Depression in Adults with a Chronic Physical Health Problem:
treatment and management

National Clinical Practice Guideline Number [X]

National Collaborating Centre for Mental Health
Commissioned by the
National Institute for Health and Clinical Excellence

Recommendations highlighted in grey are from NICE clinical guideline 23 (available from www.nice.org.uk/CG23). Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.

A partial update of NICE clinical guideline 23 is under way that will replace it – recommendation wording highlighted in blue is from the pre-publication draft of that update (pre-publication check taking place between 22 July and 12 August 2009). See Depression in adults (update) for more information.

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Acknowledgements

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1 Preface

1.1 National guideline

1.1.1 What are clinical practice guidelines?

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

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

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

1.1.2 Uses and limitations of clinical guidelines

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

Although the quality of research in this field is variable, the methodology used here reflects current international understanding on the appropriate practice for guideline development (AGREE: Appraisal of Guidelines for Research and Evaluation Instrument; www.agreecollaboration.org), ensuring the collection and selection of the best research evidence available and the systematic generation of treatment recommendations applicable to the majority of people with these disorders and situations. However, there will

always be some people and situations for which clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, in consultation with the person with depression and chronic health problems or their carer.

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

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

1.1.3 Why develop national guidelines?

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

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

Centres in conjunction with a range of professional organisations involved in healthcare.

1.1.4 The National Collaborating Centre for Mental Health

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

1.1.5 From national guidelines to local protocols

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving commissioners of healthcare, primary care and specialist mental health professionals, service users and carers should undertake the translation of the implementation plan into local protocols taking into account both the recommendations set out in this guideline and the priorities set in the National Service Framework for Mental Health (Department of Health, 1999) and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

1.1.6 Auditing the implementation of guidelines

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

1.2 The National Depression – Chronic Health Problems guideline

1.2.1 Who has developed this guideline?

The Guideline Development Group (GDG) was convened by the NCCMH and supported by funding from NICE. The GDG included a service user and carer, and professionals from psychiatry, clinical psychology, general practice, nursing and psychiatric pharmacy.

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

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

1.2.2 For whom is this guideline intended?

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

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 and chronic health problems 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 and chronic health problems.

1.2.3 Specific aims of this guideline

The guideline makes recommendations for the treatment and management of people with depression and chronic health problems. It aims to:

- improve access and engagement with treatment and services for people with depression and chronic health problems evaluate the role of specific psychological and psychosocial

interventions in the treatment of depression and chronic health problems
- evaluate the role of specific pharmacological interventions in the treatment of depression and chronic health problems
- evaluate the role of specific service level interventions for people with depression and chronic health problems
- integrate the above to provide best-practice advice on the care of people with depression and chronic health problems 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 chronic health problems, and to the methods used to update this guideline. Chapters 4 to 8 provide the evidence that underpins the recommendations about the treatment and management of people with depression and chronic health problems, with chapter 4 providing personal accounts from service users and carers, which offer an insight into their experience of depression and chronic health problems.

Each evidence chapter begins with a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted, and the structure of the chapters varies accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about the review protocol and studies included in the review. Clinical evidence summaries are then used to summarise the data presented (forest plots can be found in Appendix 19). 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[1]. On the CD-ROM, further details are provided about included/excluded studies, the evidence, and the previous guideline methodology (see for Table 1 for details).

[1] Due to the nature of pharmacological evidence, the evidence to recommendations section and recommendations can be found at the end of the chapter (rather than after each topic reviewed).

Table 1. Appendices on CD-ROM.

Evidence tables for economic studies.	Appendix 17
Included/excluded study tables	Appendix 18
Clinical evidence forest plots	Appendix 19
Case ID included study tables	Appendix 20
GRADE evidence profiles	Appendix 21

2 Depression in Adults with Chronic Physical Health Problems

2.1 Introduction

The management of depression for patients with chronic physical health problems was not specifically addressed in the NICE (2004a) guideline on Depression: management in primary and secondary care (NICE, 2004a; NCCMH, 2005). Given the size and the scope of that guideline a decision was made that as part of the updating of the 2004 guideline a separate guideline on depression in chronic physical health problems should be developed. However, it is not the intention in developing this guideline to argue that depression in chronic physical health problems is a separate disorder requiring novel and different forms of treatment, rather it is as much a recognition of the context (both in term of the illness and the service settings) and the breadth of the field. Some of the work undertaken in this guideline (e.g. on case identification was done jointly with depression update guideline) and in developing recommendations for depression in physical health care the guideline development group both explicitly drew on this evidence and extrapolated from it where this was considered appropriate .

In this guideline we pay particular attention to, cancer, heart disease, musculoskeletal disorders, respiratory disorders, neurological disorders, and diabetes as chronic physical diseases, but it must be appreciated that all chronic diseases have higher rates of depression and anxiety than physically healthy controls. However, it must also be stressed that the majority of those with chronic physical diseases do not have depressive or anxiety disorders.

2.2 Depression in adults with chronic physical health problems

This guideline is concerned with the treatment and management of people with depression in those with chronic physical illnesses. These patients are especially common in primary care and in general hospital care. The terminology and diagnostic criteria used for this heterogeneous group of related disorders has changed over the years and previous guidance (NICE, 2004a) related only to those identified by the ICD-10 Classification of Mental and Behavioural Disorders (ICD-10) (WHO, 1992) as having a depressive episode (F32), recurrent depressive episode (F33) or mixed anxiety and depressive disorder (F41.2). In this guideline, along with the update of the Depression Guideline (NICE, 2009; NCCMH, forthcoming) the scope has been widened in the recognition that a substantial proportion of people present with less severe forms of depression so that this guidance in addition considers dysthymia (F34.1) and depression falling below the threshold for depression which does not have a coding in ICD-10 but will be included in

other mood [affective] disorders (F38). It should however be noted that much of the research forming the evidence base from which this guideline is drawn has used a different classificatory system – the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, currently in its fourth edition (DSM-IV) (APA, 2000a). The two classificatory systems, while similar, are not identical especially with regard to definitions of severity. After considerable discussion the GDG have taken the decision to base the guidelines on the DSM-IV and this covers major depressive disorder single episode (296.2) and recurrent (296.3) together with dysthymic disorder (300.4) and subthreshold depressive disorder (included in 311, depressive disorder not otherwise specified) (APA, 2000a). The guideline does not address the management of depression in bipolar disorder, post-natal depression or depression in children and adolescents, all of which are covered by separate guidelines.

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Distinguishing the mood changes between clinically significant degrees of depression (e.g. major depression) and those occurring 'normally' remains problematic and it is best to consider the symptoms of depression as occurring on a continuum of severity (Lewinsohn *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 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 the need to take other aspects that need to be considered such as duration, stage of illness, treatment history there remain considerable problems when attempting to classify depression into categories. Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, reduced sleep, an exacerbation of pre-existing pains, and pains secondary to increased muscle tension and other pains (Gerber *et al*., 1992), lowered appetite (sometimes leading to significant weight loss), a lack of libido, fatigue and diminished activity, although agitation is common and marked anxiety frequent. Along with a loss of interest and enjoyment in everyday life, feelings of guilt, worthlessness and deserved punishment are common, as are lowered self-esteem, loss of confidence, feelings of helplessness, suicidal ideation and attempts at self-harm or suicide. Cognitive changes include poor concentration and reduced attention, pessimistic and recurrently negative thoughts about oneself, one's past and the future, mental slowing and rumination (Cassano & Fava, 2002).

Although it is generally thought that depression is usually a time-limited disorder lasting up to six months with complete recovery afterwards, in the WHO study of mental disorders in 14 centres across the world, 66% of those

suffering from depression were still found to satisfy criteria for a mental disorder a year later and for 50% the diagnosis was depression. In the case of depression accompanying chronic physical disease the prognosis is likely to be substantially worse since the physical disease will still be present, but objective evidence on this point is not available.

Major depression is generally diagnosed when a persistent and un-reactive 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). While depression occurring in the absence of physical disease is commonly accompanied by various somatic symptoms, when depression accompanies chronic physical illness the problem of distinguishing somatic symptoms due to the known physical disease and the depression is particularly difficult.

2.2.1 Presentations of depression in chronic physical disease

Only a minority of patients attending doctors in primary care give psychological problems as their presenting complaint. In the World Health Organisation's Psychological Problems in Primary Care study (Ustun & Sartorius 1995) only 9.4% did so in the UK Centre, to be compared with only 5% in data from all 15 centres combined (p 352, table 2). The majority are complaining of pain and other somatic complaints (63% in the UK, 62.1% across the world), with the remainder complaining of sleep problems and fatigue. This study showed that 26.2% of attendees in the UK had a diagnosable mental disorder, of which depression, at 16.9%, was the commonest disorder. It follows that depressed people are most usually presenting with non-psychological symptoms, and the doctor's first task is to investigate the possible causes of these symptoms. When a chronic physical disease is either found or is known to be present, attention may shift to this disease, and the depression may then be overlooked (Ustun & Sartorius 1995; Tiemens *et al.*, 1999; Thompson *et al.*, 2000).

2.2.2 Impairment and disability

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

Depression can also exacerbate the pain and distress associated with physical diseases, as well as adversely affecting outcomes. For example, in people with myocardial infarction (MI), death rates are significantly greater for those who are depressed following an MI, not only in the immediate post-MI period, but for the subsequent year (Lesperance *et al.*, 2000). In one community study,

patients with cardiac disease who were depressed had an increased risk of death from cardiac problems compared with those without depression, and depressed people without cardiac disease also had a significantly increased risk of cardiac mortality (Pennix *et al*., 2001). Similar findings for a range of physical illnesses also suggest an increased risk of death when co-morbid depression is present (Cassano & Fava, 2002). Von Korff *et al*., (2005) also showed that depression predicts functional disability in diabetes better than the number of physical complications of diabetes, glycaemic control or the extent of chronic disease co-morbidity.

An important distinction is that between social disability, which has a linear relationship with the number of depressive symptoms, and any functional disabilities due to physical diseases – for example impaired mobility due to arthritis, or limitation of movements due to stroke. It is likely that such functional impairments greatly increase the risk of depression among those with physical diseases.

2.2.3 Suicide risk in people with chronic physical illness

Large population-based epidemiological studies have reported higher suicide risk linked with various major physical diseases including cancer (Allebeck *et al*., 1989), diabetes (Tsang, 2004), end-stage renal disease (Kurella *et al*., 2005), epilepsy (Christensen *et al*., 2007), multiple sclerosis (Brønnum-Hansen *et al*., 2005), stroke (Teasdale & Engberg, 2001a) and traumatic brain injury (Teasdale & Engberg, 2001b). These findings indicate the importance of detecting and treating depressive disorder in people with chronic physical health problems.

2.2.4 Diagnosis of depression among those with physical diseases

Although the advent of operational diagnostic criteria has improved the reliability of diagnosis this does not get around the fundamental problem of attempting to classify a disorder that is heterogeneous and best considered on a number of dimensions. This is further complicated in patients with chronic physical health problems as somatic criteria such as fatigue, appetite disturbance, and sleep disturbance may be sequelae of medical illnesses rather than depression. Zimmerman and colleagues (2006) have suggested a simplified method of diagnosis using five non-somatic criteria as a response to the problems of overlapping symptoms. For a fuller discussion see Appendix 12.

DSM-IV and ICD-10, have virtually the same diagnostic features for a 'clinically significant' 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 5 out of 9, symptoms (which must include depressed mood and/or anhedonia) and ICD-10 requires 4 out of 10 symptoms (including at least two of depressed mood, anhedonia and loss of energy). This may mean that more people as identified as depressed using ICD-10 criteria compared with DSM-IV (Wittchen *et al*.,

2001a) or at least that somewhat different populations are identified (Andrews *et al.,* 2008) related to the need for only one of 2 core symptoms for DSM-IV but 2 out of 3 for ICD-10. These studies emphasise that, although similar, the two systems are not identical and that this is particularly apparent at the threshold taken to indicate clinical significance. In the depression Guideline update (NICE, 2009; NCCMH, forthcoming) we have widened the range of depressive disorders to be considered in this guideline update and emphasise that the diagnostic 'groupings' we use should be viewed as pragmatic subdivisions of dimensions in the form of vignettes or exemplars rather than firm categories. The guideline development group consider that it is important to acknowledge the uncertainly inherent in our current understanding of depression and its classification and that assuming a false categorical certainty is likely to be unhelpful and worst damaging.

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

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

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

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

- sub-threshold depression (2-4 symptoms with maintained function).

- mild depression (few, if any, symptoms in excess of 5 and only minor functional impairment).
- moderate depression (symptoms or functional impairment are between 'mild' and 'severe')
- severe depression (several symptoms in excess of 5 and the symptoms markedly interfere with functioning).

Psychotic symptoms can occur and are usually associated with severe depression.

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

2.2.5 Incidence and prevalence

Egede (2007) studied the one year prevalence of depression in 10,500 patients with chronic disease with 19,460 age matched healthy controls in the USA and found that as a group they were almost three times more likely to be depressed [odds ratio (OR) was 2.6 (CIs 2.31 – 2.94)]. Rates for depression were double in diabetes, hypertension, coronary artery disease and heart failure, and three times in end-stage renal failure, chronic obstructive pulmonary disease and cerebro-vascular disease. Broadly similar results are reported by Moussavi and colleagues (2007) in a WHO study of the one year prevalence of depression among 245,400 patients in 60 countries: in this study, for example, those with 2 or more chronic physical disorders experienced a prevalence of depression of 23%, whereas healthy controls only reported depression in 3.2%. Similar findings are reported in the WHO World Mental Health Survey where data is now complete in 29 countries: in this study –

these findings apply to both developing and developed countries (von Korff *et al.,* 2008).

Patients with co morbid depression and anxiety disorders – who by definition have a greater number of symptoms than either depression or anxiety disorders on their own – have a stronger relationship with chronic physical diseases than either depression or anxiety on their own (Scott *et al.,* 2007). Studies conducted in single countries are shown as Table 2.

Table 2: Difference in prevalence of depression in a range of physical health problems compared with controls

Physical health problem	Main findings
Diabetes Egede (2007), US Das-Munshi *et al.* (2007) UK	 Diabetes Mellitus (n=1794) vs no health problem (n= 19, 462) OR = 1.96 (1.59, 2.42) Diabetes vs no diabetes Adjusted OR = 1.50 (0.60, 4.10) Adjusted for demographic and combo bid health problems
Hyper-tension Egede (2007), US Kessler *et al.* (2003) US	 HTN (n=7371) vs no health problem (n= 19, 462) OR = 2.00 (1.74, 2.31) HTN vs no health problem OR = 1.80 (1.20, 2.90)
Heart problems Egede (2007), US Wilhelm *et al.* (2003) Australia Hebst *et al.* (2007) US	 CAD (n=3491) vs no health problem (n= 19, 462) OR = 2.30 (1.94, 2.63) CHF (n=391) vs no health problem (n= 19, 462) OR = 1.96 (1.23, 3.11) Heart disease: present vs absent OR = 1.94 (1.13, 3.33) *Past year:* Adjusted OR = 2.49 (1.81, 3.43) Adjusted for demographic, health and substance misuse
Stroke Egede (2007) US	Stroke (n=710) vs no health problem (n= 19, 462) OR = 3.15 (2.33, 4.35)
Cancer Wilhelm *et al.* (2003) Australia	 Cancer : present vs absent OR = 2.19 (1.05, 4.56)
Arthritis Wilhelm *et al.* (2003) Australia Kessler *et al.* (2003) US	 Arthritis: present vs absent OR = 1.58 (1.12, 2.22) Arthritis: present vs no physical health problem OR = 2.50 (1.80, 3.40)
COPD/ bronchitis/ emphysema Egede (2007) US Wilhelm *et al.* (2003) Australia Wagena *et al.* (2005) Netherlands	 COPD (n= 1681) vs no health problem (n= 19, 462) OR = 3.21 (2.72, 3.79) Bronchitis: present vs absent OR = 4.26 (2.47, 7.34) COPD (n= 93) vs no COPD (n=4427) OR = 4.38 (2.35, 8.16) Adjusted for age, sex, smoking status, education
Asthma Wilhelm *et al.* (2003) Australia Katon *et al.* (2007) US Kessler *et al.* (2003) US	 Asthma: present vs absent OR = 1.70 (1.17,2.47) Asthma vs no asthma OR = 1.89 (1.15, 3.11) Asthma vs no asthma OR = 2.5 (1.80, 3.50)
Kidney disease Wilhelm *et al.* (2003) Australia	 Kidney disease: present vs absent OR = 4.32 (2.06, 9.05)
Liver disease Wilhelm *et al.* (2003) Australia	 Liver disease: present vs absent OR = 5.43 (2.74, 10.76)
End stage renal disease Egede (2007) US	 ESRD (n=431) vs no health problem (n= 19, 462) OR = 3.56 (2.61, 4.87)
Multiple Sclerosis Patten *et al.* (2003) US	 MS vs no MS OR = 2.3 (1.6, 3.3)

2.2.6 Reasons for the increased prevalence

The chance association between two common conditions

A small increase in the rate of depression in chronic physical illness might be due to the chance association between two fairly common conditions. Using the Goldberg *et al.* (1993) data, if we assume that the prevalence of depression in consulting populations in between 8 and 10%, and the prevalence of chronic physical disease is about 50%, this would inflate the rate in chronic physical disease by about 5%. There is a problem with this calculation however, since the overall rate for depression does not take account of chronic physical disease – that is to say, many of those will indeed have chronic diseases. Thus, the estimate of 5% is at the upper limit of an increased rate. We would need the prevalence of depression in physically healthy consecutive attendees to make this estimate with better accuracy – and this is not available.

2.2.7 The reciprocal relationship between depression and chronic physical disease

Not only can chronic disease both cause and exacerbate depression, but the reverse also occurs, with depression ante-dating the onset of physical disease which goes on to become chronic. In a model of the relationship between major depression and chronic physical illness, Katon (2003) points out a number of ways that major depression and physical illness interact with one another. For example, major depression and childhood adversity are associated with risk factors such as obesity, sedantry lifestyle and smoking which are also risk factors for physical health problems. In addition, major depression is linked with poorer self-management of chronic physical illness which increases the burden of the disease. Moreover, the functional impairment associated with physical illness, as well as indirect pathophysiological factors (for example, increased cytokine levels or other inflammatory factors) may increase the risk of developing and worsening depression. These interactions between mental and physical health disorders will be discussed in further detail below.

2.2.8 Physical disease causing depression

Two population-based prospective cohort studies found that physical illness was a risk factor for the later development of depression. Patten (2001) studied people who were free of depression at baseline in a large population-based cohort (n=11,859). After 2 years 3.5% of this group had developed major depressive disorder. Physical illness was a risk factor for the development of such depressive disorder (OR = 2.5, [95%CI: 1.3-4.6]). The risk was similar for a wide range of physical illnesses, namely hypertension, asthma, arthritis and rheumatism, back pain, diabetes, heart disease and chronic bronchitis. In a Dutch cohort study of 4664 participants who had never had depressive disorder, the presence of two of three illnesses (migraine, respiratory or abdominal problems) predicted the later

development of depressive disorder (incident RR 2.85) after adjusting for confounders . In this study 2.7% of the population developed depression after one year (Smit *et al.,* 2004).

