122. The full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively.

A visual inspection of the forest plots indicated that there appears to be neither no consistent effect for different bilateral electrode placement (bifrontal or bitemporal) nor a consistent relationship between electrode placement and dose, although there are insufficient studies to allow these factors to be explored systematically.

Cognitive side effects related to electrode placement and dose

Geddes and colleagues (2003b) reported that patients who received bilateral ECT seemed to take longer to recover orientation than those treated with unilateral ECT (based on six trials that reported this), and that they showed greater impairment in retrograde memory (based on four trials that reported this) and anterograde memory (seven trials reported this). Geddes and colleagues (2003b) also report that they found only two trials reporting long-term data, which were both small and underpowered,

[208]There are 30 studies, but SACKHEIM2008 includes four treatment groups that were used as two separate comparisons.

Figure 10: Bilateral ECT versus unilateral ECT: updated forest plot

Study name	Comparison	Outcome	Hedges's g	Lower limit	Upper limit
Abrams 1969	Bi vs uni	ES from Geddes	0.017	-0.785	0.819
Abrams 1974	Bi vs uni	ES from Geddes	0.082	-0.645	0.809
Abrams 1983	Bi vs uni	ES from Geddes	-0.565	-1.116	-0.014
Abrams 1991	Bi vs uni	ES from Geddes	-0.544	-1.171	0.083
Carney 1976	Bi vs uni	ES from Geddes	-0.188	-0.762	0.386
Costello 1970	Bi vs uni	ES from Geddes	-0.342	-1.073	0.389
D'Elia 1970	Bi vs uni	ES from Geddes	-0.068	-0.568	0.432
Eschweiler 2006	Bi vs uni	Non-remission	-0.185	-0.813	0.442
Fleminger 1970	Bi vs uni	ES from Geddes	-0.317	-0.989	0.355
Fraser 1980	Bi vs uni	ES from Geddes	-0.320	-1.028	0.388
Gregory 1985	Bi vs uni	ES from Geddes	0.215	-0.390	0.820
Halliday 1968	Bi vs uni	ES from Geddes	-0.171	-0.729	0.387
Heikman 2002	Bi vs uni	Non response	0.520	-0.457	1.497
Horne 1985	Bi vs uni	ES from Geddes	-0.188	-0.740	0.364
Letemendia 1993	Bi vs uni	ES from Geddes	-0.383	-0.943	0.177
Levy 1968	Bi vs uni	ES from Geddes	-0.200	-0.802	0.402
Malitz 1986	Bi vs uni	ES from Geddes	-0.835	-1.388	-0.282
Martin 1965	Bi vs uni	ES from Geddes	0.111	-0.490	0.712
Sackeim 1987	Bi vs uni	ES from Geddes	-0.818	-1.371	-0.265
Sackeim 1993	Bi vs uni	ES from Geddes	-0.694	-1.101	-0.287
Sackeim 2000	Bi vs uni	ES from Geddes	-0.830	-1.344	-0.316
Stoppe 2006	Bi vs uni	Non-remission	0.677	-0.256	1.609
Stromgren 1973	Bi vs uni	ES from Geddes	-0.086	-0.474	0.302
Taylor 1985	Bi vs uni	ES from Geddes	-0.951	-1.618	-0.284
Valentine 1968	Bi vs uni	ES from Geddes	0.076	-0.681	0.833
Sackeim 2008 brief	Bi vs uni	Non-remission	-0.035	-0.719	0.649
Sackeim 2008 ultra	Bi vs uni	Non-remission	0.902	0.197	1.607
Tew 2002	Bi vs uni	Mean	-0.159	-0.936	0.617
Ranjkesh 2005	Bi vs uni	Mean	-0.280	-0.949	0.389
McCall 2002	Bi vs uni	Mean	-0.164	-0.607	0.280
Sienaert 2008	Bi vsuni	Mean	-0.028	-0.512	0.456
			-0.251	-0.357	-0.146

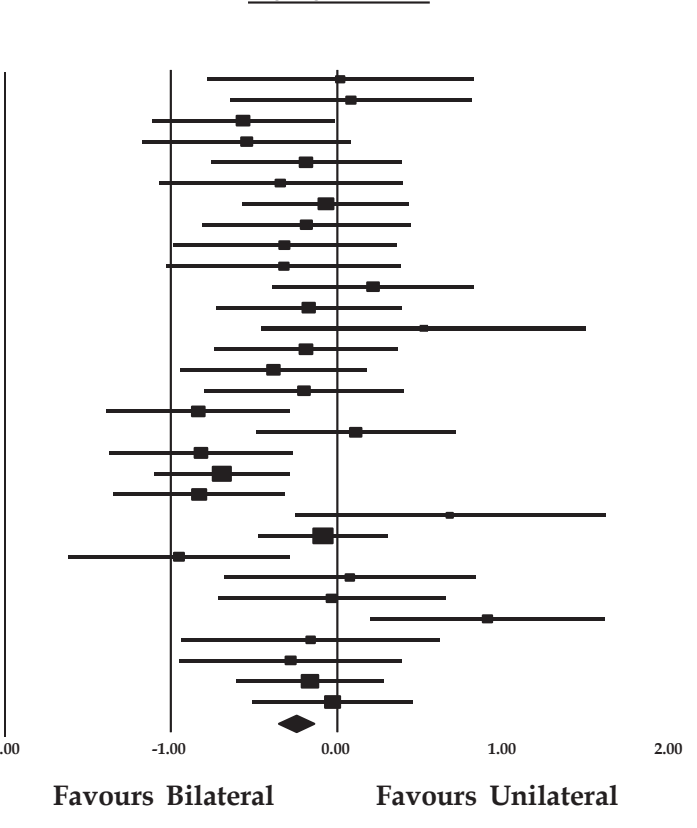

Table 121: Doses (% above seizure threshold) of bilateral ECT and unilateral ECT given in the available studies

	Bilateral group 1	Bilateral group 2	Unilateral group 1	Unilateral group 2	Unilateral group 3
ESCHWEILER2007	50%	–	150%	–	–
HEIKMAN2002	0%	–	400%	150%	–
Letemendia *et al.*, 1993*	0%	–	0%	–	–
Malitz *et al.*, 1986*	0%	–	0%	–	–
MCCALL2002	150	–	800%	–	–
RANJKESH2005	0%	50%	400%	–	–
SACKEIM1993*	0%†	250%†	0%†	250%†	–
SACKEIM2000*	150%	–	50%†	150%	500%†
SACKEIM 2008	150%	–	50%†	150%	500%†
SIENAERT2009	–	–	–	–	–
STOPPE2006	'High'	–	'High'	–	–
TEW2002	150%	–	450%	–	–

0% indicates just above seizure threshold; *From Geddes *et al.* (2003) review; †Groups used in Geddes *et al.* (2003) analysis of dose effects.

and which found no long-term differences between bilateral and unilateral ECT on cognitive functioning.

In the studies considered the GDG has taken bifronto-temporal placement as bitemporal. Combining the new studies with relevant studies from Geddes and colleagues (2003b) there was comparison between different doses of bitemporal ECT and unilateral ECT in six studies, between bifrontal ECT and unilateral ECT in four studies and between bifrontal ECT and bitemporal ECT in one study (see Table 123). In SACKHEIM1993 and SACKEIM2008 approximately 30% of patients had bipolar disorder and in SIENAERT2008 20% of patients had bipolar disorder; both were included in this review of cognitive effects.

The new studies had differences in bilateral electrode placement (bifrontal compared with the standard bitemporal placement) and in stimulus pulse width (ultra brief pulse compared with standard brief pulse). There was variation in the lower/'standard' dose of bitemporal ECT with 150% above seizure threshold often used in key US studies compared with lower UK recommendations from the Royal College of Psychiatrists (50 to 100% above seizure threshold) (Royal College of Psychiatrists, 2005). As explored quantitatively below (see Table 123), high dose (>400% above seizure threshold) unilateral ECT generally appeared as effective as low/standard dose (0 to 150% above seizure threshold) bilateral ECT, whether bitemporal or bifrontal.

Table 122: Summary evidence profile for acute-phase ECT: bilateral ECT versus unilateral ECT

	Low-dose bilateral ECT versus low-dose unilateral ECT	**Low-dose bilateral ECT versus high-dose unilateral ECT**
Mean depression scores at endpoint (clinician-rated)	SMD -0.46 (-1.69 to 0.76)	SMD 0.01 (-0.27 to 0.29)
Quality	Very low	Moderate
Number of studies; participants	K = 2; n = 91	K = 4; n = 204
Forest plot number	Pharm next-step 12.05	Pharm next-step 12.08
Non-response	RR 0.65 (0.35 to 1.21) (52% versus 69.7%)	RR 0.98 (0.74 to 1.29) (35.2% versus 36.1%)
Quality	Very low	High
Number of studies; participants	K = 4; n = 217	K = 7; n =362
Forest plot number	Pharm next-step 12.04	Pharm next-step 12.06
Non-remission	RR 0.93 (0.77 to 1.14) (64.2% versus 68.7%)	RR 1.24 (0.97 to 1.6) (52.5% versus 42.9%)
Quality	High	Moderate
Number of studies; participants	K = 2; n = 134	K = 5; n = 237
Forest plot number	Pharm next-step 12.05	Pharm next-step 12.07

One study including low dose unilateral ECT arms found them to be less effective than standard dose bilateral and high dose unilateral ECT. Another study found that threshold dose unilateral ECT was less effective than low/standard dose bilateral ECT.

The range of cognitive side-effects assessments varied between studies and were not consistent with regard to global scores (MMSE/3MS), but more consistent memory effects (including autobiographical memory impairment) were seen.

Previous studies have suggested that bifrontal ECT may cause fewer cognitive effects than bitemporal ECT but with similar efficacy (Lawson *et al.*, 1990; Letemendia *et al.*, 1993; Bailine *et al.*, 2000) so the two types of bilateral ECT were considered separately.

In the five studies in which bitemporal low/standard dose ECT was compared with unilateral high dose ECT, two found no difference in cognitive effects, two found that

Table 123: Studies comparing bilateral and unilateral ECT: reported differences in cognitive functioning and efficacy

Study	Comparison	Dose above threshold	MMSE/3MS	Other cognition	Efficacy
ESCHWEILER2007	BF versus UL	50% versus 150%	No change with treatment (BF = UL)	Reorientation time BF = UL. Non-verbal anterograde amnesia (BF < UL) and decreased verbal fluency with treatment (BF = UL)	Equal (low response rate)
HEIKMAN2002	BF versus high dose UL versus lower dose UL	0% versus 400% versus 150%	No change with treatment (BF = UL)	–	High dose UL faster onset, tendency to greater response
MCCALL2002	BT versus UL	50% versus 700%	–	AMI, anterograde amnesia with treatment but improved at 4 weeks; still below baseline for AMI (BT = UL)	Equal
RANJKESH2005	BT versus BF versus UL	0% versus 50% versus 400%	Decreased with treatment (BF < BT = UL)	–	Equal
SACKEIM1993	BT versus BT versus UL versus UL	0% versus 150% versus 0% versus 150%	Decreased BT versus UL after treatment; improved versus baseline after 2 months (BT = UL)	Prolonged disorientation BT > UL. Retrograde and anterograde amnesia: BT > UL/ higher dose > lower dose/ interaction site x dose depending on test used after treatment. Improved or no change versus baseline at 2 months	Both BT > higher dose UL > lower dose UL

Continued

Table 123: (*Continued*)

Study	Comparison	Dose above threshold	MMSE/3MS	Other cognition	Efficacy
SACKEIM2000/ LISANBY2000	BT versus 3 doses UL	150% versus 50% versus 150% versus 500%	Decreased with treatment (BT > UL-dose related)	Anterograde and retrograde amnesia, AMI, persisting to 2 months (BT > UL-mostly dose related)	BT = high dose UL, both > lower dose UL
SACKEIM2008	BT versus $^{\dagger}BT_{ub}$ versus UL versus $^{\dagger}UL_{ub}$	150% versus 150% versus 450% versus 450%	Decrease with treatment standard versus ub (BT = UL)	Reorientation time, anterograde and retrograde amnesia, AMI less in ub groups (AMI difference persisting to 6 months). AMI less in UL groups. $^{\dagger}UL_{ub}$ group had no significant cognitive effects	$^{\dagger}BT_{ub}$< other groups
SIENAERT2008	$^{\dagger}BF_{ub}$ versus $^{\dagger}UL_{ub}$	50% versus 500%	Increased with treatment (BF = UL)	–	UL faster onset, equal response
STOPPE2006	BT versus UL	Both fixed high dose	Decrease with treatment in BT versus UL	Trend to more delirium with BT versus UL. No significant change in anterograde and retrograde amnesia, AMI 1 month after treatment, some improvement with UL not BL. Overall BT = UL	Equal
TEW2002	*BT versus UL	150% versus 450%	Decrease with treatment in BT versus UL	–	Equal

*Bilateral mode not explicitly stated but taken as bitemporal; †Ultra brief pulse (0.3 msec).
Abbreviations: AMI, autobiographical memory impairment; BF, bifrontal; BT, bitemporal; UL, right unilateral; ub, ultra brief pulse.

bitemporal ECT caused a greater global decrease and one found that bitemporal ECT caused greater impairment of autobiographical memory but not other measures of retrograde and anterograde memory. In one study a global decrease in cognitive function with high dose bitemporal ECT compared with high dose unilateral ECT was seen. The studies in which bitemporal ECT worsened cognitive function compared with unilateral ECT mostly used high standard doses (150% above seizure threshold).