In clinical populations the year after the diagnosis of cancer and after first hospitalisation with a heart attack are associated with a particularly high rate of new onset of depression or anxiety – approximately 20% (Burgess *et al.,* 2005; Dickens *et al.,* 2004). Prince and colleagues (2007) also argue that there is consistent evidence for depression being a consequence of coronary heart disease, stroke and HIV/AIDS

2.2.9 Causal pathways

There are at least three distinct ways in which a chronic physical disease causes depression.

First, the number of different pains an individual experiences is directly proportional to the prevalence of depression: Dworkin and colleagues (1990) showed that primary care patients with a single pain had no increased risk of depression, those with two pains had double the risk, but those with three or more had five times the risk. Pain in turn causes emotional distress and poor sleep, irrespective of whether pain has a known cause (von Korff & Simon, 1996). Secondly, chronic physical illness carries with it the risk of disability and this can be very depressing for an adult who has previously been healthy. For example Prince and colleagues (1998) showed that the attributable fraction of disability or handicap for the prediction of onset of depression among the elderly was no less than 0.69, and Ormel and colleagues (1997) showed similar findings in Holland. Thirdly, there are physical changes in some diseases which may underlie the development of depression, such as changes in the allostatic load. Allostasis refers to the ability of the body to adapt to stressful conditions. It is a dynamic, adaptive process. Tissue damage, degenerative disease (like arthritis) and life stress all increase allostatic load and can induce inflammatory changes which produce substances such as bradykinin, prostaglandins, cytokines and chemokines. These substances mediate tissue repair and healing, but also act as irritants that result in peripheral sensitisation of sensory neurons, which in turn activate central pain pathways (Rittner *et al*., 2003). In stroke – especially left sided – cerebral ischaemia may favour development of depression, and in degenerative dementias the same processes may account for increased rates of depression. Other features of physical illness that may lead to depression include disfigurement, the necessity for undergoing stressful investigations, and the fear of impending death.

2.2.10 Depression causing physical disease

A depressive illness can also precede a new episode of physical disease. Systematic reviews of 11 prospective cohort studies in healthy populations show that depression predicts later development of coronary heart disease in

all of them. (OR 1.18 to 5.4 median = 2.05, and for new CHD events OR, after adjustment for traditional risk factors: OR=1.90 (95% CI: 1.48-2.42) (Hemingway & Marmot, 1999; Nicholson *et al.,* 2006). The occurrence of a depressive episode before an episode of myocardial infarction has been reported by Nielsen and colleagues (1989). Three prospective studies have also shown that depression is an independent risk factor in stroke (Everson *et al.,* 1998, Ohira *et al*., 2001, Larson *et al*., 2001). In prospective population-based cohort studies depression has been shown to predict the later development of colorectal cancer (Kroenke *et al.* 2005), back pain (Larson *et al.*, 2004), irritable bowel syndrome (Ruigómez *et al.,* 2007), multiple sclerosis (Grant *et al*., 1989), and there is some (inconsistent) evidence that depression may precede the onset of type 2 diabetes (Prince *et al.,* 2007). Prince and colleagues (2007) argue that there is consistent evidence for depression leading to physical ill-health in coronary heart disease and stroke, and depression in pregnancy potentially leading to infant stunting and infant mortality.

2.2.11 Causal pathways

It has been hypothesised (Wichers & Maes, 2002) that increases in pro-inflammatory cytokines in depression and increased adrenocortical reactivity may also lead to atherosclerosis, and with it increased risk for both stroke and coronary artery disease. In the latter, autonomic changes in depression may also cause ECG changes which favour development of coronary disease. Another suggested way in which depression may increase the likelihood of a person developing a physical disease is by the immune changes that occur during depression: changes in immune cell classes with an increase in white cell counts and a relative increase in neutrophils, increases in measures of immune activation, and a suppression of mitogen-induced lymphocyte proliferation with a reduction in natural killer cells (Irwin, 1999). Changes in NK cells and T-lymphocytes in depression may also lead to lowered resistance to AIDS in HIV infections. Menkes and McDonald (2000) have argued that exogenous interferons may cause both depression and increased pain sensitivity in susceptible individuals, by suppressing tryptophan availability and therefore serotonin synthesis. More prosaic explantions include reduced physcial activity in people suffering from depression (Whooley *et al.,* 2008)

2.3 Consequences of depression accompanying physical disease

Prince and colleagues (2007) argue that there is consistent evidence for depression affecting the outcome of coronary heart disease, stroke and diabetes. The evidence in support of this statement is reviewed below.

2.3.1 Effects on length of survival

Depression may lead to a shorter expectancy of life (Evans *et al.,* 2005), and therefore treatment might be expected to prolong life. However, the studies

required to demonstrate this have not been done, as they would require long follow-up periods accompanied by prolonged treatment of depression, with a control group denied or at least not in receipt of such treatment. Di Matteo and colleagues (2000) in a meta-analysis of factors related to non-compliance found that depressed patients were three times as likely to be non-compliant with treatment recommendations as non-depressed patients, suggesting that their may be real advantages to treating depression among the physically ill. In heart disease, van Melle *et al.,* (2004) report a more than double greater risk of death with co morbid depression.

2.3.2 Effects on the Quality of Life

As the severity of depression increases, the subjective quality of life decreases. One of the reasons for persevering with active treatment for depression is that even if the outlook for survival is not improved, that the quality of survival may be greatly improved. In the large study by Moussavi and colleagues (2007) particularly low health status scores were found in those with depression co morbid with physical illness.

2.3.3 Advantages of treatment of depression accompanying chronic physical disease

Effects on length of survival

Depressive disorder predicts increased mortality after a heart attack but the risk may be confined to people who develop depression after their heart attack (Frasure-Smith *et al.,* 1993). Others such as Prince and colleagues (2007) argue that there is consistent evidence for depression being a consequence of coronary heart disease, stroke and HIV/AIDS and while Bogner and colleagues (2007) claim that effective treatment of depression may decrease mortality in diabetes.

Effects on disease management of the chronic disorder

While generally reporting beneficial effects on depression, randomised trials have generally failed to show much effect that treatment of depression has on heart disease (Glassman *et al.,* 2002; Berkmann *et al*., 2003) or on diabetes (Williams *et al*., 2004; Katon *et al.,* 2006). More recently trials of collaborative care for depression (which has its origins in the management of chronic physical disease) have focused on people with depression and a chronic physical illness (e.g. Katon *et al.,* 2004). However, Gilbody and colleagues (2008a) conclude on the basis of a meta-analysis that depression can be treated effectively by collaborative care but there does not appear to be consistent evidence that such treatment improves physical outcomes.

Effects on the Quality of Life & related measures

Treatment for depression does have other beneficial effects on outcomes other than measures of depression. Simon and colleagues (2005) showed

improvements in social and emotional functioning, and disability in a mixed group of chronic physical disorders in primary care, Mohr and colleagues (2007) showed improvements in both disability and fatigue with a CBT intervention for depression in patients with multiple sclerosis, Lin and colleagues (2003) showed that treatment of depression in patients with arthritis resulted in improved arthritis-related pain and functional outcomes and better general health status and overall quality of life, in addition to having fewer depressive symptoms. Based on studies in this area Von Korff and colleagues (2008) argue that the weight of the evidence suggests that in addition to reducing depressive symptoms, the treatment of depression is effective in reducing functional disability. Severe pain, as one might expect, is associated with a smaller beneficial effect that treatment of depression has on depression itself (Thielke *et al*., 2007; Mavandadi *et al.,* 2007; Kroenke *et al.,* 2008)

2.3.4 Disadvantages of treatment of depression accompanying chronic physical diseases

We should also note the possibility of iatrogenic effects of treatment, especially with reference to interactions and side effects of antidepressant medication. Side effects may add to a patient's discomfort from the physical disease, while others may deleteriously affect the disease process, for example Broadley and colleagues (2002) argue that SSRIs such as paroxetine can inhibit the function of vascular endothelial cells in arteries: these cells are crucial to the maintenance of arterial integrity and hence to the prevention of atherosclerosis.

2.4 The economic cost of depression in those with chronic physical health problems

There is widespread recognition of the significant burden that depression alone imposes on individuals and their carers, health services and communities around the world. Within the UK, it was estimated that there were 1.24 million people with depression in England, and this was projected to rise by 17 per cent to 1.45 million by 2026. Overall, the total cost of services for depression in England in 2007 was estimated to be £1.7 billion whilst lost employment increased this total to £7.5 billion. By 2026 these figures were projected to be £3 billion and £12.2 billion respectively (McCrone *et al.,* 2008). However, whilst there is plenty of published evidence on the economic burden of depression alone, there is less evidence on the combined economic impact of depression in patients with chronic health problems, especially within the UK setting.

Two US studies assessed health care costs in relation to patients with a diagnosis of diabetes and depressive symptoms (Ciechanowski *et al.,* 2000 and Egede *et al.,* 2002). The study by Ciechanowski and colleagues assessed direct health care costs over 6-months including primary care, specialty care,

emergency department, inpatient services, mental health care and prescription medications (2000). Overall, the results showed higher health care utilisation and costs among diabetic patients with severe co-morbid depression. These increased health care costs were largely explained by increased medical, rather than mental health, utilisation. The study by Egede and colleagues compared depressed and non-depressed individuals from the 1996 Medical Expenditure Panel Survey (MEPS) to identify differences in health care use and expenditures in patients with diabetes (Egede *et al.*, 2002). Health care resource use categories included hospital inpatient days, outpatient visits, emergency department visits and medications. Overall, diabetic patients with depression had significantly higher total health care expenditures than non-depressed diabetic patients. These differences were largely due to higher numbers of outpatient visits and prescription medications among diabetic individuals with depression.

A Canadian-based study evaluated health-care costs over one-year among post-myocardial infarction patients with depressive symptoms (BDI scores of ≥ 10) (Frasure-Smith *et al.*, 2000). Medicare billing records were used to collect resource use data including: physician costs, inpatient stay, revascularisation procedures, re-admissions, emergency visits and outpatient visits. Overall, during the first year post-discharge, estimated costs were significantly higher for depressed than for non-depressed patients. Depressed post-MI patients were more likely to be re-admitted and spent more days in hospital than non-depressed patients. The major reasons for the depression-related increase in costs were due to greater use of emergency rooms and outpatient visits to physicians, although psychiatric contacts were rare. Another Canadian-based study evaluated health care costs over 3-years in a retrospective cohort of patients with heart failure who were diagnosed with depression or receiving antidepressant medication (Sullivan *et al.*, 2002). After adjusting for confounding variables, in comparison with heart failure patients with no depression, costs were 26% higher in the antidepressant prescription group and 29% higher in patients diagnosed with depression.

The limited non-UK based evidence presented here suggests that depression imposes a significant additional burden on patients with chronic health problems and society in general, in terms of health care costs and lost productivity. It is also likely that these costs will continue to rise significantly in future years. Therefore, efficient use of available health care resources is necessary in order to treat depression in chronic health problems.

3 Methods used to develop this guideline

3.1 Overview

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

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

The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence base for the clinical and cost effectiveness of the treatments and services used in the treatment and management of depression in people with chronic physical health problems. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

3.2 The scope

Guideline topics are selected by the Department of Health and the Welsh Assembly Government, which identify the main areas to be covered by the guideline in a specific remit (see The Guidelines Manual). The NCCMH developed a scope for the guideline based on the remit.

The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities

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

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

3.3 The Guideline Development Group

The GDG consisted of: professionals in psychiatry, clinical psychology, health psychology, nursing, general practice, occupational therapy, pharmacy, gerontology, cardiology, rheumatology; academic experts in psychiatry and psychology; a service user. The GDG were recruited according to the specification set out in the scope and in line with the process set out in the NICE guideline manual(NICE, 2007). 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

GDG meetings were held between 22nd January 2008 and 20th January 2009. During each day-long GDG meeting, in a plenary session, clinical questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest, and service user and carer concerns were routinely discussed as part of a standing agenda.

3.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Topic Group 1 covered questions relating to case identification and service configuration. Topic Group 2 covered pharmacology and topic Group 3 covered psychosocial interventions. These groups were designed to efficiently manage the large volume of evidence appraisal prior to presenting it to the GDG as a whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the healthcare professionals). Topic

groups refined the clinical questions, refined the clinical definitions of treatment interventions, reviewed and prepared the evidence with the systematic reviewer before presenting it to the GDG as a whole and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting the section of the guideline relevant to the work of each topic group.

3.3.3 Service users and carers

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

3.3.4 Special advisors

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

3.3.5 National and international experts

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

3.4 Clinical questions

Clinical questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. Before the first GDG meeting, clinical questions (see Appendix 7) were prepared by NCCMH staff based on the scope and an overview of existing guidelines, and discussed with the guideline Chair. The framework was used to provide a structure from which the clinical questions were drafted. Both the analytic framework and the draft clinical questions were then discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the framework

and questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. Questions submitted by stakeholders were also discussed by the GDG and the rationale for not including questions was recorded in the minutes. 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 Text Box 1).

Text Box 1: 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?

Questions relating to diagnosis do not involve an intervention designed to treat a particular condition, therefore the PICO framework was not used. Rather, the questions were designed to pick up key issues specifically relevant to diagnostic tests, for example their accuracy, reliability, safety and acceptability to the patient.

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 Text Box 2. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'. However, in all cases, a well-conducted systematic review of the appropriate type of study is likely to always yield a better answer than a single study. Deciding on the best design type to answer a specific clinical or public health question does not mean that studies of different design types addressing the same question were discarded.

Text Box 2: Best study design to answer each type of question

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial; other studies that may be considered in the absence of an RCT are the following: internally / externally controlled before and after trial, interrupted time-series
Accuracy of information (e.g. 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

3.5 Systematic clinical literature review

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific clinical questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible, and, if evidence is not available, informal consensus methods are used (see Section 3.5.7) and the need for future research is specified.

3.5.1 Methodology

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

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

3.5.2 The review process

After the scope was finalised, a more extensive search for systematic reviews and published guidelines was undertaken. Existing NICE guidelines were updated where necessary. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as

appropriate (further information about this process can be found in The Guidelines Manual (NICE, 2007).

At this point, the review team, in conjunction with the GDG, developed an evidence map that detailed all comparisons necessary to answer the clinical questions. The initial approach taken to locating primary-level studies depended on the type of clinical question and availability of evidence. The GDG decided which questions were best addressed by good practice based on expert opinion, which questions were likely to have a good evidence base and which questions were likely to have little or no directly relevant evidence. Recommendations based on good practice were developed by informal consensus of the GDG. For questions with a good evidence base, the review process depended on the type of key question (see below). For questions that were unlikely to have a good evidence base, a brief descriptive review was initially undertaken by a member of the GDG.

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

The search process for questions concerning interventions

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

Standard mental health related bibliographic databases (i.e., MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Library) were used for the initial search for all studies potentially relevant to the guideline.
Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 11 for quality criteria used to assess systematic reviews). However, in some circumstances existing data sets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

After the initial search results were scanned liberally to exclude irrelevant papers, the review team used a purpose-built 'study information' database to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). Double checking of all excluded studies was not done routinely, but a selection of abstracts was checked to

ensure reliability of the sifting. For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to (a) repeat the search using subject-specific databases (e.g. AMED, ERIC, OpenSIGLE or Sociological Abstracts) (b) conduct a new search for lower levels of evidence or (c) adopt a consensus process (see Section 3.5.7). Future guidelines will be able to update and extend the usable evidence base starting from the evidence collected, synthesised and analysed for this guideline.
In addition, searches were made of the reference lists of all eligible systematic reviews and included studies, as well as the list of evidence submitted by stakeholders. Known experts in the field (see Appendix 6), 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[2]. In addition, the tables of contents of appropriate journals were periodically checked for relevant studies.

The search process for questions of diagnosis and prognosis

For questions related to diagnosis and prognosis, the search process was the same as described above, except that the initial evidence base was formed from studies with the most appropriate and reliable design to answer the particular question. That is, for questions about diagnosis, the initial search was for cross-sectional studies; for questions about prognosis, it was for cohort studies of representative patients. In situations where it was not possible to identify a substantial body of appropriately designed studies that directly addressed each clinical question, a consensus process was adopted (see Section 3.5.7).

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 9).

Study selection

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. Appendix 8 lists the standard inclusion and exclusion criteria. More specific eligibility criteria were developed for each clinical question and are described in the relevant clinical evidence chapters. Eligible systematic reviews and primary-level studies were critically appraised for methodological quality (see Appendix 11 and Appendix 18). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

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

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

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

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

Unpublished evidence

The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline. Therefore, the GDG did not accept evidence submitted as commercial in confidence. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

3.5.3 Data extraction

Study characteristics and outcome data were extracted from all eligible studies, which met the minimum quality criteria, using a bespoke database and Review Manager 4.2.7 (Cochrane Collaboration, 2004) for most outcomes (see Appendix 18). Study characteristics (see appendix 20) and outcome data on diagnostic accuracy were extracted using Word-based forms and Stata 10 (StataCorp, 2007).

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 effects 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 some of the studies failed to report standard deviations (for a continuous outcome), and where an estimate of the variance could not be computed from other reported data or obtained from the study author, the following approach was taken[3]:

When the number of studies with missing standard deviations was less than a third and when the total number of studies was at least 10, the pooled standard deviation was imputed (calculated from all the other studies in the same meta-analysis that used the same version of the outcome measure). In this case, the appropriateness of the imputation was made by comparing the standardised mean differences (SMDs) of those trials that had reported standard deviations against the hypothetical SMDs of the same trials based on the imputed standard deviations. If they converged, the meta-analytical results were considered to be reliable.

When the conditions above could not be met, standard deviations were taken from another related systematic review (if available). In this case, the results were considered to be less reliable.

The meta-analysis of survival data, such as time to any mood episode, was based on log hazard ratios and standard errors. Since individual patient data were not available in included studies, hazard ratios and standard errors calculated from a Cox proportional hazard model were extracted. Where necessary, standard errors were calculated from confidence intervals or p-value according to standard formulae (see the Cochrane Reviewers' Handbook 4.2.7 [Cochrane Collaboration 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 data set. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer was checked by the second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad *et al*., 1996; Berlin, 2001).

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[3] Based on the approach suggested by Furukawa et al. (2006)

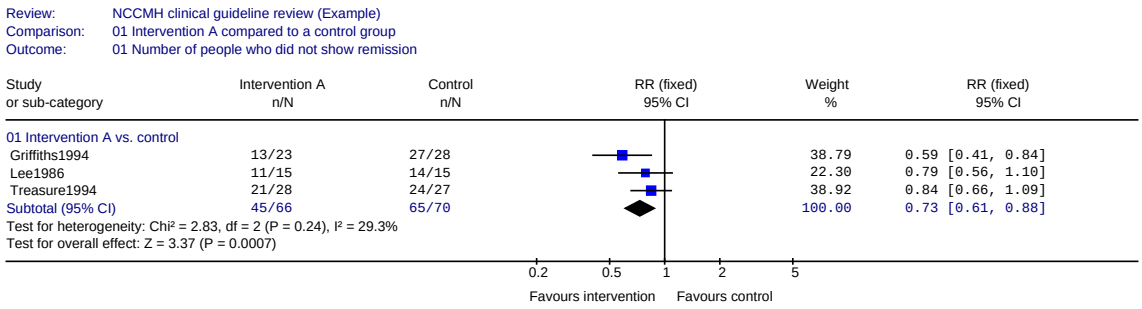
3.5.4 Synthesising the evidence

Analysis of efficacy studies

Where possible, meta-analysis was used to synthesise the evidence using Review Manager 4.2.7 (Cochrane Collaboration, 2004) for effectiveness data and Stata 10 for diagnostic accuracy. If necessary, reanalyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies or reviews.

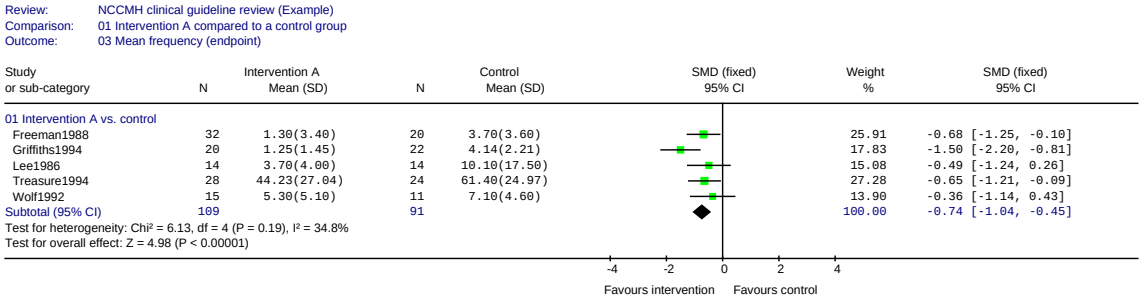
Dichotomous outcomes were analysed as relative risks (RR) with the associated 95% CI (for an example, see Figure 1). A relative risk (also called a risk ratio) is the ratio of the treatment event rate to the control event rate. An RR of 1 indicates no difference between treatment and control. In Figure 1, the overall RR of 0.73 indicates that the event rate (that is, non-remission rate) associated with intervention A is about three quarters of that with the control intervention or, in other words, the relative risk reduction is 27%.
The CI shows that 95% of the time the true treatment effect will lie within this range and can be used to determine statistical significance. If the CI does not cross the 'line of no effect', the effect is statistically significant.

Figure 1: Example of a forest plot displaying dichotomous data



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

Figure 2: Example of a forest plot displaying continuous data



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 follow way:

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

To explore the possibility that the results entered into each meta-analysis suffered from publication bias, data from included studies were entered, where there was sufficient data, into a funnel plot. Asymmetry of the plot was taken to indicate possible publication bias and investigated further.
An estimate of the proportion of eligible data that were missing (because some studies did not include all relevant outcomes) was calculated for each analysis.

Included/excluded studies tables, generated automatically from the study database, were used to summarise general information about each study (see Appendix 18). Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were also presented in the included studies table (and included, where appropriate, in a narrative review).

Analysis of diagnostic accuracy studies

The main outcomes extracted for diagnostic accuracy studies were sensitivity, specificity, positive predictive validity and negative predictive validity. These are discussed in detail below. In addition, negative likelihood ratios, positive likelihood ratios, and area under the curve will be briefly described.
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 make for poor planning and underestimating the prevalence of the disorder and the costs of treatments to the community. As the sensitivity of an instrument increases, the number of false negatives it detects will decrease.

The ***specificity*** of an instrument refers to the proportion of those without the condition being tested for who test negative. This is important so that well individuals are not given treatments they do not need. As the specificity of an instrument increases, the number of false positives will decrease.
To illustrate this: from a population in which the point prevalence rate of depression is 10% (that is, 10% of the population has depression at any one time), 1,000 people are given a test which has 90% sensitivity and 85% specificity. It is known that 100 people in this population have depression, but the test detects only 90 (true positives), leaving 10 undetected (false negatives). It is also known that 900 people do not have depression, and the test correctly identifies 765 of these (true negatives), but classifies 135 incorrectly as having depression (false positives). The ***positive predictive value*** of the test (the number correctly identified as having depression as a proportion of positive tests) is 40% (90/90+135), and the ***negative predictive value*** (the number correctly identified as not having depression as a proportion of negative tests) is 98% (765/765 +10). Therefore, in this example, a positive test result is correct in only 40% of cases, whilst a negative result can be relied upon in 98% of cases.

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

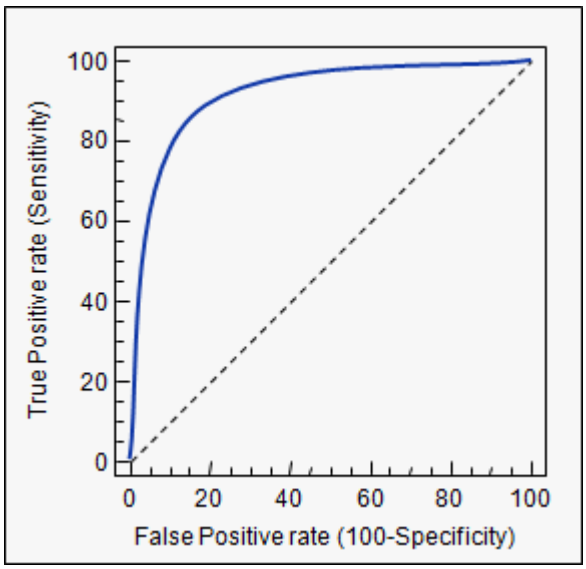
In contrast, sensitivity and specificity do not theoretically depend on prevalence (Altman & Bland, 1994b). For example, sensitivity is concerned with the performance of an identification test conditional on a person having depression. Therefore the higher false positives often associated with samples 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 'excellent' as values above 0.9, 'good' as 0.8 to 0.9, 'moderate' as 0.5 to 0.7, 'low' as 0.3 to 0.5, and 'poor' as less than 0.3.

Receiver operating curves

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

Figure 3*: receiver operator characteristic (ROC) curve*



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

Negative and positive likelihood ratios

Negative (LR-) and positive (LR+) likelihood ratios examine similar outcomes to negative and positive predictive values, for example, whether a person with a positive test actually has the disorder. The main difference is that 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 calculated as (sensitivity x specificity)/[(1-sensitivity)x(1-specificity)] and is relatively independent of changes in

prevalence. Tools with diagnostic odds ratios greater than 20 are likely to be useful for clinical practice.

3.5.5 Presenting the data to the GDG

Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the GDG in order 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** 3 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 11 for the quality checklists)
- inconsistency (see section 3.5.4 for how consistency was measured)
- indirectness (that is, how closely the outcome measures, interventions and participants match those of interest)
- imprecision (based on the confidence interval around the effect size).

For observational studies, the quality may be increased if there is a large effect, plausible confounding would have changed the effect, or 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: 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.

Table 3: Example of GRADE evidence profile

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	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)	⊕⊕⊕O 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)	⊕⊕⊕O MODERATE
Outcome 3											
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	83	81	-	MD -1.51 (-3.81 to 0.8)	⊕⊕⊕⊕ HIGH
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)	⊕⊕⊕O 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)	⊕⊕⊕O 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.

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
- 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).

3.5.6 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 evidence base for depression in people with chronic physical health problems was much more limited than the literature for depression in the general population. In the judgement of the GDG, the nature of depression in the physically ill is not fundamentally different from the broader population who do not experience additional physical illness. Therefore, the GDG decided to draw upon the evidence for depression more generally when forming recommendations. In doing so the GDG worked closely with the GDG which was updating the Depression Guideline (NICE, 2004a, NICE, 2009) and discussed the clinical questions and the outcome of the reviews with the Depression GDG.

Extrapolating evidence from other populations is a complex process therefore it is important to have transparent and clear principles guiding these judgements. Table 4 summarises the main principles used by the GDG and examples of these in the guideline. Where there was evidence in patients with physical health problems that contradicted that found in the general population then extrapolation did not take place. When there was congruent findings (positive or negative evidence) in both the general population and physically ill population then evidence from both populations was considered. When there was positive evidence in the general population but no clear or robust evidence in the physically ill then decisions on extrapolation were determined by the judgement of the GDG.

Table 4 Principles for extrapolating from general depression population

Evidence from depression in general population	Evidence from depression in chronic physical health problems	Decision whether to extrapolate	Example in the Guideline
Positive	Positive	Yes	Pharmacological interventions, see Chapter 8; Physical activity and guided self help see Chapter 7
Negative	Positive	No	Collaborative care, see chapter 6
Positive	Limited/No robust evidence	Judgement of the GDG: If considered important then extrapolate	Delivery of psychological interventions, see Chapter 7
Positive	Negative/ Contradictory	No	Interpersonal psychotherapy (IPT), see Chapter 7
Contradictory	Negative/Contradictory	No	Counselling

Finally, 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 were 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, values of the development group and society, and the group's awareness of practical issues (Eccles *et al.,* 1998). The confidence surrounding the evidence in the depression guideline also influenced the GDGs' decision to extrapolate.

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

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

Informal consensus

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

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

- A description of what is known about the issues concerning the clinical question was written by one of the topic group members
- Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the clinical question
- Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the clinical question but were thought to contain relevant data
- If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was done
- At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the clinical question were developed
- Following this, on occasions and as deemed appropriate by the development group, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements
- Recommendations were then developed and could also be sent for further external peer review
- After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.6 Health economics methods

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

- Systematic literature review of existing economic evidence
- Economic modelling, where economic evidence was lacking or was considered inadequate to inform decisions. If several such areas were identified, they were further categorised on priority

by the GDG. This prioritisation was based on anticipated resource implications and quality and availability of clinical data.

Systematic search of the economic literature was undertaken on all areas covered in this guideline.

Moreover, literature on health-related quality of life of people with depression was systematically searched to identify studies reporting appropriate utility weights appropriate for people with co morbid chronic physical health problems 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 economic modelling in this guideline:

- Cost effectiveness of Collaborative Care versus Usual care in the care of those with moderate and severe depression and chronic physical problems.
- Cost analysis of Low-intensity psychological interventions

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

Search strategy

For the systematic review of economic evidence the standard mental-health-related bibliographic databases (EMBASE, MEDLINE, CINAHL and PsycINFO) were searched. For these databases, a health economics search filter adapted from the Centre for Reviews and Dissemination at the University of York was used in combination with a general search strategy for depression. Additional searches were performed in specific health economics databases (NHS EEDOHE 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 early 2008. The searches were updated regularly, with the final search performed in January 2009. Details of the search strategy for economic studies on interventions for people with depression and chronic physical health problems are provided in Appendix 13.

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

The systematic search of the literature identified approximately 35 thousand references (stage 1). Publications that were clearly not relevant were first excluded (stage 2). The abstracts of all potentially relevant publications were then assessed against a set of selection criteria by the health economist (stage 3). Full texts of the studies potentially meeting the selection criteria (including those for which eligibility was not clear from the abstract) were obtained (stage 4). Studies that did not meet the inclusion criteria, were duplicates, were secondary publications to a previous study, or had been updated in more recent publications were subsequently excluded (stage 5). Finally, 3 papers eligible for inclusion were assessed for study quality and critically appraised (stage 6). The quality assessment was based on the checklists used by the *British Medical Journal* to assist referees in appraising full and partial economic analyses (Drummond & Jefferson, 1996) (Appendix 14).

Selection criteria

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

- only papers published in English language were considered
- studies published from 1998 onwards were included. This date restriction was imposed in order to obtain data relevant to current healthcare settings and costs
- only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context
- 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

Data extraction

Data were extracted by the health economist using a standard economic data extraction form (Appendix 15).

Presentation of economic evidence

The economic evidence identified by the health economics systematic review is summarised in the respective chapters of the guideline, following presentation of the clinical evidence. The references to included studies, as well as the evidence tables with the characteristics and results of economic studies included in the review, are provided in Appendix 17. Methods and results of economic modelling are reported in the economic sections of the respective evidence chapters.

3.7 Stakeholder contributions

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

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

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

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

3.8 Validation of the guideline

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

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted

to NICE. NICE then formally approved the guideline and issued its guidance to the NHS in England and Wales.

4 Experience of care

4.1 Introduction

The chapter provides an overview of the experience of people with depression and chronic physical health problems and their families/carers and healthcare professionals.

In the first section are first-hand personal accounts written by patients, which provide some experience of having depression and a chronic physical health problem. This is followed by a narrative review of primary qualitative studies identified by the GDG. The next section comprises a qualitative analysis of the data provided by healthtalkonline (http://www.healthtalkonline.org/). The interviews include both the experience of patients, and in some instances families/carers, and cover topics such as the psychosocial impact of a chronic physical health problem, the causal pathways to depression and the experience of depression and/or low mood.

A summary of all themes across the different types of evidence is given, which provides a basis for the clinical recommendations. The GDG felt that it was important to take into account patients' perspectives when making recommendations for their provision of care.

4.2 Personal accounts

4.2.1 Introduction

This section comprises two first-hand personal accounts written by people with depression and chronic physical health problems. It should be noted that these accounts are not representative and can only ever be illustrative. Although both of the writers of the personal accounts had a previous history of depression before the onset of the physical problem, the accounts offer very different perspectives on having depression and a chronic physical health problem. The first explores the experience of having long-standing depression and a chronic autoimmune disease and the effect that each condition had on the other; the second account chronicles the way that a diagnosis of depression was a barrier to renal cancer being identified. Despite their differences, the shared theme that emerged was the way the symptoms of existing depression can mimic and mask symptoms of serious physical illness.

4.2.2 Personal account A

My first experience of depression occurred at 16 on the death of my father from angina. I imagined I was suffering a heart attack which seemed very real. I now know this disorder to be somatisation, but at the time I believed I had a physical illness. Even at that age I was aware of the stigma associated with depression. It was 'hushed up' in the family, which may largely have

been because of my family's medical history: my mother suffered from severe postnatal depression. Whatever the reason, my family never discussed it. I felt that depression was something to be ashamed of and embarrassed about. This was compounded over the years when some friends would tell me to 'pull myself together'. If only it were as simple as that.

It may be that having this initial episode at such a young age is the reason I have relapsed. A pattern had been set and depression has always been just around the corner. Without doubt this first bout was the worst. I had little insight into what was happening. At times I wasn't even lucid.

My experience of depression has always been about loss: bereavement, break-up of relationships and redundancy. A hysterectomy at 36 caused a major depressive episode because I had always wanted children. I had counselling at various points in my life. Though helpful, I felt that it only scratched the surface and did not get to the root of my depression.

When I became ill with a chronic physical illness (Wegener's granulomotosis), which was diagnosed when I was 47, it was the loss of good physical health, a way of life, even my looks. I seemed to have aged overnight – others noticed. It would take time to manage the emotional impact of having this illness.

At onset of Wegener's, the only symptom was a general feeling of malaise. My GP thought I was depressed though I did not respond to medication (lofepramine). It was an understandable conclusion, given my medical history and subtlety of symptoms. But as the illness developed, the symptoms were more dramatic: breathlessness, nose bleeds, vomiting, persistent cough, rigors, profuse sweating, and a skin lesion.

A locum GP promised referral in a fortnight, and that promise was kept. Several invasive investigations lay ahead but confidence in the specialist allayed my fears. As I took the journey through biopsies and scans, this confidence grew. But on diagnosis (3 months after presentation), I reacted with flippancy and asked if I had only 6 months to live. (I smile at that, now after 7 years have elapsed!).

It was apparent that two of the specialists I saw, a consultant physician in respiratory medicine and an ENT surgeon, had completely different styles of imparting information. The physician used more scientific explanations—I had no experience of inflammatory disease and certainly had never heard of auto-antibodies, immuno-suppressants or knew what an ANCA reading was. My lack of comprehension may be attributed to the severity of the Wegener's attack and how ill I felt at this time but the terminology was well beyond my grasp. However, in contrast, the surgeon preferred to use layman's terms in his explanations—basically I had too much immunity, the opposite of a patient suffering from HIV. This was much easier to digest and understand.

Anxieties over my life expectancy stirred up emotions that I had not experienced in quite the same way before – frustration, anger, fear, uselessness, vulnerability and an element of grieving for myself, for the healthy person I used to be. Feelings of shame and even guilt because I could no longer be my mother's carer contributed to depression, often accompanied by anxiety attacks. In hindsight I perhaps should have expressed my fears to the clinicians; support may have been available, especially in respect to my mother's care. But we struggled on. I was attending regular hospital appointments though; actual admittance was confined to biopsy procedures, which usually involved an overnight stay.

To friends I found myself repeating the same story of how the illness emerged and was diagnosed. Many found Wegener's hard to understand because the illness is rare and the symptoms well hidden. This left me feeling isolated. Until I contacted a support group, the only one who really understood was the specialist.

When it came to intervention, there was a choice and the specialist took time to explain the options. With limited Wegener's, spontaneous remission was a possibility. But I opted for treatment, believing it would have long-term benefits. While he had not influenced my decision, I could see the specialist's relief. Medication was complex: cyclophosphamide (a chemotherapy drug), co-trimoxazole (an antibiotic) and fosamax (a bisphosphonate) to counteract effects of prednisolone (a steroid). Initially I was taking 17 tablets a day, which was overwhelming. While I was reassured that treatment may prove effective, the drugs were associated with significant side effects: hair loss, massive weight gain and mooning of the face. Other possibilities were thinning of the skin, weakening of the bones, cataracts, diabetes, stomach ulcers, cancer of the bladder, cystitis and the risk of being unable to fight off infections.

A support group was a tremendous help from this point onwards. There was always someone available on the other end of a phone who had had similar experiences and could empathise. They encouraged me to educate myself so that I would be prepared for possible complications. The group has also put me in touch with a leading specialist in rhinology. From reading her research, I discovered there may be more I can do for myself – nasal sprays, creams and douches may be helpful for treating localised inflammation. With the agreement of my specialist and GP, I have begun a course of treatment.

Thankfully the specialist has always taken a holistic approach to my healthcare, not hesitating to suggest referral to a clinical psychologist as I approached the end of the treatment when my mother died. Just as the physical illness had peaked previously, so depression peaked very suddenly.

Symptoms of depression were frequent: periods of tearfulness, irritability, insomnia, diminished libido, over-sensitivity and total apathy. Perhaps more

worryingly, I withdrew from friends who would have been only too willing to help. It was also the time when I began experiencing hypnagogic and hypnopompic hallucinations — they could be visual or auditory but were always dream-like and yet sudden, loud and vivid. It was unclear what was the cause— the physical illness or depression or both. As I become more involved in healthcare, I have come to realise that it is sometimes more than one factor which comes in to play. I have not experienced them often, but they were unpleasant, alarming and disturbed my sleep patterns.