In the three studies where bifrontal low/standard dose ECT was compared with high dose unilateral ECT, two studies found no difference in global cognitive effects and one found less impairment. A study where both doses were low found no difference in most cognitive effects except less non-verbal anterograde amnesia with bifrontal ECT. A study of low and standard doses of bitemporal and unilateral ECT found effects of both dose, electrode placement and their interaction depending on the test used, which had recovered to above baseline 2 months after ECT. In two studies there was faster onset of improvement with high dose unilateral ECT.

Ultra-brief pulse (0.3 msec) high dose ECT caused no cognitive impairment in two studies and cognitive impairment was significantly less than standard brief pulse (1.5 msec) treatment in one study.

A soon-to-be reported large study comparing bitemporal (50% above seizure threshold), bifrontal (50% above seizure threshold) and right unilateral (400% above seizure threshold) with a 1msec pulse width, similar to treatment practice in the UK, has found few differences in cognitive effects and efficacy between placements (Charles Kellner, personal communication, 2009).

The NICE TA on ECT (NICE, 2003) concluded that cognitive impairment is greater in individuals who have had electrodes applied bilaterally than in those who have had them placed unilaterally, and that unilateral placement to the dominant hemisphere causes more impairment than placement to the non-dominant hemisphere. They also found that raising the stimulus threshold above the individual's seizure threshold increased the efficacy of unilateral ECT at the expense of increased cognitive impairment. Overall the conclusion was that reduction in the risk of cognitive impairment is mirrored by a reduction in efficacy.

The new studies provide insufficient evidence to determine whether efficacy and cognitive side effects can be dissociated by manipulating electrode placement and stimulus dose or parameters. Results with high dose ultra-brief unilateral ECT need to be replicated.

Effect of ethnicity

The data from the acute phase of the KELLNER2006 trial included in the analyses above were also analysed by race, looking at data for black and white participants separately (Williams, M. D., *et al.*, 2008). Of 515 participants, 483 were white and 32 black. Of these, 63.4% of white participants and 71.9% of black participants achieved remission. The difference was not statistically significant, although may indicate a trend towards ECT being more effective in black participants. It should be noted that the study was undertaken in the US where the ethnic populations are different from those in England and Wales so the results of this study are unlikely to be generalisable.

12.4.5 Relapse prevention following successful treatment with ECT in relapse prevention

Four studies were found of continuation treatment after successful treatment with ECT, two of which included maintenance ECT (see Table 124; the full evidence profiles and associated forest plots can be found in Appendix 16c and Appendix 19c, respectively). In these studies, there was little difference after 6 months between adding ECT to an antidepressant and maintaining the antidepressant alone, or between ECT alone compared with a combination of nortriptyline and lithium. However, at 12 months, fewer participants experienced relapse if they had received ECT plus nortriptyline compared with those continuing treatment with nortriptyline alone. Similar data were not available for the other study.

In studies of pharmacological maintenance strategies (see Table 125), only nortriptyline plus lithium was effective (compared with placebo), although there was a trend towards nortriptyline plus lithium compared with nortriptyline alone being more effective. The data are weak since there is only one study comparing each strategy, with relatively low numbers. However, the data suggest that combination treatment with nortriptyline and lithium may be effective in reducing the likelihood of relapse following successful treatment with ECT.

A further small study randomised 74 patients following response to ECT to paroxetine or placebo in those with cardiovascular disease and paroxetine or

Table 124: Summary evidence profile for relapse prevention with ECT

	ECT + nortriptyline versus nortriptyline	**ECT versus nortriptyline + lithium**
Relapse – 1st follow-up	6 months RR 0.5 (0.05 to 4.98) (6.3% versus 12.5%)	6 months RR 1.16 (0.77 to 1.74) (33.7% versus 29.1%)
Quality	Low	Low
Number of studies; participants	K = 1; n = 32	K = 1; n = 201
Forest plot number	Pharm Relapse prevention 10.01	Pharm Relapse prevention 10.01
Relapse – 2nd follow-up	12 months RR 0.12 (0.02 to 0.89)	Not reported
Quality	Moderate	–
Number of studies; participants	K = 1; n = 32	–
Forest plot number	Pharm relapse-prevention 10.01	–

Table 125: Summary evidence profile for studies of pharmacological strategies for relapse prevention following successful ECT

	Fluoxetine + placebo versus fluoxetine + melatonin	**Nortriptyline + lithium versus placebo**	**Nortriptyline versus placebo**	**Nortriptyline + lithium versus nortriptyline**
Relapse – 1st follow-up	12 weeks RR 1.17 (0.4 to 3.39) (27.8% versus 23.8%)	6 months RR 0.44 (0.25 to 0.8) (32.1% versus 72.4%)	6 months RR 0.77 (0.51 to 1.15) (56.6% versus 72.4%)	6 months RR 0.6 (0.32 to 1.14) (32.1% versus 53.6%)
Quality	Low	Moderate	Low	Low
Number of studies; participants	K = 1; n = 39	K = 1; n = 57	K = 1; n = 56	K = 1; n = 56
Forest plot number	Pharm Relapse prevention 10.01	Pharm Relapse prevention 10.01	Pharm Relapse prevention 10.01	Pharm Relapse prevention 10.01

imipramine in those without (Lauritzen *et al.*, 1996). Using survival analysis there was a significant benefit for paroxetine over placebo although this was only at trend level at the end of 6 months, and for paroxetine over imipramine.

12.4.6 Continuation/maintenance ECT and cognitive function

A particular concern in the NICE TA on ECT (NICE, 2003) about continuation or maintenance ECT was the lack of evidence about potential long-term cognitive effects. Since then there have been further data published although the numbers of patients studied remains relatively small.

In the only prospective RCT of continuation ECT compared with continuation antidepressants after acute ECT treatment (Kellner *et al.*, 2007), the MMSE improved in both groups over the 6 months after the end of acute-phase treatment with no difference between those who had not relapsed or dropped out. At 3 months, however, the continuation ECT group had improved less than the antidepressant group and one of the 15 who stopped treatment early in the ECT group did so because of memory loss. Russell and colleagues (2003) reported a retrospective evaluation of 43 patients who had received maintenance ECT for at least a year. They had an improved clinical status and slight improvement in their MMSE scores compared with before starting ECT. Adverse effects included falls, delirium and cardiac dysrhythmia, each in about 10% of patients but none causing significant morbidity. Rami-Gonzalez and colleagues (2003) undertook a cross sectional study of 11 patients on maintenance ECT compared with a matched group not receiving ECT. The patients receiving ECT had impaired encoding of new information and frontal lobe test results compared with the control group but no

difference in delayed recall. Vothknecht and colleagues (2003) undertook a prospective study (mean 61 weeks) of 11 patients receiving maintenance ECT compared with 13 patients receiving only antidepressants. There was no difference between groups on a test battery including attention and concentration, anterograde memory and frontal lobe function. An equal number in each group had subjective memory complaints. Rami and colleagues (2004) reported results on a prospective assessment of 26 patients of whom 20 carried on with maintenance ECT over 1 year in comparison with 10 controls. There were no differences found between groups or significant changes over 1 year in attention and concentration, anterograde memory and frontal lobe function. There have also been a few case reports showing no effects on cognitive function with maintenance ECT (Wijkstra & Nolen, 2005; Zisselman *et al.*, 2007).

12.4.7 Health economic evidence and considerations

The systematic literature search identified only one economic evaluation on ECT by Greenhalgh and colleagues (2005) as part of the HTA on ECT. The economic evaluation was undertaken to determine the cost effectiveness of ECT for depressive illness as well as schizophrenia, catatonia and mania. The authors developed an economic model based on how ECT is used in the UK for people with major depressive disorder who require hospitalisation. The analysis compared inpatient administered ECT with other pharmacological treatments (TCAs, SSRIs, SNRIs and lithium augmentation). These therapies were sequenced in several ways so as to form eight scenarios in which ECT featured as a first-, second- and third-line therapy. Expert opinion and data from the clinical effectiveness evidence review and other relevant studies were used to develop the model. Resource use patterns and costs were sourced from published literature. Health utility scores were adapted from a study by Bennett and colleagues (2000) and incorporated in the model. The evaluation failed to demonstrate, however, that any of the scenarios had a clear economic benefit over any of the others. This was due to high levels of uncertainty around the effectiveness data and the utility estimates.

The Greenhalgh and colleagues' (2005) study was one of the first attempts to evaluate the cost effectiveness of ECT and although many of the model inputs were based on published literature many assumptions underlay the results due to the lack of available data. The authors pointed out that one of the main drawbacks in terms of cost effectiveness of prescribing ECT was the associated high resource use. They also mention a higher rate of relapse with ECT than pharmacological therapies. This statement points to one of the limitations of this evaluation. Studies with very dissimilar populations were combined to compute model inputs such as relapse and response rates, while medication trials with patient populations that were less depressed or not treatment resistant were combined with populations who were treatment resistant or referred specifically for ECT. Underlying patient characteristics do play a vital role in determining the outcomes of studies and using data in this way makes the accuracy of the effectiveness estimates used in the model questionable. However, the authors did acknowledge the lack of data and conducted many sensitivity analyses, which further emphasised the uncertainty of the results. The authors of the HTA pointed to

the clear need for RCTs that directly compare the efficacy of treating severely depressed patients with ECT versus pharmacological treatments.

For the effectiveness update, reviews of ECT with pharmacological interventions were not updated since no new studies were found. As a result, the cost effective analysis was not updated. However, the review comparing bilateral ECT with unilateral ECT, including a sub-analysis by dose, was updated. The HTA explored these differences by varying the efficacy, outcomes and cost in the sensitivity analysis to incorporate the different approaches used in providing ECT with no effect on results. There should be no resource use differences between bilateral versus unilateral treatment. The clinical evidence review shows little difference in effect between bilateral and unilateral ECT with a slight advantage for bilateral ECT. These results are in keeping with previous effectiveness evidence.