My emotions had plummeted from relief at remission, to sadness over the death of my mother. It had all been too much. I had fought hard but it felt that I was left with nothing. I was alone, desperate and afraid of what the future might hold. An antidepressant (amitriptyline) was prescribed by the GP. I was comfortable with this arrangement; however, had it been necessary in the midst of treatment, I would have preferred the specialist to prescribe. I tolerated the drug well. The only troublesome side effect was dry mouth. It suited me better than the lofepramine, which had caused insomnia and constipation. In collaboration with the clinicians it was decided that medication alone was unlikely to be the solution. I must acknowledge that communication between primary and secondary care seemed very effective – the professionals were always up to speed with my treatment. There was an atmosphere of trust and support.

Though I was referred to the psychologist because of bereavement, she happened to specialise in working with the chronically ill. This was a bonus – I could come to terms with the illness as well as the loss of my mother. The psychologist stressed that it was OK to take the time I needed. Working through my feelings I began to realise that I am the same 'me' that I was before, even though physically my body doesn't get me around as efficiently. What I was lacking in energy and stamina, I would compensate for by developing my mind. I began to understand the triggers and warning signs of a depressive episode and the sorts of distractions that were going to make me well again. Relaxation tapes were of great benefit. Aromatherapy was also on offer, which was suggested by the Macmillan nurse; as well as providing reassurance throughout, she played a vital role as a linkage between the care of my physical health and the treatment of depression (this spanned across hospitals on different sites). I had started back at work on a phased return and while aromatherapy sessions appealed, they would place a large demand on my working week and I could not justify taking time out. Besides, both my employer and colleagues had been supportive throughout and I wanted to return to normal as soon as possible.

I feel that seeing a clinical psychologist took me a stage further than counselling had done previously. I had a tendency to relate every ailment to the Wegener's. In time I discovered that this is not always the case. Another recurring theme had been that I seemed to cope with a crisis as it occurred, when a numbness or hollow feeling prevailed. But I was only to suffer badly,

perhaps 6 months down the line (when safe to do so). I explored fresh avenues and coping strategies on which I could focus whenever necessary. There were ideas for self-help: pacing, taking time out for myself (not easy for someone who had been a carer), gentle exercise such as walking and gardening and developing the ability to switch trains of negative thoughts to more positive ones. This tool has assisted me in dealing with the hallucinations. I also learnt a further tool relating to the application of verification. I had made assumptions surrounding both the illness and my mother's death—ones that I could not possibly know. I had been deceiving myself. This had been an almost constant inner commentary and it took practice to look at both events from different perspectives. The process was illuminating.

I believe I had a poor self image at this time, due to weight gain and thinning of hair. I offloaded all my concerns and worries when I saw the psychologist – it was a relief and brought some clarity to my thinking. One appointment stands out as a defining moment. We talked of serendipity and something struck a chord in my mind. I decided to put my experiences to good use. It was a sudden revelation and I was serious about it. By the next session, I had planned some fundraising, modest in aspiration but it would present opportunities. The answer had been within me all along but it took many therapy sessions for it to surface. My life changed direction.

I am convinced that the illness has been a blessing in disguise. I have tackled depression head on and subsequently moved on with my life. Entering the realms of patient involvement has changed my life into something quite extraordinary. Connecting with other patients has made me feel fulfilled and happy. The experience of illness had brought out the best in me. It has been a slow process but I have got through it. I am in a safe place. Perhaps the most significant indicator of my well-being is the ability to challenge myself, even taking a few risks. A career change beckons.

I look to the future with optimism.

4.2.3 Personal account B

In spring 2006 I started getting unwell with tummy problems and noticeably lost weight. I had three bouts of tummy problems but was working long hours as I had been for a number of years. I was referred by my GP to the local acute hospital for tests on my bowels and stomach. I was also having bouts of severe pain on my left side and this had caused me to faint on two occasions in public. I was usually a person with a very strong stomach and had never had problems in that area before. I had had depression and had been living with dysthymia for years; it was just part of my life that I successfully coped with and worked around.

The tests between June and September 2006 showed nothing, but I had a CT scan in early October 2006. When I returned to the gastroenterology

department for my CT results neither the registrar nor his staff could find them. The registrar was flippant and told me that my weight loss and abdominal pain were caused by my depression, and that there was nothing further the NHS could do for me. I tried to argue with him that I had not been ill with a depressive episode, but he did not listen to me.

When I got home, I felt guilty that I may have been wasting NHS time—perhaps I didn't know my own mind. But good sense prevailed and I rang the complaints department of the hospital and told them I would go away as long as the CT results confirmed nothing was wrong. I saw the same registrar 5 days later and he told me, without apologising, that my CT results showed a renal carcinoma in my right kidney.

If I had listened to that doctor, I would be well into the later stages of kidney cancer, if not dead now, all because on my hospital file it read 'history of depression'. Within 6 weeks I was on the operating table having my right kidney removed, which showed a stage 2 kidney cancer. It had grown 4 centimetres between October and December.

Since my operation I have looked up the symptoms for kidney cancer (weight loss, abdominal pain, tiredness, nausea) and while I accept it is an unusual cancer for a person of my age, I have since refused to return to that hospital for check ups. The doctors' assumptions about what a depressed patient looks like, and whether physical symptoms are taken seriously if you have a history of depression, don't leave me with confidence that I would be best treated there.

Also, it leaves me cold that a less articulate, less confident patient would be sitting at home having been told by the NHS that they couldn't do anything further –who looks out for the more vulnerable depressed patient?

4.3 Review of the qualitative literature

4.3.1 Introduction

To capture the experience of care for people with depression and chronic physical health problems, a systematic search was undertaken to address the question: what is the experience of care for people with depression and chronic physical health problems and where possible, families/carers and health care professionals? The aim of the review was to explore the experience of care for patients, families/carers and healthcare professionals.

4.3.2 Evidence search

The inclusion/exclusion criteria adopted in the review were systematic reviews of qualitative studies that used first-hand experiences of patients, families/carers and healthcare professionals of their experience of care for people with depression and chronic physical health problems. 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 please see Table 5.

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 November 2008
Study design	Systematic reviews of qualitative studies, surveys, observational studies
Population	People with depression and chronic physical health problems; families/carers and healthcare professionals
Outcomes	None specified

The search did not find any systematic reviews that explored the experience of care for people with depression and chronic physical health problems that met the inclusion/exclusion criteria. The review team then looked at primary qualitative studies identified by the GDG. A limitation of this review is that there was no systematic search for primary studies.

4.3.3 Patients' experience

There were four studies exploring the experience of care for people with chronic physical health problems (Thomas & Taylor, 2002; Thomas & John, 2007; Gruffydd-Jones *et al*., 2007; Conrad *et al.,* 2006). The chronic physical health problems covered in this review were sickle cell disease (Thomas & Taylor, 2002), end-stage renal disease (Thomas & John, 2007), chronic obstructive pulmonary disease (Gruffydd-Jones *et al*., 2007) and hepatitis C (Conrad *et al*., 2006). Thomas and John (2007) also provided information on the experience of care for families/carers and healthcare professionals. Three studies were conducted in the UK (Thomas & Taylor, 2002; Thomas & John, 2007; Gruffydd-Jones *et al*., 2007) and one study was conducted in Australia (Conrad *et al*., 2006).

Thomas and Taylor (2002) used non-directive focus groups to explore the psychosocial impact of living with sickle cell disease (SCD). Twenty-five people were recruited from seven hospitals in London. To be included in the study, the participants needed to have a diagnosis of sickle cell disease, be aged between 15 and 35 years with three or more hospital admissions for a painful crisis in the previous year, and be without any history of psychological or psychiatric treatment. The focus groups were tape-recorded and transcribed. Researchers read and re-read over the transcripts and jointly agreed on a set of recurring themes, all themes were reported to have emerged from the data. The results are summarised below.

Participants discussed the impact of physical health problems on families / carers. They recalled different reactions from their parents, including guilt of

passing on the disease to their offspring. This resulted in some parents coping with it through denial:

> *I mean my mum, she totally denied the fact that I was sick. She would tell people something else. I don't think she fully understands it. She's very bad at coping with me being sick.*

Other participants recalled parents being over-protective and restrictive. Some participants highlighted the importance of educating families/carers on how to make children aware of their limitations without restricting their childhood activities. Participants also reported that they were very aware of the impact that the disease had on families/carers.

Patients described the impact of the chronic physical health problem on their children. One discussed having to seek support from social services and psychologists to help her son cope with her illness:

> *They need more of a support package, more emotional rather than your physical…my blood pressure is sky high so unless they sort out my little boy's anger towards my illness, that is going to be affecting my illness…he said to the counsellor the other day 'I want to go to a children's home because I make my mummy sick'.*

Patients also discussed how acute painful episodes made it difficult to cope with the disease and exacerbated feelings of helplessness and lack of control, generating suicidal ideas during painful crises. One patient described the intensity of pain and feelings of relief from the idea of death:

> *It's a horrible thing to think about, but death can't have as much pain as what I go through, you know what I mean. Death can't be this painful, I'm telling you…I'll flick this death switch anytime, because when I'm, alive and in that sickle pain I'm telling you, you give me death, I'll have that, no trouble…..*

Participants described SCD having a psychosocial impact on daily living, interpersonal relationships, education and employment. They described how the unremitting nature of the disease affected their quality of life because they felt that they could not undertake normal activities of daily living. Participants found it difficult to have relationships with peers when they were growing up and also reported difficulties forming intimate relationships. Education was adversely affected by SCD because of the amount of time spent absent from school and the difficulty in performing to the best of their ability because of pain and hospitalisation. Participants also recalled having to work harder to keep up. Securing and maintaining employment was a major challenge for people with SCD because of absenteeism and rejection by employers. Many participants discussed the difficulty of having a job with high levels of responsibility and balancing a heavy workload with absences.

The study by Thomas and John (2007) had a sample of 118 end-stage renal patients, nine carers and 45 renal healthcare professionals. Inclusion/exclusion criteria for the patients were participants aged 16 and above who received treatment from a specialised renal service in one of London's hospitals. The study excluded participants with a known mental illness or mental health problems or those receiving psychiatric treatment. In addition, participants in the terminal stage of their illness were also excluded. Forty percent of the patient sample was from BME groups. Data were collected using semi-structured interviews and focus groups specific to patients, families/carers and healthcare professionals. The semi-structured interview specific to patients was designed to explore the use of support services, the perceived benefits of support services and patients' perceived psychological needs. A content analysis approach was undertaken and qualitative software was used to analyse the transcriptions of the interviews. The results of this study are summarised below.

Many patients said that they felt depressed and anxious because of their illness particularly due to the progressive nature of their disease and its impact on quality of life. Participants discussed being emotionally overwhelmed, feeling, 'why me?', and the inability to cope with or to adjust to their illness. This all had an impact on patients' mental health and wellbeing:

> *You can't help feeling this way. I do feel depressed and feel unhappy about the whole situation at times. What really depresses me is when I think of other things I probably would have been doing now that I'm unable to do because I'm hooked on the machine. Yes, at times like that I do feel very depressed….*

Patients also described the psychosocial impact of having a chronic physical health problem because of the physical restrictions imposed by the condition, including the need for dialysis and the inability to consume liquids, and the impact it has on activity levels and fatigue resulting in not being able to take part in leisure activities:

> *Well, I can't do what I used to do. For example, my leisure time, I don't have any social life because I don't have the energy anymore and I get really tired as well. Like before I used to, for example, meet up with my friend and maybe we'd go and visit other people, come in quite late...But I don't have that energy to stay out that late or to get engaged in any conversations that exert my energy.*

The psychosocial impact of the chronic physical health problem on body image was also reported. Although overall the study found that most patients adjusted well to the physical changes in their body some mentioned increased weight gain:

> *well I suppose that I do notice is that if my weight happens to go up more above a certain level, then I actually feel uncomfortable. It's easy for you but*

> *you get to a stage where in fact it's actually quite hard to prevent the pounds from going on….I just feel awful about it and I have to do something…*

Gruffydd-Jones and colleagues (2007) explored the needs of 25 patients discharged from hospital for COPD. Semi-structured questionnaires containing open-ended questions were conducted in focus groups and individually at the participant's home. The themes that emerged from the data were summarised to the participants for feedback on their credibility. Participants expressed psychological needs associated with having COPD. These included fear and anxiety associated with acute attacks of breathlessness.

Conrad and colleagues (2006) analysed interview transcripts for 70 people with self-reported hepatitis C for at least 12 months before interview. The interviews were semi-structured with 13 guided questions that were designed to elicit open-ended discussions and were conducted in groups and individually. Coding and analytical interpretations were discussed with researchers familiar with the data.

Many people with hepatitis C described experiencing debilitating episodes that were characterised by extreme fatigue, nausea and vomiting, sweating and headaches. This caused many people to withdraw from daily functioning during such episodes. One participant described experiencing depression and the effect that these debilitating episodes had on mood:

> *The depression I think comes from just not being able to do anything about it…yeah, just having to ride it out until it's done…gets me down.*

Stigma was associated with having hepatitis C because of the negative associations of injecting drug use and the perception that the illness is highly contagious. People with the condition had significant anxiety when deciding with whom to disclose their medical status, particularly when disclosing the information to sexual partners.

Another psychosocial impact reported by people with hepatitis C centred on transmitting the disease to others. This evoked extreme stress for the participants. For one participant this concern affected his quality of life far greater than the physical health symptoms associated with the disease:

> *I've got something that's not okay, I've got something…that might repulse people…I've got something that…people might potentially…decide they want to not be friends with me…*

4.3.4 Families' and carers' experiences

There was one study that illuminated the experience of caring for someone with a chronic physical health problem: Thomas and John (2007) as described above. This study used a semi-structured interview specific to

families/carers, who reported the psychological impact of caring for someone with an end stage renal disease. Some families/carers were happy to be labelled as carers, while others felt that the label was unnecessary. Some discussed the impact of the disease on the marital dynamic because of the change in roles when becoming a carer:

> *You still love but its different love; it's more of a care love…I feel more of a carer than a wife to be honest or mother even to some degree. It's very difficult. You just fall into a role….*

4.3.5 Healthcare professionals' experiences

Three studies explored healthcare professionals' experience of care: Thomas and John (2007), Chew-Graham and Hogg (2002) and Cocksedge and May (2005). The healthcare professionals included in these studies were those working with people with renal disease (Thomas & John, 2007) and GPs (Chew-Graham & Hogg, 2002; Cocksedge & May, 2005). All studies were conducted in the UK.

Thomas and John (2007) used a semi-structured interview specific to healthcare professionals that addressed what they considered to be the psychological needs of patients and families/carers; how they were supported in their roles; what skills and training they received to support patients; and how they were affected by their work. Healthcare professionals were aware of the psychosocial impact associated with the disease. They highlighted training needs such as how to sensitively break bad news to patients, communication skills and basic counselling skills. Healthcare professionals also said that there was a need for more support for staff, with many favouring the idea of a mandatory session with a psychologist perhaps once a year.

The study by Chew-Graham and Hogg (2002) explored the attitudes and belief systems of GPs and offered explanations for practitioners' behaviour and suggestions to improve the management of depression in people with chronic physical health problems. The study had a purposed sample of 25 GPs. Interviews were collected until category saturation was achieved. The final sample included 13 GP interviews. The interviews were semi-structured consisting of open-ended questions and the use of prompts when necessary. Interviews were modified in light of emerging themes. Interviews were transcribed and themes were collected.

Healthcare professionals had good insight into the association between depression and chronic physical health problems and understood the psychosocial impact associated with having a chronic health problem. Depression was not seen as being distinct from the physical health problem but part of it. They felt that the likelihood of getting depressed was affected by the duration of the illness and the severity of the symptoms.

Some healthcare professionals acknowledged that they did not routinely screen for depression nor did they favour the use of formal screening tools. However, they did express that screening tools are more reliable than clinical judgement alone in detecting depression and that they would be helpful in increasing the detection of depression in primary care. Although the term screening tools was used in this study, the GDG preferred the use of the term case identification to refer to the recognition of cases of depression.

Healthcare professionals discussed reasons why depression could go undetected in primary care. Reasons listed were: lack of time, patients' reluctance to talk about their depression and their resistance to taking antidepressant medication. Some healthcare professionals acknowledged their lack of confidence in detecting depression, and their reluctance to give the patients another label. In addition, GPs felt reluctant to add to their already hectic treatment regime:

> *You can sometimes think that you do not want to, as it were, act as a burden or if they are already on a list of medication, add something to that…*

Intervening to treat the depression was viewed as an important aspect of care for people with chronic physical health problems to improve patients' quality of life and to help them cope with the physical health problem. Healthcare professionals' first choice of treatment for people with depression and chronic physical health problems was a psychosocial intervention, depending on available resources. Healthcare professionals described the relative ease of prescribing antidepressants; however these were often not taken up by patients.

Healthcare professionals said that they had limited training in managing people with depression and chronic physical health problems and that they acquired their skills through experience. They stressed the need for ongoing professional learning.

Cocksedge and May (2005) used a semi-structured interview to explore GPs' experience regarding how they conceptualised their role and relationships with their patients. Twenty-three GPs were interviewed. They perceived that they had a role that went beyond treating the medical condition but to also provide a supportive role to diffuse psychosocial problems often connected with chronic conditions and depression and anxiety. However some GPs viewed engaging in this role as 'not the best use' of their time. Some expressed uncertainties and a lack of confidence to play the supportive role.

4.3.6 Provision of care

The review found one study that observed the interactions between nurses and patients with diabetes and depression who were enrolled in the collaborative care, Pathways study (Gask *et al.*, 2006). This study undertook content analysis on transcribed audio-taped recordings of consultation

sessions between nurses and patients. There were 25 patients with a total of 30 audio-taped sessions. Category saturation was achieved after 12 sessions. All emergent themes were fed back to the research team and nurses and their views were incorporated in the analysis. The study was conducted in the U.S.

The study found that patients with diabetes and depression were complex such that they experienced multiple problems that were associated with depression and having diabetes. These included additional physical health problems such as weight problems, heart diseases, mobility problems and visual impairment. Patients also experienced additional psychosocial problems such as financial, housing, relationship and employment difficulties. Many patients linked their difficulties due to the struggle of managing their chronic condition and the restrictions that it had brought on daily living.

The nurses' duties as outlined in the study protocol were not to directly intervene to improve the provision of diabetes care, except when issues arose in context of treating the depression. However in some instances, the nurses were not able to draw upon the connections between the experience of diabetes and depression that were raised by patients in their sessions. Therefore the interaction between depression and diabetes was ignored by nurses.

Issues of depression were raised by patients in various stages in their care. These were in the assessment of problems, a general discussion about treatment and in problem-solving sessions. In problem solving sessions the main issues which emerged were in relation to weight, eating, appearance and alcohol intake and in behavioural activation in relation to the patients' lack of mobility.

In the consultation sessions, the study found that a range of interventions were employed by the nurses some of which were consistent with the study's protocol such as problem solving. However, the nurses also delivered other interventions which they gained from previous experience such as counselling or psychotherapy. Therefore, nurses moved away from the dictating structure of problem solving and in some instances to offer advice rather than using the problem solving model which encouraged the patients to take responsibility and manage their own problems.

4.4 Qualitative analysis of the experience of care for people with chronic physical health problems

4.4.1 Introduction

The following section consists of a qualitative analysis of personal accounts of people with chronic physical health problems using healthtalkonline. Healthtalkonline provides interviews with people with various disorders

covering both physical health and mental health. As yet, healthtalkonline has not specifically looked at the experience of care for people with both depression and chronic physical health problems. Therefore the review team undertook a thematic analysis for this guideline using the interviews posted on the website to explore themes that are relevant to depression, including the experience of depression and or low mood, the depressogenic effects of pharmacology and the psychosocial impact of a chronic physical health problem.

4.4.2 Methods

Using the interviews available from healthtalkonline, the review team analysed the experience of 489 patients from across the UK. The chronic physical health problems covered in the analysis, which met the GDG's definition of a chronic condition, were: Parkinson's disease, diabetes (type II), epilepsy, heart attack, heart failure, arthritis, stroke, HIV, breast cancer, rheumatoid arthritis and lymphoma. Not all the conditions available on healthtalkonline could be analysed because of feasibility issues. The review team also browsed the interviews on healthtalkonline from people with depression to see if any interviewees also met criteria for a chronic physical health problem. Three further transcripts were identified.

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 in order to have a relatively unstructured, narrative data set. The second part of the interview process was a semi-structured interview 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 and chronic physical health problems. All emergent themes were discussed with the GDG, who also generated a list of anticipated themes. Each transcript was read and re-read and sections of the text were collected under different headings. The anticipated headings included: 'the experience of depression and/ or low mood', 'psychosocial interventions', 'pharmacology' and 'pain'. The headings that emerged from the data were: 'depressogenic effects of pharmacology', 'depressogenic effects of other treatments', 'psychosocial impact' and 'the interaction between physical health problems and mental health problems'.

There are some limitations to the qualitative analysis of patients' experience of chronic physical health problems undertaken for this guideline. As the review team relied on transcripts collected by other researchers with their own aims and purposes for a population with chronic physical health problems, information on issues that are particularly pertinent for people with depression and chronic physical health problems may not be available.

Moreover, the review team did not have access to the full interview transcripts and therefore had a selective snapshot of patients' experience. However using healthtalkonline did highlight issues regarding depression in people with chronic physical health problems that can be reflected upon for the purpose of this guideline.

4.4.3 The psychosocial impact of a chronic physical health problem

Patients' experience of the psychosocial impact of a chronic physical health problem was an important area often ignored in provision of care. Patients advocated for a shift in care that was currently focused on the medical aspect of the physical health condition to a holistic approach that took into account the psychosocial impact of a physical health problem.

Patients detailed how they wanted the psychosocial aspect of the chronic physical health condition to be discussed with service users:

> *We ought to go really towards having more talk about the psychosocial side of epilepsy, how it affects people on a day to day basis rather than just clinical diagnosis and talking about the stigma effects*

Patients also wanted more information on the psychosocial impact of a chronic physical health problem:

> *I find it strange that for something that's so common it's [rheumatoid arthritis] so misunderstood…there's all the information on websites and things about the medical aspects but there's not an awful lot of information about the social model of disability and how it impinges on other aspects of, of life.*

Employment

A lot of patients discussed the impact of a chronic physical health problem on retaining employment. Some people felt pressure from their employers to hand in their notice or take early medical retirement; others were advised by their doctors to stop working; and some made the decision on their own. Once unemployed many service users described the difficulty of finding a job that equalled their position prior to being ill. Some people described how their illness affected their employment status and how the psychosocial impact led to negative thoughts or feelings of depression:

> *Following my enforced medical retirement some thirteen years ago, I found it difficult, very difficult to come to terms with that... partly related to the job that I had, I was used to being in a position of authority and I found it quite difficult to find a reason for being. I got quite depressed following medical retirement…*

Finance

Patients noted that having a chronic physical health problem had a negative impact on finances, which affected their well being. People mainly attributed financial difficulties to changes in employment caused by having a physical health problem. A minority also attributed the financial difficulties to adapting their lifestyle to meet the needs of their condition. The financial implications caused by a change in employment as a result of a chronic physical health problem are described by a patient with epilepsy:

> *I was on probably £16-17 000 when I suddenly found I'd got this condition and then went to be paid about £5000 when I was given an alternative administrative job…the financial constraints were very, very difficult…*

Daily living

The effect of a chronic physical health problem on daily living was a constant reminder for patients of their disability and added to their frustrations of having an illness. Daily living was affected by a chronic physical health problem due to the associated physical restrictions imposed by having the condition. Physical activities that were affected included: gardening, DIY, playing with grandchildren, playing golf and driving. This had a psychosocial impact on mood and was often described as an element of their condition that was not taken into account by others. A patient who had had heart failure described the impact of the physical restrictions on daily living which affected his quality of life:

> *I can't dance like we [the patient and his wife] used to do…. Once round the floor and I'd be a bit fatigued, feel a bit of pressure across the chest in some cases. I miss being active and not playing my golf like I used to, and that really hurt because I used to be a good golfer…*

Body image

Several patients described the psychosocial impact of the chronic physical health problem caused by a change in body image. Many who underwent chemotherapy discussed losing their hair while others who underwent operations spoke about having visible scares. A patient with rheumatoid arthritis described the psychological impact of the change in body image caused by their illness:

> *Apart from the way I look, and feel self-conscious…the doctor says: 'you shouldn't feel like that' but I do. The fact is I do, I had a normal strong fit OK body and if I catch sight of myself in a mirror or a shop window and see the stooped shuffling individual I think 'Oh God. Do I really look that?' It's demoralising, it really is and it's some, an aspect of the disease, the psychological effect of it that isn't given any space at all.*

Interpersonal relationships

Patients reported an impact of the chronic physical health problem on interpersonal relationships for various reasons. Some patients lost friends because of their illness while others found it difficult to form new ones, particularly sexual relationships. A patient with breast cancer described losing friends as a result of her illness:

> *An issue that needs to be raised because friends who I would've expected support from shunned me and that hurts. That really, that's really difficult to come to terms with that, you know what I've done, is it my fault I've got cancer?*

For patients in long-term relationships at the time of the onset of their illness, some expressed difficulties because of changes in lifestyle or because of personality changes experienced by them because of their illness:

> *I turned from a sort of happy, outgoing kind of person to a sort of introspective, unhappy, certainly very angry…and this had a detrimental effect on my marriage and all the people around me…*

Stigma

The stigma associated with having depression or a chronic physical health problem can have a psychosocial impact upon patients which makes it harder to live with the condition. One person with diabetes discussed the stigma associated with depression:

> *[Diabetes] make me feel really low but…I don't want to go down the route where I go to the doctors and, you know, to say, 'oh, I'm feeling depressed'. So I just feel then, you know, you get labelled with depression and I don't want to be labelled with that.*

Regarding stigma associated with the physical health problem, patients objected to negative portrayals in the media and negative assumptions being made by society. This made living with the physical health problem harder:

> *I look at those adverts on the television, the old ladies showers … I think people see it as on old person's disease and I go oh no, no, no. It is rheumatoid, it is not osteo, it is rheumatoid. And I have a problem with that. I find it's labelled as on old person's disease and people don't understand as they don't unless they have exposure to it…*

4.4.4 The causal pathways to depression

The scientific literature points to several distinct ways in which a chronic physical health problem causes depression, one of which is pain. The different kinds of pain an individual experiences is directly proportional to the prevalence of depression (see Chapter 2). The following section is concerned

with the causal pathways to depression where an anticipated theme was pain. All other causal pathways emerged from the qualitative data and are summarised below.

Pain

Several patients commented on the effect of pain on their overall functioning, and some found pain unmanageable rather than the chronic physical health problem in general, which could lead to feelings of depression:

> *I talked about depression. There was one occasion when I was so, in so much pain, I, my wife came home and I was crying on, over the, I'd been doing the washing-up and you know you have to, I'm left handed, you have to hold a plate, this arm's absolutely giving me excruciating pain and I was really, I was really at a low and I just burst out crying.*

> *And occasionally, I still hit depressions because I know I'm not capable of doing what I used to do. When I wake up in the mornings I'm still aching. My back aches, my joint aches. It takes me a good hour in the mornings to get going.*

Depressogenic effects of pharmacology

Some patients described how their medication for their physical health problem caused immediate feelings of depression and how these experiences were distressing:

> *The one thing he [doctor] warned me about there are side effects with a number of the drugs…that I'm taking, can cause depression. And I could see on occasions like this black fog coming down and I knew it was depression*

For some the feelings of depression were so severe that they became suicidal:

> *The medication reached my nervous system. And I became suicidal overnight. So the anxiety the panic attacks…So I went to the clinic and said, 'You need to see me.' Spoke to the doctor. I said…'I'm going to kill myself, I don't…I cannot handle it'… So when the doctor saw me he said, 'I'm sorry. You are having a reaction that happens to one out of 10,000 people…You must go to the counsellor straightaway.*

One patient with epilepsy described how he stopped his medication because of the depressogenic effects but there were longer-term consequences, such as lack of confidence, which took a longer time to recover from:

> *I seemed to lose all my feeling, my senses, I was unable to taste things, to hear like I used to, to see like I used to. I used to cry all the time. I got terribly, terribly depressed. I still had seizures…so after three years, I gave them a good try and after three years I'm off now…it's a year exactly since I last took my*

last pill, anti-convulsant drug. And I do feel so much better. It's taken a year really to recover completely and to regain my confidence…

Depressogenic effects of other treatments

In addition to the depressogenic effects of medication, some patients described the similar effects of chemotherapy and radiotherapy:

I realised it [chemotherapy] made me depressed, which I never, that experience I never had in my life, that depression, I didn't know what depression was. And when I had depression it was really frightening. I was thinking of all sorts of things, bad things…

After about three weeks [of radiotherapy] I started to get depressed, really depressed, and I said to the girls: 'Does this make you depressions?' And they said: 'Well it does some patients, would you like us to make an appointment with the counsellor?' So I said: 'Yes'.

4.4.5 The experience of depression and/ or low mood

Many participants, as illustrated above recounted how the psychosocial impact of a chronic physical health problem could arouse feelings of depression and also highlighted some causal pathways to depression. In the following section patients describe their presentation and subjective experience of having depression and/or low mood.

Some of the behavioural and physical symptoms of depression described by patients included tearfulness, social withdrawal, irritability, a lack of libido and diminished pleasurable activity. A patient with lymphoma described a lack of pleasurable activities associated with having depression:

…it's a weird thing, depression's like you can't…like now I can sit and watch the television and be quite happy about watching the television… But when you're depressed these things don't do anything for you, they don't, they just, there's nothing, it's just everything's, I don't want to be a cliché and say everything's black, but nothing does…there's no stimulation from anything…

Symptoms of irritability and inability to sleep are described by a patient with breast cancer:

I'm taking antidepressants now. I was really, I got really depressed. I was just really flat and irritable and not sleeping…everything was just too much effort…just being confronted with your own mortality I think is a scary business.

4.4.6 The interaction between physical health problems and mental health problems

Some patients described an association between chronic physical health problems and depression:

> *There is one thing that I would associate with epilepsy is depression. It comes alongside because basically the restrictions, the stigma etc., emotionally is damaging…*

Some patients described a 'vicious circle' of periods of low mood intensifying the symptoms of their physical health problem. This in turn affected their mood causing a further depletion in their mood:

> *I find that when I'm happier I have fewer fits. When I'm unhappy I have more fits…it's a vicious circle…*

4.4.7 Psychosocial interventions

This section explores patients' experience of psychosocial interventions designed to reduce depression and other mental health problems or psychosocial stressors. Of the service users who had received some form of psychosocial intervention, the majority had counselling or peer (self-help) support and most of these had positive experiences of the interventions and found it largely beneficial. One service user discussed CBT. A minority also talked about other psychosocial interventions such as self-help materials for relaxation and physical activity.

Counselling

Patients described how counselling (this may have included a a range of psychologuicla interventiions beyond thsie traditionally referred to as counselling (see Chapter 7)) helped them deal with issues of having a chronic physical health problem and to develop strategies to help them cope with the condition:

> *I had counselling from the January until I decided that I didn't want to do it anymore. And so I did it for about 6 months and it was fantastic. It was, I think I hadn't really ever accepted that I had cancer in that way, and I don't thing I'd really ever admitted to myself how ill I as because that was too scary and too dangerous a place to go…it [lymphoma] changed me as a person, it has changed me as a person definitely. And I think counselling made me accept those changes and continue to develop myself…*

Not all patients who were offered counselling took part in the intervention. One person with rheumatoid arthritis said that counselling was not right for her:

> *If you are very down or very low and you are at home most of the time, it is worth going to your GP and talking to them about it. I did have counselling, to start with, and that didn't really work, so my GP said, 'Well, perhaps something else will.'…it is worth talking to your GP if you're really not coping, mentally*

Peer (self-help) support

Although counselling was frequently reported, not everyone received the intervention. However, the majority of patients had experienced peer (self-help) support, for whom it was a popular and beneficial treatment. The most common reasons patients gave for the intervention being helpful were that they felt that they were not alone and that there were others who had been through the same experiences as them:

> *In a support group we are all kind, sort of, all have the same problem [HIV]. And you realise that the pains you are having, others are having it too you know. Physical pains, emotional pains you know. And you tend to share you problems, you know. You feel well, I'm not alone. And that some are even worse off than you, you know physically and mentally too…*

Participants also cited the social aspects of meeting in groups as another common reason for the beneficial effects of peer (self-help) support. Others attributed the beneficial effects to the healthcare professionals who assisted and who were invited as guest speakers to give talks and to answer any questions. A minority said that the intervention was helpful because it allowed for information gathering and seeking of advice from other patients. One person said that the intervention instilled hope for their recovery from heart failure:

> *I got a letter through saying they had these meetings so I went and sat in one. They were quite good really, actually, there were a lot of people, well 8 or 9 of us there who'd had heart attacks in different stages of it, you know what I mean? Some of them had already had the operation to cure it but I never saw anybody who hadn't had something done about it…it gave me a bit of hope…*

Some patients from BME groups described some cultural benefits of peer (self-help) support groups, including meeting and sharing experiences with people with a similar background and a similar illness. One person described the perceived added benefit for black African men with HIV attending peer (self-help) support groups:

> *…one funny thing I've found, men tend to, to sort of look to their peers. So that's where the, the likes of a support group plays a very magical role basically … it can be a religion. You know peer support, some kind of… so that's where they get strength… I mean, when you are a man or a boy in African setting, you know the, the men's club is really a cultural thing…*

> *that's where men get their own power, their, their, their inspiration, from their own groups.*

Another person described how the peer (self-help) support group had replaced his blood-related community:

> *All of us have got some communities which are like blood related who are living here in the UK. But because of the situation [of having HIV], you find some of us are really rejected in those communities. So the only way to console yourself is to attend this new group [support groups] and this…becomes your community. And when you are in it, you feel happy.*

Other participants advocated for people of a similar age to meet and share their experiences because it was perceived that people of a similar age have common concerns regarding their physical health that may differ from others in a different age group:

> *I liked the idea of young stroke survivors, because it's very different to, with respect to older people, it's very different when you're 41 and disabled to when you're 75 and disabled. You've got a whole range of issues to be dealing with because you're younger…*

However not all patients were positive about peer (self-help) support; a minority described the intervention as not being right for them because listening to other people's problems made them feel worse. This was an issue for patients who were quite positive and who wanted to get on with their lives and not dwell on their physical health condition:

> *I was getting enough support at work and at home. I didn't really need to join a group…I didn't particularly want to dwell on having cancer. I wanted, it was part of my life, but I wanted to go on living the way I had before…*

Cognitive and behavioural interventions

One patient who had had a stroke described her experience with a cognitive and behavioural therapist as not beneficial but had a positive experience from a psychologist:

> *I was beginning to feel a bit depressed and she suggested a cognitive behavioural therapist and I did got to that a few times but I didn't think it would help very much…since then my GP has arranged for me to see a psychologist via the NHS… I've seen him a couple of times… he did some diagnostic tests first of all which I never got with the CBT specialist and he said it wasn't so much depression it was anxiety more than depression…*

Other psychosocial interventions

Some patients described physical activity as a psychosocial intervention with benefits in addition to its effect on improving physical health outcomes. These benefits included the social aspect of physical activity and the feeling of being in control of their physical illness:

> *I do think that swimming has helped and I know that if I don't go, I miss, I miss not only the social side, but the fact that I've had an hour or an hour and half's exercise, that's you know done me sort of good overall, not just my, my joints [because of rheumatoid arthritis]. 'Cos swimming keeps the muscles strong and of course the muscles support the joints, so it has to be good.*

Of the patients who discussed physical activity, some commented on being frightened to undertake exercise alone and others noted considerations that needed to be taken into account when exercising because of the complications of their conditions. These considerations included the difficulty of attending a general swimming pool because of not having enough space to swim.

> *We can still do the swimming but I have to go to a sheltered disabled session, I can't go to a normal swimming session because people in a normal general swimming session don't give each other space I needed to go to a sheltered session where people give each other plenty of room…*

A few patients described using self-help materials such as relaxation tapes to help manage any psychosocial stresses associated with having a chronic physical health problem:

> *It is not an easy pain to live with because it's not constant, it's here all the time but then it come, come in a quick sudden surge… I'll just… have to wait for it to subside… I found that relaxation tapes help enormously that I, I'll do a set of physio and then I'll out a tape on and I do find that, very, very positive and very therapeutic.*

4.4.8 Pharmacological interventions

The majority of patients who reported taking antidepressants to treat their depression recounted their beneficial effects but were reluctant to take the medication in the long term:

> *I wanted a lift from this awful feeling, total body feeling, quite apart from the aches, which were one, which were a major thing, it was all the other attendant feeling in the body and mind and all I wanted was a little lift and once I got that I was starting to get away…they [antidepressant drugs] were very beneficial, taken at that point. I wouldn't want to keep on with those because they are, they probably could be addictive. I don't know.*

A few participants said that medication did not help their depression at all, while another person explained how it helped the depression but still left unresolved psychosocial issues such as lack of confidence:

> *I was still on Prozac which stopped sheer depression. But my confidence you know I'd, I'd built up enough confidence to go back to work, but then that again started to drain away and I felt inadequate, I couldn't cope…*

4.5 A qualitative analysis of the experience of care for families/carers of people with chronic physical health problems

4.5.1 Introduction

In addition to undertaking a qualitative analysis of the experience of care for people with chronic physical health problems for this guideline using healthtalkonline, the experience of care for families/carers was also analysed.

4.5.2 Methods

The same methods for analysing the data for patients' experience were used as detailed above. Nineteen interviews with carers were found covering five chronic physical health problems: rheumatoid arthritis, Parkinson's disease, heart failure, stroke and epilepsy. The themes explored were care for families/ carers, families' and carers' concerns, psychological changes, the families/carers' role and the psychosocial impact.