The authors also mentioned uncertainty around the utility estimates used from the study by Bennett and colleagues (2000). In this study the depression-specific McSad health state classification system was utilised; NICE recommends using a generic tool (NICE, 2004a). The health state descriptions used referred to untreated depression. The population of the study consisted of patients who had experienced at least one episode of major unipolar depression in the previous 2 years but who were currently in remission. This is not typical of the patients who are usually prescribed ECT. This study therefore, may underestimate quality of life gains from the treatment and also potentially overestimate benefit if cognitive impairment following ECT is taken into account. However, utility data for mental health related conditions are very sparse and at the time this study was one of a very small number of studies available for patients with depression. The utility values were also subject to sensitivity analysis, with no effect on the results. To date no studies have been found describing health-related quality of life in which the health states have been determined in a group of patients with chronic or severe depression requiring or having received ECT.

ECT is resource intensive, however, patients who require such treatment usually have a chronic form of the illness or undergo several treatment options before being referred on for ECT. This group of people usually makes up a small proportion of the entire depressive population in a health system and the costs they incur to health systems can be quite significant. The clinical evidence points to ECT having a higher success rate for certain groups of people with severe depression, and providing this high cost intervention may prove to be cost effective as it may reduce subsequent resource use and potentially improve quality of life if prescribed as recommended.

12.4.8 From evidence to recommendations

The review of ECT for the updated guideline found relatively little additional data to update the reviews undertaken for the original NICE TA (NICE, 2003). There were no new data comparing ECT with sham ECT, antidepressants, or combination treatment in the acute phase and limited new data in the continuation phase after acute treatment.

Integrating the evidence for ECT with that for other treatments for depression it is evident that many people with depression have a poor response to treatment. In addition the definition of the severity of depression has altered between the previous

guideline and this guideline update so that many patients previously defined as severely depressed would now be included in the moderate severity category. For this reason, while ECT is still not recommended as a routine treatment for moderately severe depression, it is presented as an option in those with moderate depression who have repeatedly not responded to both drug and psychological treatment.

The new data comparing bilateral ECT with unilateral ECT did not change the conclusion that bilateral ECT is more effective than unilateral for people with depression, although the effect size is small and complicated by variations in dosing and electrode placement. A sub-analysis by dose suggests that high dose unilateral ECT (doses over 150% above seizure threshold) may be at least as effective as low/standard dose bilateral ECT but there are relatively few data and it was not possible to explore this quantitatively.

For cognitive impairment, it is still not clear to what degree the trade-off between efficacy and cognitive side effects can be avoided by manipulating dose and electrode placement. There is, however, evidence that bilateral ECT causes more cognitive impairment than unilateral ECT and that the cognitive impairment and efficacy from unilateral ECT are dose related. This has now been included in the guidance together with more detailed advice on how and when to measure cognitive side effects and on the principles of choice of electrode placement and dose in relation to efficacy and cognitive side effects.

There are some data on continuation/maintenance ECT that support at least equal efficacy in preventing relapse compared with pharmacotherapy but the evidence is limited. Systematic, prospective assessment of longer-term cognitive effects of continuation/maintenance ECT are also limited although those available do not suggest cumulative cognitive adverse effects. Given the relative lack of data, no treatment recommendation is made with regard to continuation/maintenance ECT.

However, in recognition that continuation/maintenance ECT will continue to be used in exceptional circumstances, and that conclusive RCT data are unlikely to be available in the short-to- medium term, a research recommendation on collecting data for national audit when continuation/maintenance ECT is used has been added (see Section 12.4.10).

Relapse prevention using pharmacological strategies has also been examined, and the data suggest that continuation antidepressants particularly with lithium augmentation of antidepressants is effective.

12.4.9 Recommendations

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

12.4.10 Research recommendations

12.4.10.1 The effectiveness of maintenance ECT for relapse prevention in people with severe and recurring depression that does not respond to pharmacological or psychological interventions

Is maintenance ECT effective for relapse prevention in people with severe and recurring depression that does not respond to pharmacological or psychological

Depression not adequately responding to treatment and relapse prevention interventions?

Why this is important

A small number of people do not benefit in any significant way from pharmacological or psychological interventions but do respond to ECT. However, many of these people relapse and need repeated treatment with ECT. This results in considerable suffering to them and it is also costly, because ECT often necessitates inpatient care. A small number of studies suggest possible benefits from maintenance ECT but it is used little in the NHS. The outcome of the audit and clinical trial should supply information on patient characteristics, outcomes, feasibility and acceptability in relation to the use of maintenance ECT and potentially inform its wider use in the NHS. The results therefore may have important implications for the provision of ECT in the NHS.

This question should be addressed through first establishing a national audit for the collection of data on all people receiving maintenance ECT. The characteristics of the people who are likely to be considered for maintenance ECT make a randomised controlled trial unfeasible, but a clinical trial using alternative methods (for example, mirror image or a carefully characterised non-randomised study) should be undertaken depending on the outcome of the audit.

The number of people receiving maintenance ECT is small, and considerable uncertainty surrounds its use, such as its long-term efficacy and acceptability and possible side effects, which include cognitive impairment. The outcomes chosen for the audit and clinical trial should reflect both observer and patient-rated assessments of improvement, the impact on cognitive function and an assessment of the acceptability of ECT as a maintenance treatment.

12.5 OTHER NON-PHARMACOLOGICAL PHYSICAL TREATMENTS

12.5.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) involves focal stimulation of the superficial layers of the cerebral cortex using a rapidly changing magnetic field applied using an external coil. It does not require anaesthesia and can be performed on an outpatient basis. Treatment with TMS usually involves daily sessions lasting about 30 minutes for 2 to 4 weeks and possibly longer. Its use in the treatment of depression has recently been the subject of NICE Interventional Procedures Guidance (IPG 242; NICE, 2007d).

The main points highlighted in the review and guidance were:

- Uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date.
- No major safety concerns associated with TMS.

Included in the review was consideration of a meta-analysis of 33 short-term RCTs in depression (Herrmann & Ebmeier, 2006), which found a large significant effect size of 0.71 against sham treatment. However, the studies were small, heterogeneous in methodology and effect size and it was not possible to identify any significant predictors of outcome. A more recent meta-analysis for patients with treatment-resistant depression, which included 24 studies (1,092 patients) meeting their inclusion criteria

(Lam *et al.*, 2008), found that active repetitive transcranial magnetic stimulation (rTMS) was significantly superior to sham conditions in producing clinical response, with a risk difference of 17%. However the pooled response and remission rates were only 25% and 17%, and 9% and 6% for active rTMS and sham conditions respectively. They concluded that further studies are required before adopting rTMS as a first-line treatment for treatment-resistant depression.

12.5.2 From evidence to recommendations

The guideline uses the recommendation from the current NICE Interventional Procedure Guidance on TMS (IPG 242, NICE, 2007d).

12.5.3 Recommendation

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

12.5.4 Vagus nerve stimulation

Vagus nerve stimulation (VNS) therapy is a type of treatment where a small electrical pulse is administered through an implanted neurostimulator to a bipolar lead attached to the left vagus nerve. A battery-powered pulse-generating device is implanted under the skin of the upper left chest. A wire is tunnelled under the skin and connected to the left vagus nerve in the neck.

The stimulation parameters (pulse width and frequency, current intensity, and on/off cycles) are programmed into the pulse generator via a programming wand. The battery lasts 8 to 10 years and can be replaced under local anaesthesia. A typical treatment regimen might comprise intermittent stimulation for 30 seconds every 5 minutes throughout the day and night. This procedure has been studied in patients with treatment-resistant epilepsy and it is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients who are refractory to anti-epileptic medication. NICE guidance on VNS for refractory epilepsy in children concluded that current evidence appears adequate to support the use of this procedure 'provided that the normal arrangements are in place for consent, audit and clinical governance' (IPG 50, NICE, 2004c). In addition antidepressant effects of VNS in epilepsy patients have been described, independent of reduction of seizure frequency (for example, Harden *et al.*, 2000).

The efficacy and safety of VNS for treatment-resistant depression is currently under consideration by the NICE Interventional Procedures Advisory Programme. Readers concerned with the efficacy and safety of VNS, and recommendations about its use to treat depression, should refer to this document which is expected to be published in 2010.

13 THE MANAGEMENT OF SUBTHRESHOLD DEPRESSIVE SYMPTOMS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

14 SUMMARY OF RECOMMENDATIONS

This section was updated and replaced in 2022. Please see the NICE website for the updated guideline.

14.11 RESEARCH RECOMMENDATIONS

14.11.1.1 Sequencing antidepressant treatment after inadequate initial response
What is the best medication strategy for people with depression who have not had sufficient response to a first SSRI antidepressant after 6 to 8 weeks of adequate treatment?

Why this is important
Inadequate response to a first antidepressant is a frequent problem but the best way of sequencing treatments is not clear from the available evidence. There is good evidence that the likelihood of eventual response decreases with the duration of depression and number of failed treatment attempts, so maximising the response at an early stage may be an important factor in the final outcome. The results of this study will be generalisable to a large number of people with depression and will inform choice of treatment.

This question should be addressed using a randomised controlled trial design to compare the effects of continuing on the same antidepressant (with dose increase if appropriate) and switching to another SSRI or to an antidepressant of another class. Built into the design should be an assessment of the effect of increased frequency of follow-up and monitoring alone on improvement. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design, and mediators and moderators of response should be investigated.

14.11.1.2 The efficacy of short-term psychodynamic psychotherapy compared with CBT and antidepressants in the treatment of moderate to severe depression
In well-defined depression of moderate to severe severity, what is the efficacy of short-term psychodynamic psychotherapy compared with CBT and antidepressants?

[229]This recommendation is taken from 'Transcranial magnetic stimulation for severe depression' (NICE interventional procedure guidance 242).

Why this is important

Psychological treatments are an important therapeutic option for people with depression. CBT has the best evidence base for efficacy but it is not effective for everyone. The availability of alternatives drawing from a different theoretical model is therefore important. Psychotherapy based on psychodynamic principles has historically been provided in the NHS but provision is patchy and a good evidence base is lacking. It is therefore important to establish whether short-term psychodynamic psychotherapy is an effective alternative to CBT and one that should be provided. The results of this study will have important implications for the provision of psychological treatment in the NHS.

This question should be answered using a randomised controlled trial design that reports short-term and medium-term outcomes (including cost-effectiveness outcomes) of at least 18 months' duration. Particular attention should be paid to the reproducibility of the treatment model and training and supervision of those providing interventions in order to ensure that the treatments are both robust and generalisable. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design, and mediators and moderators of response should be investigated.

14.11.1.3 The cost effectiveness of combined antidepressants and CBT compared with sequenced treatment for moderate to severe depression

What is the cost effectiveness of combined antidepressants and CBT compared with sequenced medication followed by CBT and vice versa for moderate to severe depression?

Why this is important

There is a reasonable evidence base for the superior effectiveness of combined antidepressants and CBT over either treatment alone in moderate to severe depression. However the practicality, acceptability and cost effectiveness of combined treatment over a sequenced approach is less well-established. The answer has important practical implications for service delivery and resource implications for the NHS.

This question should be answered using a randomised controlled trial design in which people with moderate to severe depression receive either combined treatment from the outset, or single modality treatment with the addition of the other modality if there is inadequate response to initial treatment. The outcomes chosen should reflect both observer and patient-rated assessments for acute and medium-term outcomes to at least 6 months, and an assessment of the acceptability and burden of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design together with robust health economic measures.

14.11.1.4 The efficacy of light therapy compared with antidepressants for mild to moderate depression with a seasonal pattern

How effective is light therapy compared with antidepressants for mild to moderate depression with a seasonal pattern?

Why this is important

Although the status of seasonal depression as a separate entity is not entirely clear, surveys have consistently reported a high prevalence of seasonal (predominantly winter) depression in the UK. This reflects a considerable degree of morbidity, predominantly in the winter months, for people with this condition. Light therapy has been proposed as a specific treatment for winter depression but only small, inconclusive trials have been carried out, from which it is not possible to tell whether either light therapy or antidepressants are effective in its treatment. Clarification of whether, and to what degree, treatments are effective would help to inform the decisions that people with seasonal depression and practitioners have to make about the treatment of winter depression.

This question should be answered using a randomised controlled trial design in which people with mild to moderate depression with a seasonal pattern (seasonal affective disorder) receive light therapy or an SSRI antidepressant in a partially placebo-controlled design. The doses of both light and SSRI should be at accepted or proposed therapeutic levels and there should be an initial phase over a few weeks in which a plausible placebo treatment is administered followed by randomisation to one of the active treatments. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects, and mediators and moderators of response should be investigated.

14.11.1.5 The efficacy of CBT compared with antidepressants and placebo for persistent subthreshold depressive symptoms

What is the efficacy of CBT compared with antidepressants and placebo for persistent subthreshold depressive symptoms?

Why this is important

Persistent subthreshold depressive symptoms are increasingly recognised as affecting a considerable number of people and causing significant suffering, but the best way to treat it is not known. There are studies of the efficacy of antidepressants for dysthymia (persistent subthreshold depressive symptoms that have lasted for at least 2 years) but there is a lack of evidence for CBT. Subthreshold depressive symptoms of recent onset tend to improve but how long practitioners should wait before offering medication or psychological treatment is not known. This research recommendation is aimed at informing the treatment options available for this group of people with subthreshold depressive symptoms that persist despite low-intensity interventions.

This question should be answered using a randomised controlled trial design that reports short-term and medium-term outcomes (including cost-effectiveness outcomes) of at least 6 months' duration. A careful definition of persistence should be used which needs to include duration of symptoms and consideration of failure of low-intensity interventions and does not necessarily imply a full diagnosis of dysthymia. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of

clinically important effects using a non-inferiority design, and mediators and moderators of response should be investigated.

14.11.1.6 The efficacy of counselling compared with low-intensity cognitive behavioural interventions and treatment as usual in the treatment of persistent subthreshold depressive symptoms and mild depression

In persistent subthreshold depressive symptoms and mild depression, what is the efficacy of counselling compared with low-intensity cognitive behavioural interventions?

Why this is important

Psychological treatments are an important therapeutic option for people with subthreshold symptoms and mild depression. Low-intensity cognitive and behavioural interventions have the best evidence base for efficacy but the evidence is limited and longer-term outcomes are uncertain, as are the outcomes for counselling. It is therefore important to establish whether either of these interventions is an effective alternative to treatment as usual and should be provided in the NHS. The results of this study will have important implications for the provision of psychological treatment in the NHS.

This question should be answered using a randomised controlled trial design which reports short-term and medium-term outcomes (including cost-effectiveness outcomes) of at least 18 months' duration. Particular attention should be paid to the reproducibility of the treatment model and training and supervision of those provid- ing interventions in order to ensure that the treatments are both robust and generalis- able. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design, and mediators and moderators of response should be investigated.

14.11.1.7 The efficacy of behavioural activation compared with CBT and antidepressants in the treatment of moderate to severe depression

In well-defined depression of moderate to severe severity, what is the efficacy of behavioural activation compared with CBT and antidepressants?

Why this is important

Psychological treatments are an important therapeutic option for people with depression. Behavioural activation is a promising treatment but does not have the substantial evidence base that CBT has. The availability of alternatives drawing from a different theoretical model is important because outcomes are modest even with the best supported treatments. It is therefore important to establish whether behavioural activation is an effective alternative to CBT and one that should be provided. The results of this study will have important implications for the provision of psychological treatment in the NHS.

This question should be answered using a randomised controlled trial design which reports short-term and medium-term outcomes (including cost-effectiveness

outcomes) of at least 18 months' duration. Particular attention should be paid to the reproducibility of the treatment model and training and supervision of those providing interventions in order to ensure that the treatments are both robust and generalisable. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design, and mediators and moderators of response should be investigated.

14.11.1.8 The efficacy and cost effectiveness of different systems for the organisation of care for people with depression

In people with mild, moderate or severe depression, what system of care (stepped care versus matched care) is more clinically effective and cost effective in improving outcomes?

Why this is important

The best structures for the delivery of effective care for depression are poorly understood. Stepped-care models are widely implemented but the efficacy of this model compared with matched care is uncertain. Evidence on the relative benefits of the two approaches and the differential effects by depression severity is needed. The results of this study will have important implications for the structure of depression treatment services in the NHS.

This question should be answered using a randomised controlled trial design which reports short-term and medium-term outcomes (including cost-effectiveness outcomes) of at least 18 months' duration. In stepped care the majority of patients will first be offered a low-intensity intervention by a paraprofessional unless there are significant risk factors dictating otherwise. In matched care a comprehensive mental health assessment will determine which intervention a patient should receive. The full range of effective interventions (both psychological and pharmacological) should be made available in both arms of the trial. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects, and moderators (including the severity of depression) of response should be investigated.

14.11.1.9 The efficacy and cost effectiveness of CBT, IPT and antidepressants in prevention of relapse in people with moderate to severe recurrent depression

In people with moderate to severe recurrent depression, what is the relative efficacy of CBT, IPT and antidepressants in preventing relapse?

Why this is important

Psychological and pharmacological treatments are important therapeutic options for people with depression, but evidence on the prevention of relapse (especially for psychological interventions) is limited. All of these treatments have shown promise in reducing relapse but the relapse rate remains high. New developments in the style

and delivery of CBT and IPT show some promise in reducing relapse but need to be tested in a large-scale trial. The results of this study will have important implications for the provision of psychological treatment in the NHS.

This question should be answered using a randomised controlled trial design which reports short-term and medium-term outcomes (including cost-effectiveness outcomes) of at least 24 months' duration. Particular attention should be paid to the development and evaluation of CBT, IPT and medication interventions tailored specifically to prevent relapse, including the nature and duration of the intervention. The outcomes chosen should reflect both observer and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. The study needs to be large enough to determine the presence or absence of clinically important effects using a non-inferiority design, and mediators (including the focus of the interventions) and moderators (including the severity of the depression) of response should be investigated.

14.11.1.10 The effectiveness of maintenance ECT for relapse prevention in people with severe and recurring depression that does not respond to pharmacological or psychological interventions

Is maintenance ECT effective for relapse prevention in people with severe and recurring depression that does not respond to pharmacological or psychological interventions?

Why this is important

A small number of people do not benefit in any significant way from pharmacological or psychological interventions but do respond to ECT. However, many of these people relapse and need repeated treatment with ECT. This results in considerable suffering to them and it is also costly, because ECT often necessitates inpatient care. A small number of studies suggest possible benefits from maintenance ECT but it is used little in the NHS. The outcome of the audit and clinical trial should supply information on patient characteristics, outcomes, feasibility and acceptability in relation to the use of maintenance ECT and potentially inform its wider use in the NHS. The results therefore may have important implications for the provision of ECT in the NHS.

This question should be addressed through first establishing a national audit for the collection of data on all people receiving maintenance ECT. The characteristics of the people who are likely to be considered for maintenance ECT make a randomised controlled trial unfeasible, but a clinical trial using alternative methods (for example, mirror image or a carefully characterised non-randomised study) should be undertaken depending on the outcome of the audit.

The number of people receiving maintenance ECT is small, and considerable uncertainty surrounds its use, such as its long-term efficacy and acceptability and possible side effects, which include cognitive impairment. The outcomes chosen for the audit and clinical trial should reflect both observer and patient-rated assessments of improvement, the impact on cognitive function and an assessment of the acceptability of ECT as a maintenance treatment.

15 APPENDICES

Appendices

APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

GUIDELINE TITLE

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

Short title

Depression in adults (update)

BACKGROUND

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

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

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

CLINICAL NEED FOR THE GUIDELINE

Depression refers to a range of mental health disorders characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and

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

The symptoms of depression can be disabling and the effects of the illness pervasive. Depression can have a major detrimental effect on people's personal, social and occupational functioning, placing a heavy burden on individuals and their carers and dependents, as well as placing considerable demands on the healthcare system. Among all diseases, depression is currently the fourth leading cause of burden to society. World Health Organisation projections indicate that it will be the highest ranking cause of disease burden in developed countries by the year 2020.

Each year 6% of adults will experience an episode of depression and over the course of their lifetime more than 15% of the population will experience an episode. The average length of an episode of depression is between 6 and 8 months. For many people the episode will be mild but for more than 30%, the depression with be moderate or severe and have a significant impact on their daily lives. Recurrence rates are high; there is a 50% chance of recurrence after a first episode, rising to 70% and 90% after a second or third episode respectively.

Estimated prevalence rates for men do not vary greatly among ethnic groups but those for women differ remarkably. In the UK significantly higher rates of depression are reported in women of Asian and Oriental family origin or background compared with other groups, with the next highest rates being in white women and the lowest rates in women of West Indian or African family origin or background. However, these estimates are based on relatively small samples.

Depression is the leading cause of suicide, which accounts for less than 1% of all deaths. Nearly two-thirds of deaths by suicide occur in people with depression (that is, about 2,600 suicides per year in England alone).

Data from the Prescription Cost Analysis (PCA; Department of Health, 2008a) system show that in the 12 months to March 2006, antidepressant drugs accounted for 4.1% of all items dispensed in the community in England, at a net ingredient cost of £31 million.

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

THE GUIDELINE

The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' (NICE, 2007b) describes how organisations can become involved in the development of a guideline.

'The guidelines manual' (NICE, 2007c) provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The areas that will be addressed by the guideline are described in the following sections.

POPULATION

Groups that will be covered

- Adults (aged 18 years and older) who have a clinical diagnosis of depression established by a recognised diagnostic system such as DSM–IV or ICD–10. The guideline will be relevant to people with mild, moderate and severe major depressive disorders.
- People in the above group who also have learning difficulties, acquired cognitive impairments, or language difficulties.

Groups that will not be covered

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

HEALTHCARE SETTING

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

CLINICAL MANAGEMENT

- Recognition, assessment and classification of depression, including variations to the assessment to take account of the needs of people with learning difficulties, acquired cognitive impairments or language difficulties.
- Treatment of depressive episodes of differing severity, including the appropriate use of psychosocial interventions (such as guided self-help, formal psychological interventions, support groups and programmes aimed at facilitating employment), pharmacological interventions (including antidepressants and other medication), and physical interventions (such as exercise and electroconvulsive therapy).

- Variations to the systems for accessing and delivering treatment required to take account of the needs of people with learning difficulties, acquired cognitive impairments or language difficulties.
- Interventions to reduce the risk of relapse after an acute depressive episode.
- Assessment and management of the known side effects and other drawbacks of psychotropic medication, physical interventions, and psychosocial interventions, including long-term side effects and risks of suicide.
- Combined psychosocial and pharmacological treatments, the use of combined pharmacological treatments and the sequencing of both pharmacological and psychosocial interventions.
- The safe withdrawal/discontinuation of psychotropic medication.
- Interactions between psychotropic medication and common prescription and over-the-counter drugs.
- The varying approaches of different races and cultures, and issues of internal and external social exclusion.
- The role of the families and carers in the treatment and support of people with depression.
- The ways in which services are delivered, including models of care such as case management and collaborative care, and the structured delivery of care in primary and secondary care services.

Note that guideline recommendations for pharmacological interventions will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual service users.

The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning an intervention for optimal use or changing an approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

AREAS THAT WILL NOT BE COVERED BY THE GUIDELINE

The guideline will not cover:

- diagnosis of depression
- primary prevention of depression.

STATUS

Scope

This is the final scope.

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

They will also update and replace the following NICE guidance:

- Computerised cognitive behaviour therapy for depression and anxiety. NICE technology appraisal guidance 51 (2006a).
- Guidance on the use of electroconvulsive therapy. NICE technology appraisal guidance 59 (2003).

GUIDELINE

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

FURTHER INFORMATION

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS' (NICE, 2007b).
- 'The guidelines manual' (NICE, 2007a).