4.5.3 Care for families/carers

Some families/carers commented on the current lack of support and care for families/carers of people with a chronic physical health problem. They highlighted the need for care and support and information on where families/carers can access these services:

> *[The social worker] told us about what was available for [my husband] but it was only really through the stroke club that I found what was available for me as a carer and the, the carers set up where we were. So I think it would have been helpful if, right from the outset, they could have said what was available for me as well as what was available for him…*

One family / carer detailed how without any support or acknowledgement of his difficulties for caring for his wife with a heart failure left him feeling isolated:

> *…nobody in the hospital or anywhere like that except for one sister and the nurses, ever came to me and spoke to me about it, 'how are you coping? How are you getting on?' Nobody offered any sort of back-up or any sort of help to get you through it, you know, they just accepted that you were somebody who just came to see as a visitor you know…so you do feel a bit alone…*

4.5.4 Families' and carers' concerns

Many families/carers described their worries and concerns about looking after someone with a chronic physical health problem. Some worried about leaving patients on their own; others were concerned about the progressive deterioration of the physical health problem and what that meant in the future; and one carer described her financial worries. When families/carers described these concerns some also detailed how these led to feelings of anxiety:

> *I was always concerned about going out of the house and leaving her – you never quite knew whether you were going to come back to her being alive, being walking about or being collapsed in a big heap somewhere. And that in fact still happens today I mean even, today I'll wake up in the middle of the night to see if she's still breathing, which is silly.*

4.5.5 Psychological changes

Many families/carers described how, in their experience, a chronic physical health problem impacted on the patient's personality. Many stated that the patient was 'not the same' person since they had become ill. The person was often described as having outbursts of anger and frustration that were not apparent before their illness. Some described how this can have an emotional impact on families/carers:

> *as long as he's okay and it's just when he takes these, I call them 'maddies', when he, he gets frustrated and he starts shouting and…that upsets me…well, you're, we've got you on tablets. The doctor gave you tablets…but it's horrible. I mean, the nurse tell me just to go out when he does it. Go out for a few hours but I'm always frightening in case he hurts himself because he bangs and you know…*

4.5.6 The families/carers' role

Some families /carers described the difficulties in their role, particularly finding a balance between being too restrictive and allowing the patient some independence. Some families/carers initially did too much for the patient, but then gradually learned to enable them to be more independent. One carer (a wife) spoke of the difficulty of not knowing when it was appropriate to help:

> *It's really difficult for carers and family to get the hang of how much to offer help. On the one hand you're trying to allow somebody to be independent, on the other hand they want to do something faster. There are different answers at different times*

4.5.7 The psychosocial impact

Some families/carers described the different areas in which caring for someone with a chronic physical health problem had a psychosocial impact on different areas of their life, including their daily/home life, their work and their social life:

> *I was a very spoiled person, [husband] has always allowed me to do my own thing, I've gone to work, I've gone and done, socially I've always gone line-dancing on my own and swimming with my friends, now I can't, that's completely gone, he has to come with me.*

The husband/carer of someone with rheumatoid arthritis described the impact of the illness and the need to balance his work and home life:

> *It's been juggling that work/life balance and needing to be around at home for [wife's name …the system we developed to help. She'd cope with our daughter during the day... then I'd come home and I would take over for the evening, sort of bath, bed, sort of routine before getting her to bed. And I used to do the early morning, get up, give her first bottle and get her up and before going off to work. And that's really how we coped…it's been quite difficult to juggle work and home life and that's been probably the biggest strain on me...so yes, I have good days and I have bad days…*

4.6 Summary of themes

The two personal accounts had one common theme, which was the way symptoms of depression in people with a previous history of depression can mimic and mask some symptoms of physical illness making it difficult to diagnose physical illness, or creating a barrier for healthcare professionals which means that depression is seen as the 'dominant' health problem. The implication from the literature and qualitative analysis is that the opposite might also be the case: that the physical illness can be the 'dominant' problem leading to a marginalisation or misrecognition of features of depression. Whichever the case, what emerges from the personal accounts and the evidence is that there needs to be a holistic approach to the treatment of adults with depression and chronic physical health problems, in which the effect of each on the other is recognised and the care of both is finely balanced. What is striking about the differences between the two personal accounts is the relationship with the healthcare professionals involved. In account A, the relationship is built on trust, respect and careful consideration of the patient's preferences. Good communication both with the patient and other professionals is a keynote of this personal account. In account B, the healthcare professional could only see the illness, and in this particular instance it was the wrong illness.

Themes from the literature and the qualitative analysis also echo in the personal accounts. In terms of causal pathways to depression, personal account A speaks of 'loss' as the defining feature of her depression which resurfaced after the onset of the physical illness when she experienced loss of good physical health, previous way of life and positive body image. In terms of the relationship between depression and a chronic physical illness, the physical illness in personal account A exacerbated the feelings of depression that had been with the person at points in their adult life. However, as a result

of having the physical illness the person had effective psychological treatment and came to terms with both conditions.

The literature and qualitative analysis provide important information on the relationship between a chronic physical health and depression. The qualitative analysis points to some causal pathways that may lead to depression such as distressing levels of pain. Patients also described the depressogenic effects of treatments for their physical health problems including pharmacological interventions, chemotherapy and radiotherapy. When prescribing medication for the chronic physical health problem it is therefore important to consider the depressogenic effects of the medication.

Across the different types of evidence it was clear that a chronic physical health problem had a psychosocial impact on patients; the impact on employment status was a consistent theme reported by patients leading to feelings of depression and low mood and having an effect on patients' confidence and self-esteem. Having a chronic physical health problem also had an effect on personal finances, daily living, physical activities (including driving), confidence, body image and interpersonal relationships, all of which are also adversely affected in depression. Stigma also added to the psychosocial impact of having a chronic physical health problem. Patients advocated for a shift in care currently focused on the medical aspect of the physical health condition to a holistic approach that took into account the psychosocial effects. The literature revealed that healthcare professionals who included both primary care staff and specialist staff working with end stage renal disease were aware of the psychosocial impact of chronic physical health problems on patients and how these could lead to feelings of depression. However, it is the experience of patients that this information is not communicated to them by healthcare professionals, and that it is important that it should be done sensitively at the start of care.

Similar themes emerged from the experience of families/carers. Both patients and families/carers reported how a patient's personality might change as a consequence of their physical health problem and commented on the impact on the families/carers. Families/carers detailed the need for support for themselves for caring for someone with a chronic physical health problem and information on where they could receive support.

Healthcare professionals highlighted the need for training and continuing professional development in order to care for people with depression and chronic physical health problems. In addition, healthcare professionals also discussed the need for more support when working with this client group.

Patients described their experience of psychosocial and pharmacological interventions. The majority had counselling or peer (self-help) support and reported these interventions to be largely beneficial. The majority of patients who reported taking medication to treat their depression recounted beneficial

effects of the antidepressants but a reluctance to keep on taking the medication long term. Healthcare professionals said that their preferred treatment choice for people with depression and chronic physical health problems was a psychosocial intervention, but that this was not often possible because of limited resources.

In an observation study on the provision of care for patients with diabetes and depression the study found that these patients were complex as they had additional problems associated with depression and diabetes. Nurses providing mainly problem solving did not link issues regarding the patients' diabetes to their depression and only focused on the patients' depression. Diabetes was raised in various stages of their care by patients particularly when carrying out problem-solving and the difficulties in partaking in behavioural activation due to their decreased mobility.

4.7 From evidence to recommendations

The recommendations set out in section 4.8 emerged from a discussion of the reviews of patient experience described in this chapter. These were discussed both with the patient member of this guideline and also with the patient and carer members of the depression update guideline. However, key aspects of the information reviewed in this chapter also had a direct impact on the generation of other recommendations in particular on assessment and case identification and on providing information of the likely impact of treatment. These can be found in the relevant chapters.

4.8 Recommendations

Providing information and support, and obtaining informed consent

4.8.1.1 When working with patients with depression and a chronic physical health problem and their families or carers:

- build a trusting relationship and work in an open, engaging and non-judgemental manner
- explore treatment options for depression in an atmosphere of hope and optimism, explaining the different courses of depression and that recovery is possible
- be aware that stigma and discrimination can be associated with a diagnosis of depression and take into account how this may affect the patient with a chronic physical health problem
- ensure that discussions take place in settings in which confidentiality, privacy and dignity are respected.

4.8.1.2 When working with patients with depression and a chronic physical health problem and their families or carers:

- provide information appropriate to their level of understanding about the nature of depression and the range of treatments available
- avoid clinical language without adequate explanation
- ensure that comprehensive written information is available in the appropriate language and in audio format if possible
- provide and work proficiently with independent interpreters (that is, someone who is not known to the patient) if needed.

4.8.1.3 Inform patients with depression and a chronic physical health problem about self-help groups, support groups and other local and national resources for people with depression.

4.8.1.4 Make all efforts necessary to ensure that a patient with depression and a chronic physical health problem can give meaningful and informed consent before treatment starts. This is especially important when a patient has severe depression or is subject to the Mental Health Act.

4.8.1.5 Ensure that consent to treatment is based on the provision of clear information (which should also be available in written form) about the intervention, covering:

- what it comprises
- what is expected of the patient while having it
- likely outcomes (including any side effects).

Supporting families and carers

4.8.1.6 When families or carers are involved in supporting a patient with severe or chronic depression and a chronic physical health problem, consider:

- providing written and verbal information on depression and its management, including how families or carers can support the patient
- offering a carer's assessment of their caring, physical and mental heath needs if necessary
- providing information about local family or carer support groups and voluntary organisations, and helping families or carers to access these
- negotiating between the patient and their family or carer about confidentiality and the sharing of information.

5 The identification of depression in people with chronic physical health problems

5.1 Introduction

The accurate identification of depression is an essential first step in the treatment and care of people with depression, and is particularly important for people with chronic physical health problems who appear to have a higher prevalence of depression than the general population (for example, Moussavi *et al*., 2007). Moreover, having depression and a chronic physical health problem may have greater adverse consequences than having a physical illness alone (Stein *et al*., 2006a).

There is likely to be greater problems detecting depression in people with chronic physical health problems. For example, Bridges and Goldberg (1985) found that GPs had much greater difficulty diagnosing people with depression and chronic physical health problems. They reported a detection rate by GPs of 23% for people with chronic physical health problems compared with 94% for people with depression alone. In addition, Zimmerman and colleagues (2006) suggest the current DSM-IV definition of depression may present difficulties when diagnosing depression in this population as somatic criteria such as fatigue, appetite disturbance and sleep disturbance may be caused by the physical illness rather than depression.

Older people and people from black and minority ethnic (BME) groups are of interest to this guideline because of an increased prevalence of chronic physical health problems. Conditions such as arthritis and diabetes are more common in older adults. An increased rate of physical health problems has also been established in some black and minority ethnic groups. South Asians have a higher prevalence of diabetes compared with white populations (Chowdhury *et al.,* 2003) and some conditions such as sickle cell anaemia are almost exclusively found in people of Black African and African-Caribbean origin. Physical health problems have been shown to be a risk factor for persistent depression in people of Pakistani origin living in UK (Grater *et al*., 2008).

5.2 Methods for detecting depression

5.2.1 Introduction

Healthcare professionals have reported that they find the various case identification tools for depression confusing and time consuming for routine practice (Andersen & Harthorn, 1989). This confusion is perhaps intensified by the vast number of primary studies claiming the validity of different tools

combined with a lack of systematic reviews to synthesise this considerable literature.

Williams and colleagues (2002) have probably produced the most comprehensive review of the literature assessing a range of instruments mainly in primary care settings and their work formed the basis for the US preventive services task force review on screening (see Pignone *et al*., 2002). This review consisted of 38 studies; however pooled data on specific instruments were only available for the CES-D, GHQ, MOSD and SDDS-PC. In addition, it appears that more robust HSROC or bivariate meta-analytic approaches were not used in the analysis (Gilbody *et al*., 2007). Therefore the validity of sensitivities and specificities reported in the paper may be compromised (see for example, Cochrane Collaboration, 2008).

A more recent review by Gilbody and colleagues (2007) consisted of a bivariate meta-analysis of PHQ-9 and PHQ-2 instruments. They argue their study is the first to conduct a diagnostic accuracy meta-analysis on depression (and in the whole field of psychometrics) using the most updated and robust techniques. However, the limitation to this review is the focus on just the PHQ-9 and PHQ-2 scales. It is not possible to assess how these scales compare with many other depression identification tools in widespread use in clinical practice.

In order to address the limitations in the literature, a meta-analysis was conducted to assess the most widely validated case identification instruments for depression using a bivariate approach recommended by the Cochrane Collaboration. Furthermore, little is known concerning the validity of these instruments in different populations. Therefore subgroup analyses and meta-regressions were conducted to assess if there are differences in the psychometric properties of these scales when assessing people in consultation (such as primary care or general hospital settings), those with chronic physical health problems, and community or older adult samples.

Current practice

The previous NICE (2004a) guideline on depression recommended the use of the Whooley questions to target groups thought to be at higher risk of depression including people with dementia, diabetes and other functional impairments. These recommendations have been integrated into the primary care system in the UK through the QoF providing GPs with incentives for asking case identification questions to those groups thought to be at risk of depression (DH, 2004).

Definition and aim of topic of review

Case identification instruments were defined in the review as validated psychometric scales used to identify people with depression. The review was limited to identification tools likely to be used in UK clinical practice, that is, the Beck Depression Inventory, Patient Health Questionnaire, General Health

Questionnaire, Centre of Epidemiology Studies-Depression, Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Zung Self Rated Depression Scale, and any one- or two- item measures of depression in primary care, hospital and community settings. 'Gold standard' diagnoses were defined as DSM-IV or ICD-10 diagnosis of depression. Studies were excluded if they did not clearly state that the comparator was DSM-IV or ICD-10, used a scale with more than 28 items, or did not provide sufficient data to be extracted in the meta-analysis.

5.2.2 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/ exclusion criteria used for this section of the guideline can be found in Table 6.

Table 6: Databases searched and inclusion/exclusion criteria for the accuracy of case identification tools aimed at detecting depression

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	Beck Depression Inventory, Patient Health Questionnaire, General Health Questionnaire, Centre of Epidemiology Studies-Depression, Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Zung Self Rated Depression Scale , and any 1 or 2 item measures of depression
Outcomes	Sensitivity, specificity, area under the curve, diagnostic odds ratio, positive likelihood, negative likelihood

5.2.3 Studies considered[4]

The review team conducted a new systematic search for cross-sectional studies to assess tools for identifying depression (see Appendix 9)
A total of 129 studies met the eligibility criteria of the review. Seventy-seven studies were conducted in consultation samples (primary care and general medical settings), 52 were on people with chronic physical health problems. Of these studies, 60 were on older people (over 65 years of age).

In terms of scales: 16 were on the PHQ-9, five on the PHQ-2, seven on the Whooley, 18 on the BDI, five on the BDI: short form, five on the BDI:fast screen, 28 on the GHQ-12, 17 on the CES-D, 27 on the GDS, 26 on the GDS-15, 24 on the HADS-D, 10 on one-item measures (see appendix 20 for further details of the included studies).

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).

[4] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

5.2.4 Evaluating identification tools for depression in people with chronic physical health problems, people in primary care, and older people

A bivariate diagnostic accuracy meta-analysis was conducted using Stata 10 with the midas (Dwamena, 2007) commands in order to obtain pooled estimates of sensitivity, specificity, likelihood ratios and diagnostic odds ratio (for further details, see 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). However, the limitations of taking a fixed cut-off approach should be acknowledged as there is some evidence that the optimal cut-off of a scale may differ according to the prevalence of depression in the population investigated (see Furukawa *et al.*, 2001).

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
Short form (13 items)	10
Fast screen (7 items)	4
PHQ	
9 items	10
2 items	3
Whooley (2 items)	1
GHQ*	
28 items	5
12 items	3
HADS-D	8-10 mild, 11-14 moderate 15+severe
CES-D	16
GDS	
30 item	10
15 items	5
Zung	50 mild, 60 moderate, 70 severe
* see below for further discussion on cut-offs for GHQ	

Table 8 summaries the results of the meta-analysis in terms of pooled sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, diagnostic odds ratios and area under the curve. There was very high heterogeneity when the scales were combined across different samples. Therefore tools were analysed separately for people in consultation samples (primary care or general medical settings), people with chronic physical health problems, and older people (defined as over 65 years of age).

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

Population and instrument	Sensitivity	Specificity	Likelihood ratio+	Likelihood ratio -	Diagnostic odds ratio	AUC
PHQ9 Physical health problem samples: 5 studies	0.79 (0.65, 0.89)	0.89 (0.84, 0.93)	7.27 (4.91, 10.77)	0.23 (0.13, 0.42)	31.13 (14.41, 67.71)	0.92 (0.89, 0.94)
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)
Physical health problem samples: 14 studies	0.85 (0.80, 0.89)	0.73 (0.65, 0.79)	3.09 (2.40, 3.98)	0.21 (0.15, 0.29)	14.71 (8.94, 24..21)	0.87 (0.84, 0.90)
BDI-non somatic items Consultation sample: 5 studies	0.82 (0.57, 0.94)	0.73 (0.61, 0.83)	3.02 (1.86, 4.90)	0.25 (0.09, 0.69)	11.92 (3.02, 47.04)	0.83 (0.79, 0.86)
Physical health sample: 5 studies	0.87 (0.62, 0.97)	0.74 (0.65, 0.82)	3.39 (2.22, 5.17)	0.17 (0.05, 0.63)	19.71 (3.89, 99.78)	0.83 (0.79, 0.86)
BDI fast screen (all populations): 4 studies	0.81 (0.68, 0.90)	0.75 (0.66, 0.82)	3.21 (2.47, 4.17)	0.25 (0.15, 0.43)	12.86 (6.97, 23.72)	0.85 (0.81, 0.88)
BDI short form (all populations): 4 studies	0.76 (0.36, 0.95)	0.86 (0.79, 0.91)	5.32 (3.16, 8.95)	0.28 (0.08, 1.04)	19.13 (3.45, 106.05)	0.88 (0.85, 0.91)
CES-D Physical health sample: 6 studies	0.79 (0.73, 0.83)	0.84 (0.77, 0.89)	4.81 (3.23, 7.16)	0.26 (0.19, 0.34)	18.72 (9.86, 35.57)	0.86 (0.82, 0.88)
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 Physical health sample: 6 studies	0.79 (0.71, 0.85)	0.74 (0.67, 0.80)	3.02 (2.33, 3.93)	0.29 (0.21, 0.39)	10.61 (6.53, 17.26)	0.82 (0.78, 0.85)
GDS-15 Physical health sample: 4 studies	0.83 (0.77, 0.88)	0.80 (0.75, 0.84)	4.12 (3.30, 5.16)	0.21 (0.15, 0.29)	19.85 (12.51, 31.51)	0.86 (0.83, 0.89)
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)
Nursing home sample: 6 studies	0.86 (0.76, 0.93)	0.76 (0.66, 0.83)	3.54 (2.52, 4.95)	0.18 (0.10, 0.32)	19.53 (9.43, 40.43)	0.87 (0.84, 0.90)
1-item Primary care: 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)
GHQ-12 Physical health: 28 studies	0.84 (0.59, 0.95)	0.75 (0.70, 0.79)	3.32 (2.48, 4.44)	0.21 (0.07, 0.65)	15.66 (4.00, 61.34)	0.68 (0.64, 0.72)

Patient Health Questionnaire

The patient health questionnaire (PHQ) developed out of the more detailed PRIME-MD (Spitzer *et al*., 1994). There are three main versions of this scale used for identification: 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 a cut-off of 10. Although the PHQ-2 and the Whooley questions use the same two items, the PHQ-2 follows the scoring format of the PHQ-9 (Likert scales), while the Whooley version dichotomises the questions (yes/no) and has a cut-off of 1 compared with 3 for the PHQ-2. In total, 16 trials were conducted on the PHQ-9, five trials on the PHQ-2 and six trials on the Whooley questions. Studies of the PHQ-9 were analysed by population because there was very high heterogeneity in a combined analysis. McManus and colleagues (2005) had to be removed from the meta-analysis of the PHQ-9 for people with chronic physical health problems because this appeared to be an outlier resulting in a reduction in heterogeneity (I^2= 84.81%). There was slightly less heterogeneity in the consultation sample analysis (I^2= 74.04%).

In both consultation (primary care and general medical settings) and chronic physical health populations, the PHQ-9 was found to have good sensitivity (physical health: 0.79, CIs 0.65, 0.89; consultation: 0.82, CIs 0.77, 0.86) and specificity (physical health: 0.89, CIs 0.84, 0.93; primary care: 0.83, CIs 0.76, 0.88).

Short forms of the PHQ

The PHQ-2 could not be meta-analysed as there was very high heterogeneity. However, it was possible to analyse the Whooley questions as there was less heterogeneity (I^2 = 63.25%). The Whooley questions were found to have high sensitivity (0.95, CIs 0.91, 0.97) but lower specificity (0.66, CIs 0.55, 0.76). Due to lack of studies the data for the Whooley scale could not be broken down into sub-groups.

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 can provide data on the severity of depression; commonly 13 is used as a cut-off in identification studies.

In addition, the short form (cognitive-affective sub-scale) of the BDI has often been used to identify depression (Beck *et al*., 1979; Beck *et al*., 1996) and the BDI-fast screen has been specifically developed for use in primary care (Beck, *et al.,* 1997). Both of these scales have a cut-off of 4 points.

There were a large number of studies on the BDI, 19 on the 21-item BDI and 9 BDI versions just containing non-somatic items (7-item BDI-fast screen, 13-item BDI-short form).

For the 21-item BDI there was very high heterogeneity when combining all populations. The heterogeneity slightly reduced when analysed by sub-groups but was still high for both consultation (people in primary care and general medical) samples (I^2 =88.61%), where Laprise (1991) was removed as an outlier, and for the chronic physically ill samples (I^2 =77.78%). For people in consultation populations the BDI appeared to perform relatively well in terms of sensitivity (0.85, CIs 0.79, 0.90) and specificity (0.83, CIs 0.70, 0.91). However, this is based on only four studies so it is difficult to draw conclusions from this data.

Comparable sensitivity (0.85, CIs 0.79, 0.89) but lower specificity (0.73, CIs 0.65, 0.79) was found for this scale in people with chronic physical health problems.

BDI with somatic items removed

The BDI-fast screen was relatively consistent across populations (I^2 =67.69%) suggesting the possible benefit of removing somatic items from the full BDI; however, the meta-analysis was based on only four studies. There was evidence of good sensitivity (0.81, CIs 0.68, 0.90) but less specificity (0.75, CIs 0.66, 0.82).

When analysed, studies looking at the BDI-short form were too heterogeneous, therefore Whooley and colleagues (1997) was removed because it appeared to be an outlier and only four studies were included in the meta-analysis. This resulted in reduced sensitivity (0.76, CIs 0.36, 0.95) but higher specificity (0.86, CIs 0.79, 0.91) and slightly reduced, but still high, heterogeneity (I^2 = 86.17%).

Data from BDI fast-screen and BDI-short form were combined to assess the impact of removing somatic items because data from both scales were relatively sparse. There was sufficient consistency between studies to assess these scales (BDI: non-somatic) in consultation (I^2 = 75.71%) and chronic physical health problem populations (I^2 = 85.6%).

In consultation populations there was high sensitivity (0.82, CIs 0.57, 0.94) but less specificity (0.73, CIs 0.61, 0.83). In people with chronic physical health problems, the BDI-non-somatic scales performed relatively similarly. The instruments were associated with relatively high sensitivity (0.87, CIs 0.62, 0.97) and reduced specificity (0.74, CIs 0.65, 0.82).

GHQ

The GHQ was developed as a general measure of psychiatric distress and this allows it be used as an identification measure for depression and anxiety. The

main versions used for identification purposes are the GHQ-28 and GHQ-12. Furukawa and colleagues (2001) have shown that the optimal cut-offs for the above versions of GHQ differ according to the prevalence of depression in the sample. However, most included studies in this review did not provide sufficient data in order to calculate the optimal cut-offs as recommended by Furukawa and colleagues (2001).

There were only two trials of the GHQ-28, therefore only the GHQ-12 was meta-analysed. Heterogeneity was very high when all populations were combined, therefore studies were broken down into sub-groups. There remained very high heterogeneity (I^2 >90%) for studies of consultation samples, therefore meta-analyses were not conducted for this population. However, there was high but acceptable heterogeneity for community samples (I^2 = 77.59%). In addition, when Reuter and Härter (2000) was removed as an outlier the heterogeneity was high but acceptable also in chronic physical health problem samples (I^2 = 87.65%).

There was relatively high sensitivity (0.84, CIs 0.59, 0.95) but less specificity (0.75, CIs 0.70, 0.79) found for this scale in people with chronic physical health problems.

CES-D

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

There were a total of 17 trials on the CES-D; meta-analyses were conducted on consultation, chronic physical health and older adult populations. There was high but acceptable heterogeneity in the consultation (I^2 =84.63%) sample. There was an outlier (McQuillan *et al*., 2003) in the chronic physical health meta-analysis but once this study was removed heterogeneity completely disappeared (I^2 =0%). For the older adult population, Harringsma and colleagues (2004) was removed from the analysis resulting in acceptable heterogeneity (I^2 =61.09%).

For people with chronic physical health problems the instrument was approaching acceptable sensitivity (0.79, CIs 0.73, 0.83) and had relatively good specificity (0.84, CIs 0.77, 0.89). The diagnostic odds ratio was below 20 (18.72, CIs 9.86, 35.57).

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

GDS

The GDS was developed to assess depression in older people. The original 30-item scale (cut-off of 10 points) was developed by Yesavage and colleagues (1982) and more recently 15-item (cut-off of 5 points) versions have been validated.

The largest number of studies in the review was identified for the GDS, 20 on the full scale, and 17 on the GDS-15. There was very high heterogeneity for the GDS for the consultation sample therefore no meta-analyses could be conducted. For the physical health problem population, there was low sensitivity (0.78, CIs 0.71, 0.84) and specificity (0.76, CIs 0.69, 0.82). There were no problems with heterogeneity ($I^2 = 0\%$).

For the GDS-15, there was both acceptable sensitivity (0.83, CIs 0.77, 0.88) and specificity (0.80, CIs 0.75, 0.84) in chronic physical health problem populations. There was very low heterogeneity ($I^2 = 0\%$). In the consultation population there was higher sensitivity (0.87, CIs 0.80, 0.91), but specificity (0.75, CIs 0.69, 0.80) was relatively low. Heterogeneity was relatively acceptable ($I^2 = 70.96\%$).

HADS

The HADS (Zigmund & Snaith, 1983) is a measure of depression and anxiety developed for people with physical health problems. The depression sub-scale has 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 in all possible sub-groups ($I2 > 90\%$). Although sensitivity analyses were conducted removing outliers there continued to be very high heterogeneity.

One-item measures

There were five studies found to assess a one-item measure in consultation samples. There was a relatively good sensitivity (0.84, CIs 0.78, 0.89), but very low specificity (0.65, CIs 0.55, 0.73). There was significant heterogeneity between studies in physical health populations therefore meta-analysis was not conducted.

Distress Thermometer

The distress thermometer is also a one-item instrument, specifically designed for people with physical health problems, and is measured on a visual analogue scale so is particularly helpful for people with language and communication difficulties. There was evidence of good sensitivity (0.80) and less specificity (0.61) for this measure (Akizuki *et al.,* 2003). Although the specificity was comparable with other 1- or 2-item measures. Similar findings were reported in a follow up study (Akizuki *et al.,* 2005) when an impact thermometer was added to the distress thermometer suggesting good sensitivity (0.89) and less specificity (0.70).

5.2.5 Comparing validity coefficients between populations

There was high heterogeneity for most scales when investigating different populations, therefore it was only possible to combine data between populations for the GDS-15, Whooley, BDI-fast screen and BDI short form (see Table 9). This consistency across populations may be explained to some extent by each of these scales focusing on non-somatic items.

The impact of physical illness, old age, and residing in a nursing home on the validity coefficients of the case identification tools were assessed through meta-regression. Due to lack of data the PHQ-2, Whooley, Zung, and one-item measures were not included in the analysis.

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

Population and instrument	Beta-coefficient	I^2 (%)	p-value
PHQ9 Comparing DCHP with primary care and community)	Sensitivity =1.13		0.32
	Specificity= 2.08		0.71
		Joint I2= 1.05	0.59
Comparing over 65s with under 65s	Sensitivity = 1.23		0.65
	Specificity = 1.84		0.73
		Joint I2= 0	0.83
BDI Comparing DCHP with primary care and community	Sensitivity = 1.66		0.07
	Specificity = 0.96		0.08
		Joint I2= 56.69	0.10
Comparing over 65s and under 65s	Sensitivity = 1.58		0.34
	Specificity = 0.74		0.79
		Joint I2 = 0%	0.65
BDI-non somatic items Comparing DCHP with primary care and community	Sensitivity = 1.87		0.32
	Specificity = 1.24		0.82
		Joint I^2=0	0.60
Comparing over 65s and under 65s	Sensitivity = 1.58		0.80
	Specificity = 2.12		0.02
		Joint I^2=58.64	0.09
CES-D Comparing DCHP with consultation and community	Sensitivity = 1.40		0.06
	Specificity = 1.21		0.98
		Joint I^2=39.65	0.19
Comparing over 65s with under 65s	Sensitivity = 1.23		0.09
	Specificity = 1.61		0.18
		Joint I^2 = 43.30	0.17
GDS Comparing DCHP with consultation and	Sensitivity = 1.10		0.23

community	Specificity = 1.35		0.25
		Joint I^2 = 0%	0.40
Comparing nursing home and non-nursing home	Sensitivity = 1.54		0.85
	Specificity = 1.13		0.65
		Joint I^2= 0%	0.80
GDS-15 Comparing DCHP with consultation and community	Sensitivity = 1.63		0.53
	Specificity = 1.46		0.04
		Joint I^2=53.01%	0.12
Comparing nursing home and non-nursing home	Sensitivity = 2.14		0.36
	Specificity = 0.91		0.34
		Joint I^2= 0%	0.44
HADS Comparing DCHP with consultation and community	Sensitivity = 1.14		0.60
	Specificity = 1.53		0.49
		Joint I^2 = 89.26%	0.01
GHQ-12 Comparing DCHP with consultation and community	Sensitivity = 1.56		0.26
	Specificity = 0.89		0.48
		Joint I^2= 0%	0.50
Comparing over 65s to under 65s	Sensitivity = 0.43		0.14
	Specificity = 1.45		0.33
		Joint I^2= 11.28%	0.32

People with chronic physical illness

There was a trend in reduction in sensitivity (p=0.07) and specificity (p=0.08) on the BDI for people with chronic physical health problems. For the CES-D there was a trend for reduction in sensitivity (p=0.06) but not specificity. For the GDS-15 there was an improvement in specificity (p=0.04) for people with chronic physical health problems. For all other scales there was limited evidence of differences in validity coefficients between people with chronic physical illness and those in consultation and community populations.

Older adults

There was some evidence that the BDI versions with no somatic items (p=0.02) and the GDS-15 (p=0.04) were associated with improved specificity in older adults. There was a trend towards reduction in sensitivity for the CES-D (p=0.09) in older adults.

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 for both scales when assessing people either in nursing homes or in the community.

5.3 Case identification in black and minority ethnic populations

5.3.1 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 (1999b) indicated that women from BME groups had an increased incidence of common mental disorders including both depression and anxiety. Such findings cannot wholly be explained by differences in factors such as urbanism, socioeconomic status, reduced social support and perceptions of disadvantage (Weich *et al*. 2004*;* Bhugra & Cochrane, 2001; Grater *et al.,* 2008). Furthermore, culture is known to exert an influence on the presentation and subjective experience of illness. Individual perception of what constitutes an illness, and whom people seek for treatment, are affected by an individual's culture and ethnicity. With regards to depression, a number of findings have indicated both ethnic and cultural variations in the subjective experience and initial presentation of the illness. For example, Commander and colleagues (1997) are among researchers to suggest that 'Asians', which includes 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 (Grater, *et al.* 2008). However, Wilson and MacCarthy (1994) 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.

It has been shown that, in general, people with chronic physical health problems are more likely to somatisise their symptoms of depression. Therefore, in addition to the impact of an increased prevalence of some psychical disorders in people from BME communities, the above research suggests that additional cultural and ethnic factors may further exacerbate differences in the presentation and subjective experience of depression in people from BME groups.

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

Despite an increased awareness that different cultural and ethnic factors may influence the presentation of depression, the majority of case identification

tools used in routine clinical practice were originally created and validated on white populations (Husain *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 people from BME groups 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.

5.3.2 Definition and aim of topic of review

The GDG were aware of a number of important issues associated with the access and engagement of people from black and minority ethnic populations. However, for the purposes of the guideline this review was specifically focused on case identification. 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 were aware of studies from outside the UK, most notably from the US, the decision was taken to only include UK studies. As discussed above, the presentation and subjective experience of depression is known to be influenced by cultural and ethnic factors, therefore it was felt that findings from non-UK ethnic minority populations would not be generalisable due to the differences both ethnically and culturally between the populations studied. The review also assessed the validity of established depression case identification tools for different ethnic minority populations within the UK[5].

5.3.3 Databases searched and inclusion/exclusion criteria

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

[5] 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 for the accuracy of case identification tools aimed at detecting depression in BME participants

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 communities
Instruments	1. Any ethnic-specific depression case identification instrument 2. Any culturally 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 1- or 2-item measures of depression 3. Any of the above validated identification tools, assessed in a UK BME population.
Outcomes	Sensitivity, specificity, area under the curve, diagnostic odds ratio, positive likelihood, negative likelihood

Studies considered

A total of four studies met the eligibility criteria of the review. All four papers were conducted within the community or primary care. One included study compared the Amritsar Depression Inventory (ADI) to the GHQ-12 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.

In addition, 10 studies were excluded from the analysis. The most common reason for exclusion was a non-UK based study/population or the paper presented no usable evaluation of a screening tool.

Evaluating identification tools for depression

Due to both the paucity of data on ethnic-specific scales in the UK and differences in the populations and instruments investigated, it was not possible to conduct a meta-analysis of the included studies. Instead the findings from these studies are summarised in a narrative review. In addition, it should be noted these studies were not conducted in people with chronic physical health problems, which is an important limitation of this review.

Amritsar Depression Inventory (ADI)

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

Using the ADI and the GHQ-12, Bhui 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 language barriers, 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 CIS-R was administered by a bilingual psychiatrist.

Results of the validity coefficient 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 did not perform as well 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 than for white English people, 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 (CCSS)

The CCSS (Abas *et al.*, 1998) is a 13-item dichotomous (yes/no) culture-specific screen developed through a process of generating locally derived classifications of mental disorders in Caribbean people and gathering commonly used terms for emotional distress. The majority of participants interviewed in the piloting stages of the screen were from Jamaica with a number of participants identifying themselves as from other Caribbean countries including Guyana, Barbados, Trinidad and Grenada.

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

The sample in Abas 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 Exam (MMSE). Responders were categorised as high scorers if they

scored ≥4 on either measure, and as 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 were selected to attend a further interview. During this second stage interview, the GMS-AGECAT and a culturally specific diagnostic interview, which was informed through a process of consultation with African-Caribbean religious healers/ministers, were administered to the selected participants.

Rait 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 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 note that the small sample size prevents any meaningful test of statistical significance. As it was noted that considerable variation may exist among people of Caribbean origin from different islands, results of the Rait and colleagues' (1999) paper were presented for the sample as a whole and for a sub-group of Jamaican participants who constituted the majority. Although there was slight variation 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 were deemed acceptable, with no resulting suggestion for changes being 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, instead of 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 BME 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 Pakistanis 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.

Consecutive primary care attendees of Pakistani family origin aged 16 to 64 were included in the sample. Eligible participants were identified through either their name and/or language or via direct questioning. As with the other screening studies, a two stage process was employed. All eligible participants firstly completed the 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-10 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 PPV of 82.6 and a NPV 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.,* 2007) did not experience any difficulties in understanding and answering the screening questions.

Limitations with the evidence base

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

specificity for caseness when compared with these diagnostic measures. Further research into this area is required to answer such questions.

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

5.4 Overall summary

There was limited evidence of differences between scales on validity coefficients. Some of the shorter item scales had very high levels of sensitivity (for example, the Whooley) but lower levels of specificity. Scales with more items (such as the PHQ-9 and GDS-15) were slightly less sensitive but still had acceptable sensitivity and specificity.

There was insufficient evidence to suggest that using a scale tailored to people with chronic physical health problems improved identification in this population. The more limited data on older adults suggests the GDS-15 maybe preferred in this population.

The review of ethnic specific scales failed to identify any benefit for use of these measures above established case identification tools, when assessing for depression in black and minority ethnic populations. Established scales including the GDS, GHQ-12 and personal health questionnaire appeared to perform well in a range of UK black and minority ethnic groups.

5.5 From evidence to recommendations

The GDG noted the different nature of the scales contained in the review and their psychometric properties and the possible benefit of a two stage process of case identification.

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. Given that using the Whooley questions is already current practice in primary care, the GDG concluded that the data supported the continuing use of this measure as the first stage of case identification for depression. Moreover, the GDG also noted the lack of specificity found for the Whooley questions and judged that people with a positive test results would benefit from a more detailed clinical assessment, which may include a more detailed instrument possessing better overall psychometric properties.

In addition, there was some positive evidence for the performance of established case identification tools in black and minority ethnic groups. It was however noted in a number of studies that the cultural competence of the person delivering the case identification tool may be of pivotal important. In particular, delivering the identification measure in a culturally sensitive way may have an effect on both the acceptability of the measure and on the amount of information disclosed to the person administering the tool.