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

APPENDIX 2: DECLARATIONS OF INTEREST BY GUIDELINE DEVELOPMENT GROUP MEMBERS

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

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

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

Categories of interest

- Paid employment
- Personal pecuniary interest: financial payments or other benefits from either the manufacturer or the owner of the product or service under consideration in this guideline, or the industry or sector from which the product or service comes. This includes holding a directorship, or other paid position; carrying out consultancy or fee paid work; having shareholdings or other beneficial interests; receiving expenses and hospitality over and above what would be reasonably expected to attend meetings and conferences.
- Personal family interest: financial payments or other benefits from the healthcare industry that were received by a member of your family.
- Non-personal pecuniary interest: financial payments or other benefits received by the GDG member's organisation or department, but where the GDG member has not personally received payment, including fellowships and other support

provided by the healthcare industry. This includes a grant or fellowship or other payment to sponsor a post, or contribute to the running costs of the department; commissioning of research or other work; contracts with, or grants from, NICE.

- Personal non-pecuniary interest: these include, but are not limited to, clear opinions or public statements you have made about depression, holding office in a professional organisation or advocacy group with a direct interest in depression, other reputational risks relevant to depression.

Declarations of interest – GDG members	
Professor Ian Anderson, Chair, Guideline Development Group	
Employment	Professor of Psychiatry, University of Manchester
Personal pecuniary interest	Consultant for Wyeth Ltd Global Depression and Anxiety Strategy Consultant Board (specific), ended August 2007 Consultant for Bristol-Myers Squibb Pharmaceuticals Ltd/Otsuka Pharmaceuticals UK Ltd Bipolar Disorder Advisory Board (non-specific), ended August 2007 Consultant for Servier Ltd Agomelatine Advisory Board, ended August 2007 Honoraria for speaking at non-promotional meetings from the following companies: AstraZeneca, Wyeth, Janssen Cilag, Lundbeck, 2007–2008
Personal family interest	None
Non-personal pecuniary interest	AstraZeneca investigator – initiated grant (specific) Honorarium paid into university research fund by Wyeth Ltd for speaking at non-promotional meeting Talk on Managing Depression (independent content) at meeting supported by Lilly P1vital commercial study sponsored by Servier

Continued

Declarations of interest – GDG members (*Continued*)	
Personal non-pecuniary interest	Member of MHRA Psychiatry Expert Advisory Group Member of Royal College of Psychiatrists Special Committee on ECT
Ms Alison Barnes	
Employment	Social Worker
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Carolyn Chew-Graham	
Employment	General Practitioner and Senior Lecturer in Primary Care, University of Manchester
Personal pecuniary interest	Mental health clinical adviser for Manchester Joint Commissioning Team (Manchester Primary Care Trust, Central PBC Hub)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Jeremy Clarke	
Employment	Psychological Therapist, Lambeth Primary Care Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Research and development lead for the Association of Psychoanalytic Psychotherapy in the NHS

Continued

Declarations of interest – GDG members (*Continued*)	
	Member of Expert Reference Group for Improving Access to Psychological Therapies (IAPT)
Ms Catherine Harris	
Employment	Labour Councillor for Haringey
Personal pecuniary interest	Mental Health Act Commissioner from April 2008
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Role as councillor does not entail a portfolio for health issues although the Labour Party campaigns on health issues Member of Mental Health Carers Support Association
Dr Mark Kenwright	
Employment	Consultant Cognitive Behavioural Psychotherapist, Ealing Cognitive Behavioural Therapy Service
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Coordinator of two pilot studies and an RCT on computerised cognitive behavioural therapy (CCBT), guided self-help for panic disorder and phobias formed focus of doctoral thesis and three publications in *British Journal of Psychiatry* (1999 to 2002) Manager of Stress Self-Help Clinic research project in first CCBT clinic in primary care which offered CCBT for panic/phobia (Fearfighter), obsessive-compulsive disorder (BT Steps) and depression (COPE). Published in *Psychological Medicine* (2001 to 2003)

Continued

Declarations of interest – GDG members (*Continued*)	
	Project lead for Improving Access to Psychological Therapies (IAPT) Pathfinder Site for London and South East (Ealing CBT Service). The service received £200,000 from IAPT for the period October 2007 to 2008
Professor Willem Kuyken	
Employment	Professor of Clinical Psychology and Co-Director Mood Disorders Centre, University of Exeter Psychology
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-director of Mood Disorders Centre, funded by Devon Partnership NHS Trust and Devon Primary Care Trust Co-principal investigator, NHS HTA (£1.2 million, 1.7 million with NHS costs). Cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment resistant depression in primary care: a randomised control trial. 2008 to 2011. (Principal Investigator: Dr Nicola Wiles, University of Bristol) Principal Investigator, Medical Research Council (£233,000). Trial platform: Preventing depression relapse in NHS practice using mindfulness-based cognitive therapy (MBCT) 2005 to 2007
Professor Glyn Lewis	
Employment	Professor of Psychiatric Epidemiology, University of Bristol
Personal pecuniary interest	Occasional payment from pharmaceutical companies for non-promotional talks, for example, to other departments of psychiatry or at conferences
Personal family interest	None

Continued

Appendix 2

Declarations of interest – GDG members (*Continued*)	
Non-personal pecuniary interest	Colleagues in department at Bristol University received funds from pharmaceutical industry to carry out research which I am not involved in
Personal non-pecuniary interest	None
Mr Brendan Masterson	
Employment	Clinical Nurse Leader, Affective Disorders Unit, Bethlem Royal Hospital
Personal pecuniary interest	Presented a session on NICE guidelines for bipolar disorder at a study day sponsored by Janssen Cilag (February 2007)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Alan Meudell	
Employment	Healthy Minds at Work
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Member of Mind Expert Policy Group on Psychiatric Medicine and other Therapies Member of Pwyllgor Cymru (Governance body of Mind Cymru, Mind Wales) Member of Caerphilly Borough Council Mental Health Strategy Group Member of Adult Mental Health NSF Implementation Advisory Group (WAG)
Dr Alex Mitchell	
Employment	Consultant Psychiatrist and Honorary Lecturer in Liaison Psychiatry, University of Leicester

Continued

Declarations of interest – GDG members (*Continued*)	
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Richard Moore	
Employment	Clinical Psychologist, Cambridge and Peterborough NHS Foundation Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Interest in effectiveness of treatments for depression including taking part in related RCTs and the production of a treatment manual for treatment of chronic depression
Ms Carol Paton	
Employment	Chief Pharmacist, Oxleas NHS Foundation Trust
Personal pecuniary interest	Eli Lilly Advisory Board and consultancy for duloxetine. Involvement has been since phase three trials and is not ongoing (2003–2007) Attendance at European Congress of Neuropsychopharmacology (ECNP) 2007, sponsored by Janssen Cilag, without personal financial gain Eli Lilly Advisory Board for other products currently subject to clinical trials: depot IM olanzapine and novel drugs in phase two studies. None of these drugs was currently licensed and none was intended to treat depression (February 2008)
Personal family interest	None
Non-personal pecuniary interest	None

Continued

Appendix 2

Declarations of interest – GDG members (*Continued*)	
Personal non-pecuniary interest	Co-author of paper describing clinical use of depot antipsychotics in the United Kingdom, to be published in *British Medical Journal* supplement. The supplement is funded by Eli Lilly who have no influence over the content. No personal payment has been or will be received for this (April 2008)
Dr Thomas Shackleton	
Employment	General Practitioner, Suffolk
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Jane Wood	
Employment	Nurse, Strategic Development Manager, Mental Health, Leeds Primary Care Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Declarations of interest – NCCMH staff	
Professor Stephen Pilling – Facilitator, Guideline Development Group	
Employment	Director, NCCMH Director, Centre for Outcomes Research and Effectiveness, University College London
Personal pecuniary interest	In receipt of funding from NICE to develop clinical guidelines
Personal family interest	None

Continued

Declarations of interest – NCCMH staff (*Continued*)	
Non-personal pecuniary interest	RCT to evaluate multi-systemic therapy. Chief Investigator is Professor Peter Fonagy. Department of Health funding of £1,000,000 (2008 to 2012)
Personal non-pecuniary interest	None
Ms Victoria Bird	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Rachel Burbeck	
Employment	Systematic Reviewer, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Matthew Dyer (from 2008)	
Employment	Health Economist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Sarah Hopkins (2007 to 2008)	
Employment	Project Manager, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Continued

Appendix 2

Declarations of interest – NCCMH staff (*Continued*)	
Ms Angela Lewis	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Ryan Li (2008)	
Employment	Project Manager, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Nick Meader	
Employment	Systematic Reviewer, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Suffiya Omarjee (from 2008)	
Employment	Health Economist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Peny Retsa (until 2008)	
Employment	Health Economist, NCCMH
Personal pecuniary interest	None
Personal family interest	None

Continued

Declarations of interest – NCCMH staff (*Continued*)	
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Maria Rizzo	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Jennie Robertson	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Rob Saunders	
Employment	Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Christine Sealey (from 2008)	
Employment	Centre Manager, NCCMH
Personal pecuniary interest	On secondment from NICE
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Beth Shackleton (until 2008)	
Employment	Project Manager, NCCMH
Personal pecuniary interest	None

Continued

Appendix 2

Declarations of interest – NCCMH staff (*Continued*)	
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Sarah Stockton	
Employment	Information Scientist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Clare Taylor	
Employment	Editor, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

APPENDIX 3: SPECIAL ADVISERS TO THE GUIDELINE DEVELOPMENT GROUP

Dr John Eagles
Professor Steven Hollon

APPENDIX 4: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

STAKEHOLDERS

Association for Family Therapy
Association for Psychoanalytic Psychotherapy in the NHS
Association of Counsellors and Psychotherapists in Primary Care (CPC)
AstraZeneca UK Ltd
British Association for Behavioural and Cognitive Psychotherapies (BABCP)
British Association for Counselling and Psychotherapy
British Association for Psychopharmacology
British Association of Art Therapists
British Psychoanalytic Council
British Psychological Society
Central and North West London NHS Foundation Trust
Centre for Clinical Practice Health Economists, NICE
Centre for Clinical Practice Technical Adviser
Centre for Psychological Services Research
Counselling Haverhill
Critical Psychiatry Network
Department of Health
Depression Alliance
Diabetes UK
Eli Lilly and Company Limited and Boehringer Ingelheim
GlaxoSmithKline UK Limited
Headway – The Brain Injury Association
Institute of Group Analysis
Institute of Psychiatry
Intapsych Ltd
Leeds Partnerships NHS Foundation Trust
Lundbeck Ltd
Medicines and Healthcare products Regulatory Agency
Mental Health Providers Forum
Mind

Appendix 4

NHS Direct
Oxfordshire and Buckinghamshire Mental Health NHS Foundation Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Pathologists
Royal College of Psychiatrists
Royal Pharmaceutical Society of Great Britain (RPSGB)
Servier Labatories Ltd
Sheffield Health and Social Care Foundation Trust
South London and Maudsley NHS Foundation Trust
St Mungo's
Tavistock and Portman NHS Foundation Trust
Tees Esk and Wear Valleys NHS Foundation Trust
Tuke Centre
UK Psychiatric Pharmacy Group (UKPPG)
Ultrasis UK Limited
United Kingdom Council for Psychotherapy (UKCP)
Young Minds
Youth Access

EXPERTS

Professor Aaron Beck
Professor John Cape
Professor Mick Cooper
Professor Steven Hollon
Professor Wayne Katon
Professor Tony Kendrick
Dr Roslyn Law
Professor Helen Lester
Dr John Markowitz
Professor Keith Matthews
Professor Declan McLoughlin
Professor Robert Peveler
Professor David Richards
Professor Myrna Weissman

APPENDIX 5: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE PRE-PUBLICATION CHECK

STAKEHOLDERS

Association of British Neurologists
Cambridgeshire and Peterborough NHS Foundation Trust
CPC Association of Counsellors in Primary Care
Department of Health
Eli Lilly and Company Limited and Boehringer Ingelheim Ltd
GlaxoSmithKline UK Limited
Lundbeck Ltd
National Hospital for Neurology and Neurosurgery (NHNN)
Ultrasis UK Limited

EXPERTS

Dr David Healy

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

Dr Allan Abbass
Professor Anthony Bateman
Professor Paul Crits-Christoph
Dr John Eagles
Dr Robert Golden
Professor Hayes
Dr Mark Hilsenroth
Professor Peter Fonagy
Professor Charles Kellner
Professor Falk Leichsenring
Dr Chris Martell
Professor Glenys Parry
Professor Carolyn Webster-Stratton
Professor Kenneth Wilson

APPENDIX 7:
CLINICAL QUESTIONS

Clinical questions for Depression Update Guideline		**Clinical question in previous guideline**
A	***Service configuration for people with depression***	
A1	What methods are effective in identifying people with depression in primary care and community settings, including sexual health clinics, emergency departments, and drug and alcohol services? In which populations (excluding those with chronic physical health problems) should identification methods be used?	A1
A2	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), which models of care produce the best outcomes? – collaborative care – stepped care – case management – stratified (matched) care – attached professional model Are different models appropriate to the care of people in different phases of the illness, such as treatment resistant depression and relapse prevention?	A5
B	***Psychology/psychosocial interventions for people with depression***	
B1	In depression, does guided self-help improve outcomes compared with other interventions?	A2
B2	Does computerised CBT (CCBT) improve patient outcomes compared with other treatments?	A3
B3	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold	A4

	depressive symptoms), do any of the following improve outcomes compared with other interventions? – exercise – support including groups, befriending, and non-statutory provision – programmes to facilitate employment	
B4	Do non-statutory support groups improve outcomes?	A6
B5	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), do any of the following (either alone or in combination with pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual): – CBT – BT/behavioural activation – counselling/person-centred therapy – problem solving – psychodynamic psychotherapy – family interventions/couples therapy – ACT (acceptance and commitment therapy) – systemic interventions – psychoeducation – cognitive analytic therapy (CAT) – solution-focused therapy – self-help, including guided self-help – CCBT Does mode of delivery (group-based or individual) impact on outcomes? Are there specific therapist characteristics that improve outcomes? Are there specific patient characteristics (for example, anxiety, previous episodes) that predict outcomes? Are brief interventions (for example, 6 to 8 weeks) effective? Are psychological interventions harmful?	B1 B2
B6	Following poor response to treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), which psychological or psychosocial interventions are appropriate?	

B7	In people whose depression has responded to treatment, what psychological and psychosocial strategies are effective in preventing relapse (including maintenance treatment)?	
C	***Pharmacological/physical interventions***	
C1	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), which drugs (either not covered by the previous guideline or where significant new evidence exists) improve outcomes compared with other drugs and with placebo? – TCAs – duloxetine – desvenlafaxine – escitalopram – agomelatine – St John's wort – antipsychotics (for example, quetiapine)	C1
C2	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), to what extent do the following factors affect the choice of drug? – adverse events (in particular, cardiotoxicity), including long-term adverse events – discontinuation problems	C2
C3	In the pharmacological treatment of depression, what are the most effective strategies for treating patients experiencing treatment side effects, including sexual dysfunction and weight gain?	C3
C4	In people whose depression has responded to treatment, what strategies are effective in preventing relapse (including maintenance treatment)?	C6
C5	In people whose depression has atypical features, what are the most effective treatment strategies?	C6
C6	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), do any of the following improve outcomes compared with other interventions? – ECT – TMS (integrate NICE Interventional Procedure Guidance)	C7 A9

	– light therapy – VNS – neurosurgery – deep brain stimulation	
C7	For people with depression (major depressive disorder, dysthymia, and so on), who are receiving pharmacological treatment, does therapeutic drug monitoring improve outcomes?	
C8	What are appropriate ways to promote adherence? (Link to NICE guideline on medicines adherence, CG76)	
C9	In the treatment of depression (major depressive disorder, dysthymia, subthreshold depression and subthreshold depressive symptoms), how can equal access to services for all be ensured? [What promotes access to effective care particularly for people with learning difficulties, acquired cognitive impairment and language difficulties?]	A9
D	***General***	
D1	In the treatment of depression, which patient characteristics predict response and relapse? For example, childhood trauma, age of onset, number of previous episodes, gender, and so on.	
D2	In the treatment of depression, are there specific clinician approaches that improve outcomes?	

APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

1. General search strategies

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

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

b. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials – Wiley Interscience interface[230]

#1 MeSH descriptor Depression, this term only
#2 MeSH descriptor Depressive Disorder explode all trees

[230]With respect to 1b, this search was generated for the *Depression in Adults with a Chronic Physical Health Problem* guideline (NCCMH, 2010) and was sifted for relevance to the clinical areas of both that guideline and this guideline update.

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

2. Systematic review search filters

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

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

3. Randomised controlled trial search filters

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

1 exp clinical trial/ or exp clinical trials/ or exp clinical trials as topic/ or exp controlled clinical trials/
2 (placebo$1 or random allocation or random assignment or random sample or random sampling or randomization).sh,id.
3 (double blind$ or single blind$ or triple blind$).sh,id.

Appendix 8

4 (crossover procedure or crossover design or cross over studies).sh,id.
5 (clinical adj2 trial$).tw.
6 (crossover or cross over).tw.
7 (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
8 (placebo$ or random$).mp.
9 (clinical trial$ or controlled clinical trial$ or random$).pt. or treatment outcome$.md.
10 animals/ not (animals/ and human$.mp.)
11 animal$/ not (animal$/ and human$/)
12 (animal not (animal and human)).po.
13 (or/1-9) not (or/10-12)

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

APPENDIX 9:
CLINICAL STUDY DATA EXTRACTION FORM

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

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

Trial length:
Interventions (Dose): 1 2 3

Notes:

APPENDIX 10: QUALITY CHECKLISTS FOR CLINICAL STUDIES AND REVIEWS

See pages 624–627.

Appendix 10

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

2 TREATMENT GROUP:												
Leaving treatment early (any reason) (side effects)		**Leaving treatment early reporting)**		**Side Effects (total number**				**Remission [non-remission]**				
n	*N*	*n*	*N*	*N*	*N*			*n*	*N*			
Definition of remission **Definition of response**												
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:

3 TREATMENT GROUP:											
Leaving treatment early (any reason) (side effects)		**Leaving treatment early reporting)**		**Side Effects (total number**		**Remission [non-remission]**					
n	*N*	*n*	*N*	*N*	*N*	*n*	*N*				
Definition of remission **Definition of response**											
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*

4 TREATMENT GROUP:												
Leaving treatment early (any reason) (side effects)		**Leaving treatment early reporting)**		**Side Effects (total number**		**Remission [non-remission]**					
n	*N*	*n*	*N*	*N*	*N*	*n*	*N*				
Definition of remission **Definition of response**											
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*

APPENDIX 11: THE CLASSIFICATION OF DEPRESSION AND DEPRESSION RATING SCALES/QUESTIONNAIRES

BACKGROUND

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

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

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

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

CLASSIFICATION OF DEPRESSION AND NICE GUIDANCE

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

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

DIAGNOSIS OF A DEPRESSIVE/MAJOR DEPRESSIVE EPISODE

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

DSM–IV the patient must have five or more out of nine symptoms with at least one from the first two (depressed mood and loss of interest). Both diagnostic systems require symptoms to have been present for at least 2 weeks to make a diagnosis (but can be shorter in ICD–10 if symptoms are unusually severe or of rapid onset). In both ICD–10 and DSM–IV the symptoms must result in impairment of functioning that increases with the episode severity. Table 143 compares the symptoms required in ICD–10 and DSM–IV.

DETERMINING SEVERITY OF A DEPRESSIVE/MAJOR DEPRESSIVE EPISODE

Both ICD–10 and DSM–IV classify clinically important depressive episodes as mild, moderate and severe based on the number, type and severity of symptoms present and degree of functional impairment. Table 144 shows the number of symptoms required by each diagnostic system, which are less specific than DSM–IV. The prescriptive

Table 143: Comparison of symptoms of depression in ICD–10 and DSM–IV

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

*Core symptoms.

Table 144: Number of symptoms required in ICD–10 and DSM–IV for a diagnosis of depressive episode/major depression (but note they also need assessment of severity and functional impairment to ascertain diagnosis and severity)

	ICD–10 depressive episode	DSM–IV major depression
Mild	4	Minimal above the minimum (5)
Moderate	5–6	Between mild and severe
Severe	7+	Several symptoms in excess of 5

symptom counting approach of ICD–10 tends to lend itself to using symptom counting alone to determine severity.

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

DIAGNOSIS OF SUBTHRESHOLD DEPRESSIVE SYMPTOMS

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

There is no accepted classification for this in the current diagnostic systems with the closest being minor depression, a research diagnosis in DSM–IV. At least two but less than five symptoms are required, of which one must be depressed mood or diminished interest. This includes ICD–10 depressive episode with four symptoms and, given the practical difficulty and inherent uncertainty in deciding thresholds for

significant symptom severity and disability, there is no natural discontinuity between minor depression and mild major depression in routine clinical practice. There is however a danger of 'medicalising' distress by adopting minor depression as a discrete diagnosis, which would inevitably broaden the concept of depression. For this guideline update the GDG therefore use the term 'subthreshold depressive symptoms' to avoid this problem while providing a way of describing this part of the depressive spectrum.

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

ICD–10 has a category of mixed anxiety and depression, which is less clearly defined than minor depression, and is largely a diagnosis of exclusion in those with anxiety and depressive symptoms subthreshold for specific disorders. Not unexpectedly it appears to be a heterogeneous category with a lack of diagnostic stability over time (Wittchen *et al.*, 2001b; Barkow *et al.*, 2004). For this reason it has not been included in this guideline.

DURATION

The duration of a depressive episode can vary considerably among individuals. The average course of an untreated depressive episode is between 6 and 8 months with much of the improvement occurring in the first 3 months, and 80% recovered by 1 year (Coryell *et al.*, 1994). There is evidence to suggest that patients who do not seek treatment for their depression may recover more quickly than those who seek but do not receive treatment (Posternak *et al.*, 2006). There is also some evidence to suggest that people who do not seek help have a shorter mean duration of depressive episode (Posternak *et al.*, 2006).

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

(for example, Khan *et al.*, 1991). However there seems little to be gained by redefining duration for the guideline as long as it is recognised that the conventional definitions are merely signposts to include consideration of duration in relation to outcome and need for treatment.

COURSE OF DEPRESSION

An influential model of the course of major depression proposes that the onset of an episode of depression consists of a worsening of symptoms in a continuum going from depressive symptoms through to major depression. Phases of improvement with treatment consist of response (significant improvement) to remission (absence of depressive symptoms) which if stable for 4 to 6 months results in (symptomatic) recovery, meaning that the episode is over (Frank *et al.*, 1991). It is important to distinguish this use of recovery from more recent concepts related to quality and meaning of life in spite of continued symptoms. After recovery a further episode of depression is viewed as a recurrence to distinguish it from a relapse of the same episode. There has been no consensus as to how long a period of remission should be in order to be able to declare recovery; different definitions result in different definitions of episode length and time to full or subthreshold depressive recurrence (Furukawa *et al.*, 2008). Therefore, in practice it can be difficult to distinguish between relapse and recurrence, particularly when people have mild residual symptoms. Follow-up studies of people with depression have shown that, overall, more time is spent with subthreshold depressive symptoms than major depression and there is a variable individual pattern ranging from persisting chronic major depression, through significant but not full improvement (partial remission), to full remission and recovery (Judd *et al.*, 1998). DSM–IV defines full remission when there has been an absence of symptoms for at least 2 months. For partial remission, full criteria for a major depressive episode are no longer met, or there are no substantial symptoms but 2 months have not yet passed. DSM–IV specifies 'with full inter-episode recovery' if full remission is attained between the two most recent depressive episodes and 'without full inter-episode recovery' if full remission is not attained. In DSM–IV, therefore, separate episodes are distinguished by at least 2 months of not meeting major depression criteria, which is in contrast to the more stringent ICD–10 requirements of 2 months without any significant symptoms. There is therefore some ambiguity as to whether full remission is required to define separate episodes.

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

Appendix 11

DEPRESSION SUBTYPES

Different symptom profiles have been described and are included in the classification systems. In DSM–IV, severe major depression can be without or with psychosis (psychotic depression) and there are specifiers that include melancholia, atypical features, catatonia, depression with a seasonal pattern (seasonal affective disorder) and post-partum onset. ICD–10 also provides specifiers for psychotic and somatic symptoms, the latter similar to DSM–IV melancholia. However, these subtypes do not form distinct categories (for example, Kendell, 1968; Angst *et al.*, 2007) and they add a further complexity to the diagnosis of depression. The GDG judged that these specifiers were best considered where appropriate after the diagnosis of a depressive disorder is made and they are not discussed in detail here. Some specifiers, particularly psychosis and seasonal pattern depression, have potential treatment implications and are considered in the guideline update where evidence is available.

CLASSIFICATION OF DEPRESSION IN THE GUIDELINE UPDATE

The depression classification system adopted for the guideline update had to meet a number of criteria, notably the use of:

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

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

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

Core symptoms of depression

1) Depressed mood most of the day, nearly every day.
2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

Somatic symptoms

3) Significant weight loss when not dieting or weight gain (for example, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4) Insomnia or hypersomnia nearly every day.
5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6) Fatigue or loss of energy nearly every day.

Other symptoms

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

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

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

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

- persistent depressed mood
- markedly diminished interest or pleasure.

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

- feelings of worthlessness or guilt
- impaired concentration
- recurrent thoughts of death or suicide.

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

Severity

While recognising that severity is not a unitary dimension, practically it is useful to make a judgement of severity consisting, at least, of number of symptoms, severity of

individual symptoms and functional impairment. This leads to a classification of depression into the following severity groupings based on DSM–IV criteria, which should be viewed as exemplars not discrete categories. In the guideline update the term 'depression' refers to major depression:

- subthreshold depressive symptoms: fewer than five symptoms of depression
- mild depression: few, if any, symptoms in excess of the five required to make the diagnosis, and the symptoms result in only minor functional impairment
- moderate depression: symptoms or functional impairment are between 'mild' and 'severe'
- severe depression: most symptoms, and the symptoms markedly interfere with functioning; can occur with or without psychotic symptoms.

Symptom severity and degree of functional impairment correlate highly (for example, Zimmerman *et al.*, 2008), but in individual cases this may not be the case and some mildly symptomatic individuals may have marked functional impairment while some people who are severely symptomatic may, at least for a time, maintain good function, employment and so on.

Duration

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

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

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

Course

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

1) Number of lifetime depressive episodes and the interval between recent episodes: the number varies from a single/first episode to increasingly frequent recurrences. At least 2 months of full or partial remission is required to distinguish episodes.
2) Stage of episode: this refers to where an individual is in the course of their depression. In an episode it is useful to determine if the depression is worsening, static or improving and whether subthreshold depressive symptoms may reflect partial remission from prior major depression.

Conventionally, classification has distinguished between a single episode and two or more episodes (recurrent depression) irrespective of how long there has been between episodes and how many recurrences have occurred. However, someone who has had two episodes separated by decades has a different clinical course from

someone with three episodes in a few years, therefore, noting the number of episodes and their recent pattern is important. There is uncertainty about the duration and extent of the recovery that is required to distinguish between different episodes of depression and a fluctuating course of a single episode. In practice this is less important than recognising the risk of persistent symptoms and of major depressive relapse/recurrence.

CLASSIFICATION IN RELATION TO DEPRESSION RATING SCALES AND QUESTIONNAIRES

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

Nevertheless it is necessary to try and translate trial evidence (which may only provide rating scales or questionnaire scores) into a meaningful clinical context as well as relating this guideline update to the previous guideline which used the APA (2000a) cut-offs. The change to DSM–IV-based diagnosis and the inclusion of minor depression (subthreshold depressive symptoms) in the update means that the descriptors of ranges previously given are no longer tenable. Table 145 gives the descriptors and ranges used in this guideline update, with the important caveat that these must not be taken as clear cut-offs or a short-cut to classify people with depression.

IMPLICATIONS OF THE PROPOSED CLASSIFICATION

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

Another very important point to emphasise is that making a diagnosis of depression does not automatically imply a specific treatment. Making and agreeing a diagnosis of depression is a starting point in considering the most appropriate way of helping that individual in their particular circumstances. The evidence base for treatments considered in this guideline are based primarily on RCTs in which

Table 146: Levels of depression in relation to the HRSD and BDI in the guideline update compared with those suggested by the APA (2000a)

17-item Hamilton Rating Scale for Depression (HRSD)					
Guideline update	**Not depressed**	**Subthreshold**	**Mild**	**Moderate**	**Severe**
APA (2000a)*	Not depressed	Mild	Moderate	Severe	Very severe
Score	0–7	8–13	14–18	19–22	23+

Beck Depression Inventory (BDI)				
Guideline update	**Not depressed**	**Subthreshold**	**Mild to moderate**	**Moderate to severe**
APA (2000a)*	Not depressed	Mild	Moderate	Severe
Score	0–9	10–16	17–29	30+

*Used in the previous guideline.

standardised criteria have been used to determine entry into the trial. Patients seen clinically are rarely assessed using standardised criteria reinforcing the need to be circumspect about an over-rigid extrapolation from RCTs to clinical practice.

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

APPENDIX 12: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMIC EVIDENCE

1. General search strategies

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

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

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

#1 MeSH descriptor Depression, this term only
#2 MeSH descriptor Depressive Disorder explode all trees
#3 MeSH descriptor Mood Disorders, this term only

#4 (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ti or (depress* or dysphori* or dysthym* or seasonal affective disorder* or melanchol*):ab
#5 (#1 OR #2 OR #3 OR #4)

c. OHE HEED – Wiley interface

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

2. Health economics and quality-of-life search filters

a. MEDLINE, EMBASE, PsycINFO, CINAHL – Ovid interface[231]

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

[231]With respect to 2a, search request 6 was ANDed with or/1–4 from the general search strategy only.

APPENDIX 13:
QUALITY CHECKLIST FOR ECONOMIC STUDIES

Author: **Date:**

Title:

	Study design	**Yes**	**No**	**NA**
1	The research question is stated			
2	The economic importance of the research question is stated			
3	The viewpoint(s) of the analysis are clearly stated and justified			
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 is stated			
7	The choice of form of economic evaluation used is justified in relation to the questions addressed			
	Data collection			
1	The source of effectiveness estimates used is stated			
2	Details of the design and results of effectiveness study are given (if based on a single study)			
3	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)			
4	The primary outcome measure(s) for the economic evaluation are clearly stated			
5	Methods to value health states and other benefits are stated			
6	Details of the subjects from whom valuations were obtained are given			

Appendix 14

7	Indirect costs (if included) are reported separately	👎	👎	👎
8	The relevance of indirect costs to the study question is discussed	👎	👎	👎
9	Quantities of resources are reported separately from their unit costs	👎	👎	
10	Methods for the estimation of quantities and unit costs are described	👎	👎	
11	Currency and price data are recorded	👎	👎	
12	Details of currency, price adjustments for inflation or currency conversion are given	👎	👎	
13	Details of any model used are given	👎	👎	👎
14	The choice of model used and the key parameters on which it is based are justified	👎	👎	👎
	Analysis and interpretation of results			
1	The 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	👎	👎	👎
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	👎	👎	

Validity score: Yes/No/NA:

APPENDIX 14:
DATA EXTRACTION FORM FOR ECONOMIC STUDIES

Reviewer: **Date of review:**

Authors:

Publication Date:

Title:

Country:

Language:

Economic study design:

- CEA
- CCA
- CUA
- CBA
- CA
- CMA

Modelling:

- No
- Yes

Source of data for effect size measure(s):

- Meta-analysis
- Cohort study
- RCT
- Mirror image (before-after) study
- Quasi experimental study
- Expert opinion

Comments _____

Primary outcome measure(s) (please list):

_____

Interventions compared (please describe):

Treatment: _____

Comparator: _____

Appendix 14

Setting (please describe):

_____

_____

Patient population characteristics (please describe):

_____

_____

_____

Perspective of analysis:

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

Time frame of analysis: _____

Cost data:

- Primary
- Secondary

If secondary please specify: _____

Costs included:

Direct medical	Direct non-medical	Lost productivity
direct treatment	social care	income forgone due to illness
inpatient	social benefits	income forgone due to death
outpatient	travel costs	income forgone by caregiver
day care	caregiver out-of-pocket	
community healthcare	criminal justice	
medication	training of staff	

Or

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

Others: _____

Currency: _____ **Year of costing:** _____

Was discounting used?

☐ Yes, for benefits and costs ☐ Yes, but only for costs ☐ No

Discount rate used for costs: _____

Discount rate used for benefits: _____

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17 ABBREVIATIONS

3MSE	Modified Mini-Mental State Examination
5-HT	5-hydroxytryptymine
AD	antidepressant (in the Appendices only)
AD	antidepressant treatment given for 12 weeks with 6 months' maintenance therapy and 6 months' follow-up (*Strategy A* in this guideline)
ADI	Amritsar Depression Inventory
ADQ	average daily quantities
A&E	Accident and Emergency Department
AfC	Agenda for Change
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AMED	Allied and Alternative Medicine Database
AMI	autobiographical memory impairment
AMI/AMT	amitriptyline (in the Appendices only)
AMS	amisulpride
AP	antipsychotic
APA	American Psychiatric Association
APNR	acute phase non-responders
ASEX	Arizona Sexual Experience scale
AUC	area under the curve
BABCP	British Association for Behavioural and Cognitive Psychotherapies
BAC	British Association for Counselling
BACP	British Association for Counselling and Psychotherapy
BAI	Beck Anxiety Inventory
BASDEC	Brief Assessment Schedule depression cards
BD	bipolar disorder
BDI	Beck Depression Inventory
BDT	brief dynamic therapy
BIDS	Brief Inventory for Depressive Symptoms
BLIPS	Brief Limited Intermittent Psychotic Symptons
BLRI	Barrett-Lennard Relationship Inventory
BME	black and minority ethnic
BMJ	*British Medical Journal*
BMQ	Beliefs about Medicines Questionnaire
BMT	behavioural marital therapy

BPD	borderline personality disorder
BPI	Brief Pain Inventory
BPIT	brief psychodynamic-interpersonal therapy
Bpn	bupropion XL
BSP/BS	brief supportive psychotherapy
BT	behaviour therapy
BtB	Beating the Blues
BZD	benzodiazepine
C	completers analysis
CADET	Collaborative Depression Trial
CAGE	A short assessment for alcohol misuse
CARE	Comprehensive Assessment and Referral Evaluation
CAT	cognitive analytic therapy
CAU	care as usual
C-BDI	Chinese Beck Depression Inventory
CBT	cognitive behavioural therapy
CCBT/cCBT	computerised cognitive behavioural therapy
CCSS	Caribbean Culture-Specific Screen for emotional disorders
CCT	client-centered treatment
CDRS-SR	Carroll Depression Rating Scale (Self-Report)
CDS	Chronic Disease Score
CEAC	cost-effectiveness acceptability curve
CEEG	continuous electroencephalography
CES-D	Centre of Epidemiology Studies-Depression
CGI	Clinical Global Impressions
CI	confidence interval
CIDI (-SF)	Composite International Diagnostic Interview (-Short Form)
CIGP-CD	cognitive-interpersonal group psychotherapy for chronic depression
CINAHL	*Cumulative Index to Nursing and Allied Health Literature*
CIS (-R)	Clinical Interview Schedule (-Revised)
Cit/cital	citalopram
clr	cluster randomised (adjusted)
CM	care management/clinical management
CMB	combined
CMBN	combined arms
CMHN	community mental health nurse
CMHT	community mental health team
CNS	central nervous system
CNSLNG	counselling
Cntl	control
CNTRL	control

COMB	Combination of 12 weeks' antidepressant treatment and 16 sessions of CBT with 6 months' maintenance therapy and 6 months' follow-up (*Strategy B* in this guideline)
Combo	combined treatment (used in the Appendices only)
COPE	Calendar of Premenstrual Experiences
CORE	Centre for Outcomes, Research and Effectiveness
CORE (-OM)	Clinical Outcomes in Routine Evaluation (-Outcome Measure)
CPA	Care Programme Approach
CPN	community psychiatric nurse
C-R	clinician-reported
CRHTT	crisis resolution and home treatment team
CSPRS	Collaborative Study Psychotherapy Rating Scale
CSQ (-8)	Client Satisfaction Questionnaire (-8 items)
CT	cognitive therapy
Ctp	citalopram
CTS	Cognitive Therapy Scale
CWD	Coping with Depression
D	dysthymia
DA	dopamine
DAI	Drug Attitude Index
DALY	disability adjusted life years
DBM	demineralised bone matrix
DESS	Discontinuation Emergent Signs and Symptoms
df	degrees of freedom
DIS	Diagnostic Interview Schedule
DP	day patient
DPDS	depression subscale of the Short-CARE
DRP (-PC)	Depression Recurrence Prevention Program (-psychiatric consultation)
DSM (–II, –III, –IV, –TR, –R)	*Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (2nd edition, 3rd edition, 4th edition, Text Revision, Revision)
Dsp	desipramine
dul/dulox	duloxetine
ECG	electrocardiogram
ECT	electroconvulsive therapy
EDS	Edinburgh Depression Scale
EED	Economic Evaluation Database
EEG	electroencephalography
EFT	emotion-focused therapy
EMBASE	Excerpta Medica Database

EQ-5D	European Quality of Life-5 Dimensions
ER	extended release
ERIC	Education Resources Information Center
Escit/esc	escitalopram
EuroQOL	European Quality of Life
F	female
FDA	US Food and Drug Administration
Flp	flupenthixol
FLU/fluox/flx/flu	fluoxetine
Flv/Fvx	fluvoxamine
G	group
GAD	generalised anxiety disorder
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
gCBT	group cognitive behavioural therapy
GDG	Guideline Development Group
GDS	Geriatric Depression Scale
GHC	Group Health Cooperative
GHQ	General Health Questionnaire
GMS-AGECAT	Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy
GP	general practitioner
GPc	general practitioner care
GPRD	General Practice Research Database
GPT	group psychotherapy
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GRP	Guideline Review Panel
GSH	guided self-help
GSS	Global Seasonality Score
HADS (-D)	Hospital Anxiety and Depression Scale (-Depression)
HAM-A	Hamilton Anxiety Rating Scale
HAMD/HAM-D	Hamilton Depression Rating Scale
HAP	Human Activities Profile
HAQ	Health Assessment Questionnaire
HCl	hydrochloride
HLM	hierarchical linear modelling
HMIC	Health Management Information Consortium
HMO	health maintenance organisation
HMSO	Her Majesty's Stationery Office
HMU	head-mounted unit
HRQoL	health-related quality of life

HRSD	Hamilton Rating Scale for Depression
HRT	hormone replacement therapy
HSCL	Hopkins Symptom Checklist
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
ICC	intracluster correlation coefficient
ICD (-9, -10)	*International Classification of Diseases* (9th revision; 10th revision)
ICER	incremental cost-effectiveness ratio
ICM	imipramine + clinical management
ICSD-2	International Classification of Sleep Disorders-2
ICT	integrative cognitive therapy
IDS	Inventory for Depressive Symptomatology
IHD	ischaemic heart disease
Imp	imipramine
IMPACT	A collaborative care for depression programme at the University of Washington
Int	intervention
Ip	interpersonal therapy for dysthymic disorder
IP	inpatient
IPD	interpersonal difficulties
IPT (-M, -D)	interpersonal therapy (-maintenance, -for dysthymia)
ITT	intention to treat
JAMA	*Journal of the American Medical Association*
K	number of studies
K10	Kessler-10
KPDS	Kleinian Psychoanalytic Diagnostic Scale
LD3	low dose (three times per week)
LD5	low dose (five times per week)
LED	light-emitting diode
li	lithium
LOCF	last observation carried forward
LOF	lofepramine
LR-	negative likelihood ratio
LR+	positive likelihood ratio
LVCF	last value carried forward
M	male
MADRS	Montgomery–Åsberg Depression Rating Scale
MAJOR	major depression arm of study
MAOI	monoamine oxidase inhibitor

MBCBT	mindfulness-based CBT
MBCT	mindfulness-based cognitive therapy
MBSR	mindfulness-based stress reduction
mcl	moclobemide
MD	mean difference/major depression
MDD	major depressive disorder
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHI (-5)	Mental Health Inventory (-5 items)
MHRA	Medicines and Healthcare products Regulatory Agency
MHT	Mental Health Team
MI	myocardial infarction
MIDAS	Module for Meta-analytical Integration of Diagnostic Test Accuracy Studies
MINI	Mini International Neuropsychiatric Interview
MINOR	minor depression arm of study
MMPI	Minnesota Multiphasic Personality Inventory
MMQ	Maudsley Marital Questionnaire
MMRM	Mixed-Effect Model Repeated Measure
MMSE	Mini-Mental State Examination
Mnp	minaprine
MOS-SF-20	Medical Outcomes Study-Short Form-20 items
MPS	Maier and Philipp (core mood stability) Subscale
Mpt	maprotiline
MRC	Medical Research Council
MSE	Mental State Examination
MSQ	Mental Status Questionnaire
N/A	not applicable
N/n	number of participants
N/R	not reported
NA	noradrenaline
NA	not available
NARI	noradrenaline reuptake inhibitor
NaSSA	noradrenaline and specific serotonin antidepressant
NCC	National Collaborating Centre
NCCMH	National Collaborating Centre for Mental Health
ND	non-directive
NEF	nefazodone
NEO (-FFI)	NEO Personality Inventory (-Five-Factor Inventory)
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIMH (TDCRP)	National Institute of Mental Health (Treatment of Depression Collaborative Research Program)
nm	nanometers

NNH	number needed to harm
NNT	number needed to treat
Nort	nortriptyline
NOS	not otherwise specified
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
NSF	National Service Framework
OCD	obsessive-compulsive disorder
OHE HEED	Office of Health Economics Health Economic Evaluations Database
Olz	olanzapine
OpenSIGLE	System for information on Grey Literature in Europe
OR	odds ratio
OT	occupational therapy/therapist
Parox/prx/px	paroxetine
PARQ	Physical Activity Readiness Questionnaire
PASE	Physical Activity Scale for the Elderly
PCA	Prescription Cost Analysis
P-CM	placebo + clinical management
PCMHW	primary care mental health worker
PCP	primary care practitioner
PCT	Primary Care Trust
PD	personality disorder
PE	process experiential treatment
PEP (+PC)	psychoeducational prevention programme (+psychiatric consultation)
PF-SOC	Problem-Focused Style of Coping scale
PGEM	pharmacist guided education and monitoring
PGI	Patient Global Impression scale
PGMS	Philadelphia Geriatric Morale Scale
PHD3	public health dose (180 minutes of moderate-intensity exercise per week, three times per week)
PHD5	public health dose (180 minutes of moderate-intensity exercise per week, five times per week)
PHQ (-9)	Patient Health Questionnaire (-9 items)
Phz	phenelzine
PICO	patient, intervention, comparison and outcome
PLA/Plb/pbo/pb	placebo
POMS	Profile of Mood States
PP	psychodynamic psychotherapy
PRIME-MD	Primary Care Evaluation of Mental Disorders

PR interval	The part of the electrocardiogram between the beginning of the P-wave (atrial depolarisation) and the QRS complex (ventricular depolarisation)
PRT	progressive resistance training
PS	problem solving
PSE	Present State Examination
PSS	personal social services
PSSRU	Personal Social Services Research Unit
PST/PS (PC)	problem-solving therapy (-primary care)
PsycBOOKS	A full-text database of books and chapters in the APA's electronic databases
PsycEXTRA	A grey literature database, which is a companion to PsycINFO
PsycINFO	Psychological Information Database
Pt/s	patient/s
PTSD	post-traumatic stress disorder
QALM	quality-adjusted life month
QALY	quality-adjusted life year
QI	quality improvement
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
QLDS	Quality of Life Depression Scale
QoL	Quality of Life
QoLI	Quality of Life Inventory
QRS interval	period from the start of the Q wave to the end of the S wave (time for ventricular depolarisation)
QTc	corrected QT interval
QT interval	period from the start of the Q wave to the end of the T wave (duration of ventricular electrical activity)
QWB-SA	Quality of Well-Being Scale
RAND-36	A 36-item health survey by RAND
RANLab	Random Agent Networks model application
RCT	randomised controlled trial
RD	risk difference
RDC	Research Diagnostic Criteria
REBT	rational emotive behaviour therapy
RIMA	reversible inhibitors of monoamine oxidase
ROC	receiver operator characteristic
RR	relative risk/risk ratio
RS	rating scale
RSMD	Rating Scale for Mania and Depression
Rts	ritanserin

SAD	seasonal affective disorder
SAS	Spielberger State/Trait Anxiety Scale
SASS	Social Adaptation Self-evaluation Scale
SC	standard care
SCID (-IV, -PQ)	Structured Clinical Interview for DSM (-IV, -Personality Questionnaire)
SCL (-20, -90, -R)	Symptom Checklist (-20 items, -90 items, -Revised)
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SEM	standard error of the mean
SF-12, -36	12-/36-item short form health survey
SFS	Social Functioning Schedule
SFX	significant effects
SG	standard gamble
Short-CARE	Comprehensive Assessment Referral Evaluation (short)
SIGH (-SAD, -SR)	Structured Interview Guide for the Hamilton Depression Rating Scale (-Seasonal Affective Disorders, -Self Rating)
SIGN	Scottish Intercollegiate Guidelines Network
SJW	St John's wort
SMD	standardised mean difference
SNRI	serotonin–noradrenaline reuptake inhibitor
SOFAS	Social and Occupational Functioning Assessment Scale
SQ-SS	Symptom Questionnaire-Somatic Subscale
S-R	self-reported
SR	sustained release
Srtl/stl/st	sertraline
SSRI	specific serotonin reuptake inhibitor
STAI	State-Trait Anxiety Inventory
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
STPP	short-term psychodynamic psychotherapy
T1	end of trial
T2	6 months after end of trial
T3	triiodothyronine
TA	technology appraisal
TAU	treatment as usual
TCA	tricyclic antidepressant
TCM (-TP)	telephone care management (-telephone psychotherapy)
TDM	telephone disease management programme
t.i.d	three times a day
TMS	transcranial magnetic stimulation
TRD	treatment resistant depression
TTO	time trade-off

UC	usual care
UKCP	United Kingdom Council for Psychotherapy
VAMC	Veterans Affairs Medical Center
VAS	Visual Analogue Scale
VAX	virtual address eXtension
Ven/vfx	venlafaxine
VNS	vagus nerve stimulation
vrbl	verbal
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organization
WHOQOL (-BREF)	World Health Organization Quality of Life Assessment (-BREF [26 items])
WL/WLC	waitlist/waitlist control
WMD	weighted mean differences
WSAS	Work and Social Adjustment Scale
WSDS	Work and Social Disability Scale
XL/XR	extended release

"This guideline is an authoritative, comprehensive and up-to-date review of the evidence-based treatment of depression. It provides clear guidance on the effective treatment of depression and will be of real value to all clinicians and patients."

Steven D. Hollon, Professor of Psychology, Vanderbilt University, Nashville, Tennessee

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