5.6 Recommendations

Principles for assessment, coordination of care and choosing treatments

5.6.1.1 When assessing a patient with a chronic physical health problem who may have depression, conduct a comprehensive assessment that does not rely simply on a symptom count. Take into account both the degree of functional impairment and/or disability associated with the possible depression and the duration of the episode. **[KP]**

5.6.1.2 In addition to assessing symptoms and associated functional impairment, consider how the following factors may have affected the development, course and severity of a patient's depression:

- any history of depression and comorbid mental health or physical disorders
- any past history of mood elevation (to determine if the depression may be part of bipolar disorder[6])
- any past experience of, and response to, treatments
- the quality of interpersonal relationships
- living conditions and social isolation.

5.6.1.3 Be respectful of, and sensitive to, diverse cultural, ethnic and religious backgrounds when working with patients with depression and a chronic physical health problem, and be aware of the possible variations in the presentation of depression. Ensure competence in:

- culturally sensitive assessment
- using different explanatory models of depression
- addressing cultural and ethnic differences when developing and implementing treatment plans
- working with families from diverse ethnic and cultural backgrounds.

[6] Refer if necessary to 'Bipolar disorder' (NICE clinical guideline 38; available at www.nice.org.uk/CG38)

5.6.1.4 When assessing a patient with a chronic physical health problem and suspected depression, be aware of any learning disabilities or acquired cognitive impairments, and if necessary consider consulting with a relevant specialist when developing treatment plans and strategies.

5.6.1.5 When providing interventions for patients with a learning disability or acquired cognitive impairment who have a chronic physical health problem and a diagnosis of depression:

- where possible, provide the same interventions as for other patients with depression
- if necessary, adjust the method of delivery or duration of the intervention to take account of the disability or impairment.

5.6.1.6 Always ask patients with depression and a chronic physical health problem directly about suicidal ideation and intent. If there is a risk of self-harm or suicide:

- assess whether the patient has adequate social support and is aware of sources of help
- arrange help appropriate to the level of risk (see recommendations 5.6.1.12 to 5.6.1.15)
- advise the patient to seek further help if the situation deteriorates.

Step 1: recognition, assessment and initial management in primary care and general hospital settings

Case identification and recognition

5.6.1.7 Be alert to possible depression (particularly in patients with a past history of depression or a chronic physical health problem with associated functional impairment) and consider asking patients who may have depression two questions, specifically:

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

5.6.1.8 If a patient with a chronic physical health problem answers 'yes' to either of the depression identification questions (see 5.6.1.7) but the practitioner is not competent to perform a mental health assessment, they should refer the patient to an appropriate professional. If this professional is not the patient's GP, inform the GP of the referral.

5.6.1.9 If a patient with a chronic physical health problem answers 'yes' to either of the depression identification questions (see 5.6.1.7), a practitioner who is competent to perform a mental health assessment should:

- review the patient's mental state and associated functional, interpersonal and social difficulties
- review and consider the role of both the chronic physical health problem and any prescribed medication in the development or maintenance of the depression
- ascertain that the optimal treatment for the physical health problem is being provided and adhered to, seeking specialist advice if necessary.

5.6.1.10 When assessing a patient with suspected depression, consider using a validated measure (for example, for symptoms, functions and/or disability) to inform and evaluate treatment.

5.6.1.11 For patients with significant language or communication difficulties, for example patients with sensory impairments or a learning disability, consider using the Distress Thermometer[7] and/or asking a family member or carer about the patient's symptoms to identify possible depression. If a significant level of distress is identified, investigate further.

Risk assessment and monitoring

5.6.1.12 If a patient with depression and a chronic physical health problem presents considerable immediate risk to themselves or others, refer them urgently to a specialist mental health service.

5.6.1.13 Advise patients with depression and a chronic physical health problem of the potential for increased

[7] The Distress Thermometer is a single-item question screen that will identify distress coming from any source. The patient places a mark on the scale answering: 'How distressed have you been during the past week on a scale of 0 to 10?' Scores of 4 or more indicate a significant level of distress that should be investigated further. (Roth AJ, Kornblith AB, Batel-Copel L, et al. (1998) Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 82: 1904–8)

agitation, anxiety and suicidal ideation in the initial stages of treatment for depression; actively seek out these symptoms and:

- ensure that the patient knows how to seek help promptly
- review the patient's treatment if they develop marked and/or prolonged agitation.

5.6.1.14 Advise a patient with depression and a chronic physical health problem, and their family or carer, to be vigilant for mood changes, negativity and hopelessness, and suicidal ideation, and to contact their practitioner if concerned. This is particularly important during high-risk periods, such as starting or changing treatment and at times of increased personal stress.

5.6.1.15 If a patient with depression and a chronic physical health problem is assessed to be at risk of suicide:

- take into account toxicity in overdose if an antidepressant is prescribed or the patient is taking other medication; if necessary, limit the amount of drug(s) available
- consider increasing the level of support, such as more frequent direct or telephone contacts
- consider referral to specialist mental health services.

Step 2: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression

General measures

Depression with Anxiety

5.6.1.16 When depression is accompanied by symptoms of anxiety, the first priority should usually be to treat the depression. When the patient has an anxiety disorder and comorbid depression or depressive symptoms, consult the NICE guideline for the relevant anxiety disorder and consider treating the anxiety disorder first (since effective treatment of the anxiety disorder will often improve the depression or the depressive symptoms).

6 Service-level interventions for people with depression and chronic physical health problems

6.1 Introduction

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

Within the IAPT framework, the presence of a chronic physical health problem has been recognised as an additional barrier to receiving psychological treatments for depression (DH, 2008b). For example, many of the physical symptoms of depression may be common in those with a chronic physical health problem, and equally, depression may exacerbate existing physical symptoms, both of which may have a detrimental impact upon the recognition of depression by medical and mental health staff. Within the IAPT framework, it is suggested that specialist medical staff working in both primary and secondary care may be best placed to detect depression in people with chronic physical health problems and could provide an important referral route in helping people to access psychological services (DH, 2008b).

Initiatives similar to IAPT are found within secondary care and specialist physical health settings. In particular, National Service Frameworks for chronic conditions such as renal diseases (DH, 2005) for example, have suggested that clinical and health psychologists should form part of the multidisciplinary team managing the chronic condition. Additionally, many

secondary services e.g. cancer and sickle cell, now include a dedicated psychological team offering support and services for people with depression and chronic physical health problems. However, within this context, the physical health problem may still be seen as primary, where the additional aims of treating any psychological condition are to increase the efficacy of and adherence to any physical treatment and to improve the physical health condition.

This chapter focuses on the range of different service-delivery mechanisms that have emerged in recent years. These approaches to service delivery fall under a number of broad headings including: systematic approaches for organising care and making 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. Most of the developments in service delivery discussed below have occurred in the context of the care of depression in general, rather than being designed specifically for those who have chronic physical health problems and are depressed. However there is reason to believe that a systematic approach to the management of depression in those with complex physical health problems is of clinical importance. It is also the case that the management of other chronic disorders is becoming increasingly systematised in primary care (for example, DH, 2001).

As indicated above, there have been a considerable number of service-focused developments since the publication of the original depression guideline (NCCMH, 2004). In this guideline and in the updated depression guideline (NICE, 2009) the over-arching term 'enhanced care' has been used to refer to them all. This includes a number of interventions or models that often have some degree of overlap or where individual interventions are contained within larger models. For example, collaborative care interventions (Gilbody *et al*., 2006b) may include a stepped-care component (Bower & Gilbody, 2005; Katon *et al.,* 1999; Unutzer *et al*., 2002). Some of the more prominent models are listed below.

Graduated access

One way of improving access is to modify service provision at the point at which people want to access services (Rogers *et al.,* 1999). This may involve 'graduated access' to services, including the use of 'direct health services', which people can access without having face-to-face contact with professionals and which maximise the use of technologies such as the internet.

The consultation-liaison model

This model (for example, Gask *et al.,* 1997; Darling & Tyler, 1990; Creed & Marks, 1989) is a variant of the training and education model (which is outside of the scope of the guideline) in that it seeks to improve the skills of primary care professionals, resulting in improved quality of care. Specialists

enter into an ongoing educational relationship with the primary care team in order to support them in caring for specific patients who are currently undergoing care. Referral to specialist care is only expected to be required in a small proportion of cases.

The attached professional model

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

Stepped care

Stepped care (for example, Bower & Gilbody, 2005) is a system for delivering and monitoring treatment with the explicit aim of providing the least intrusive, most effective intervention first and to promote the organisation and delivery of care in a way which is understandable to patients and carers, and professionals. Typically stepped care starts by providing low-intensity, minimal interventions. In some stepped care systems low-intensity care is received by all individuals, although in some systems, patients are stepped up to a higher-intensity intervention on immediate contact with the service, for example if they are acutely suicidal.

Stratified (or matched care)

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

Case management

This is a system where an individual healthcare professional takes responsibility for the co-ordination of care of an individual patient (for example, Gensichen *et al.*, 2006), but is not necessarily directly involved in providing interventions; they may also be involved in the co-ordination of follow up.

Collaborative care

This model (for example, Katon *et al.*, 2001; Wagner *et al.*, 1996) emerged from the chronic disease model and has four essential elements:

- the collaborative definition of problems, in which patient-defined problems are identified alongside medical problems diagnosed by healthcare professionals
- a focus on specific problems where targets, goals and plans are jointly developed by the patient and professional to achieve a

reasonable set of objectives, in the context of patient preference and readiness
- the creation of a range of self-management training and support services in which patients have access to services that teach the necessary skills to carry out treatment plans, guided behaviour change and promote emotional support
- the provision of active and sustained follow up in which patients are contacted at specific intervals to monitor health status, identify possible complications and check and reinforce progress in implementing the care plan.

In addition, most collaborative care models include a 'case manager' who often has particular responsibility for delivering the care plan. In mental health services collaborative care also typically includes a consultation liaison role with a specialist mental health professional and generic primary care staff. It may also include elements of many of the other interventions described above.

6.1.1 Current practice and aims of the review

Over the past 20 years, there has been growing interest in the development of systems of care for managing depression, including managing depression in people with chronic physical health problems. This work has been influenced by organisational developments in healthcare in the US, such as managed care and Health Maintenance Organisations (Katon *et al.,* 1999), developments in the treatment of depression, the development of stepped care (Davison, 2000), and innovations in physical healthcare, for example chronic disease management (Wagner & Groves, 2002). A significant factor in driving these developments has been the recognition that for many people depression is a chronic and disabling disorder. Furthermore, co-morbid depression has detrimental effects on the prognosis and experience of physical health conditions. In particular, co morbid depression has been linked to an increase in healthcare utilisation, disability and work absenteeism in people with chronic physical illness, even after controlling for the varying burden of the physical health condition (Stein, *et al.* 2006).

The implementation in the NHS of the various developments described in the introduction is very variable. Perhaps the model that has been adopted most consistently is the stepped care model within the IAPT programme. However, outside demonstration sites and experimental studies (Layard, 2006; van Stratten *et al;* 2006) there has been no consistent adoption of any single model. Developments have been limited by lack of resources. There have also been changes in mental healthcare policy that have influenced implementation, for example the varying developments of the attached professional role over the past 20 years (Bower & Sibbald, 2000).

The aim of the review was to assess the efficacy of any service level intervention or configuration aimed at treating depression in people with chronic physical health problems. Interventions where the primary aim was to manage the chronic physical health problem or to prevent depression in non-depressed participants were not eligible for the review. One consistent factor is the limited evidence base for most, if not all, of these interventions. Perhaps the most notable exception is the evidence base for collaborative care, which has grown considerably in the past 10 years and has led some (such as Simon, 2006) to call for the widespread implementation of collaborative care. However it should be noted that the evidence base for collaborative care is largely from the US and care must be taken when considering its adoption in different healthcare systems because it is a complex intervention (Campbell *et al*, 2003).

6.2 Stepped care

6.2.1 Studies considered

The review team conducted a new systematic search for studies of stepped care for people with depression, including those with chronic physical health problems. This was undertaken as a joint review for this guideline and the updated depression guideline (NICE, 2009). Information about the databases searched and the inclusion/exclusion criteria used are presented in Table 11. Details of the search strategies used are in Appendix 9.

Table 11. Databases searched and inclusion/exclusion criteria for clinical effectiveness of stepped care

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 according to DSM, ICD or similar criteria or screening positive on a recognised depression scale
Treatments	Stepped care

The review identified no high-quality studies of stepped care in people with depression and chronic physical health problems and only one high-quality study (VANSTRATEN2006) was identified for the updated depression guideline (NICE, 2009). However, this study included a sample of mixed depression and anxiety disorders; it was therefore decided to conduct a narrative review, which is set out below.

6.2.2 Narrative review of stepped care

As outlined in the definitions, stepped care seeks to identify the least restrictive and least costly and effective intervention (Davison, 2000). In establishing a stepped care approach, consideration should not only be given to the degree of restrictiveness associated with a treatment, its costs and effectiveness, but the likelihood of its uptake by a patient and the likely

impact that an unsuccessful intervention will have on the probability of other interventions being taken up. This consideration may be particularly important for those with chronic physical health problems, who may face additional barriers to accessing treatments.

In the field of mental health in the UK, stepped care models are currently popular and underpin the organisation and delivery of care in a number of recent NICE mental health guidelines (see for example the guidelines for depression [NICE, 2004a] and anxiety [NICE, 2004b]). However, despite this current enthusiasm, the model is not supported by a strong evidence base. In their review of the evidence for the use of stepped care in the provision of psychological therapies, Bower and Gilbody (2005) set out three assumptions on which they argue a stepped care framework is built and which need to be considered in any evaluation. These assumptions concern the equivalence of clinical outcomes (between minimal and more intensive interventions at least for some patients), the efficient use of resources (including healthcare resources outside the immediate provision of stepped care) and the acceptability of minimal interventions (to both patients and professionals). They reviewed the existing evidence for stepped care against these three assumptions and found some limited evidence to suggest that stepped care might be a clinically and cost-effective system for the delivery of psychological therapies but no evidence that strongly supports the overall effectiveness of the model. For further details of this review see Chapter 5 in the updated depression guideline (NCCMH, forthcoming). Bower and Gilbody (2005) suggest that some of the problems highlighted in their evaluation could be addressed by taking into account patient choice (possibly by offering a choice from a range of minimal interventions) and also by adjusting the entry level into the stepped care system to consider the severity of the disorder. Past experience of treatment or treatment failure may also be a useful indicator regarding the level at which a patient should enter the stepped care model.

In a study by van Stratten and colleagues (2006) of stepped care for over 720 patients with depression and anxiety, two forms of stepped care were compared with a 'matched care' control. Both forms of stepped care involved assignment to a psychological therapy, brief behaviour therapy (BT) with a strong self-help component and therapist-delivered CBT. The matched care control involved patients being allocated to an appropriate psychological treatment as determined by the responsible clinician, unlike the other two arms of the trial where the type and duration of treatment was determined by the trial protocol. Patients in the matched control received more treatment sessions but outcomes were no better than for those patients in the other two arms. Both stepped care arms had higher attrition rates and there was some diversion, especially in the BT group, into additional treatments other than those delivered in the study.

Outside the area of stepped care for psychological therapies for depression, treatment of many physical illnesses within primary and secondary care services employ a stepped care approach. For example, the triage system for dealing with acute illness within the NHS is built upon a stepped care process whereby the level of staff expertise increasing at each stage of care. With regards to chronic physical illnesses such as asthma, diabetes and congestive heart failure, Katon and colleagues (2001) have described a stepped care approach that advocates the use of primary care physicians and nurses for less complex cases and specialist services for those with complex problems or whose symptoms show an inadequate response to the lower-intensity steps. The authors based this model on the evidence that in the US system, simply increasing access to stand-alone and ambulatory specialist services, particularly when people presented with multiple problems, did not always increase patient satisfaction and improve outcomes. Instead, patients valued the input from primary care physicians and acknowledged the importance of the primary care physician in integrating their medical care (Katon, *et al.*, 2001). This was supported by Von Korff (2001) who concluded that stepped care provided 'a framework for achieving professional support of chronic illness that is cost-effective and is based on patients' observed response to treatment'.

Although UK data is more limited, a number of US-based studies have provided empirical support for the efficacy of stepped care programmes in physical and behavioural health conditions. For example, Carels and colleagues (2005) demonstrated in their RCT that a stepped care approach including behavioural management techniques, improved weight loss and physical activity in obese participants and increased motivation when compared with behavioural management alone. Furthermore, Zatzick and colleagues (2004) increased the support for a stepped care approach when dealing with acutely injured trauma survivors. Compared to usual medical care, their randomised effectiveness trial indicated that patients undergoing a stepped care approach were less likely to go on to develop psychological problems including post traumatic stress disorder and alcohol dependence (Zatzick, *et al.,* 2004)

Considerable use has been made of stepped care programmes in many collaborative care interventions, including those specifically aiming to treat depression in chronically ill populations[8]. Specifically, a number of the studies of collaborative care for depression in people with chronic health problems have been built on a stepped care model with all individuals receiving a lower-intensity intervention at the first point of contact (Ell *et al.,* 2007 & 2008; Hunkeler *et al.,* 2000, Fortney, *et al.,* 2007; Oslin *et al.,* 2003). In many of these studies participants were offered the choice of either

[8] A full review of the collaborative care literature is contained in the section on service-level interventions below.

antidepressant medication or low-intensity psychosocial interventions as first-line treatments (Katon *et al.*, 2004; Ell *et al.*, 2007 & 2008). The decision whether to 'step up' to another intervention was then based on lack of, or sub-optimal, response to treatment. A more limited number of studies have offered only psychological interventions or only antidepressant medication as the first point of contact in a collaborative care programme (Fortney, *et al.*, 2007; Katzelnick *et al.*, 2000), and where benefit has not been obtained have stepped up either to more intensive pharmacological or psychological treatments or a combination of both. It must be noted, however, that in addition to a stepped care approach, a number of other factors including the role of case management may have had an influence on the outcome. It is also the case that more complex interventions that typify collaborative care for people with depression and chronic physical health problems (for example, longer duration of intervention and follow up and integration of primary and secondary care) tend to be associated with better outcomes. Whether this reflects the specific contribution of a stepped care framework is uncertain. In addition, meta-regression studies such as those by Bower and colleagues (2006) and Gilbody and colleagues (2006b) did not identify the presence of stepped care or specific algorithms of care (which may be taken as a rough equivalent or proxy for stepped care) as being associated with a more positive outcome.

Finally, a report on the two IAPT demonstration sites (Clark *et al.*, 2008), which provided a stepped psychological care programme, examined the effectiveness of the model. In the demonstration projects there was good evidence for increased patient flows through the system while at the same time the outcomes obtained were broadly in line with those reported in RCTs for depression and anxiety.

In summary there is limited evidence from direct studies in the support of a stepped care model. Bower and Gilbody (2005) provide some further limited evidence in favour of the model in psychological therapies, but with the single exception of van Stratten and colleagues' (2006) study no formal trials of the relative efficiency or effectiveness of a pure stepped care model for depression were identified. Beyond the area of depression in fields such as addiction (Davison, 2000) and physical healthcare (Carels *et al.*, 2005) there is more evidence, including RCT trials, for the effectiveness of this model. There is some suggestion that the integration of stepped care into a more complex model of collaborative care may be associated with better outcomes. The evidence for this is discussed below.

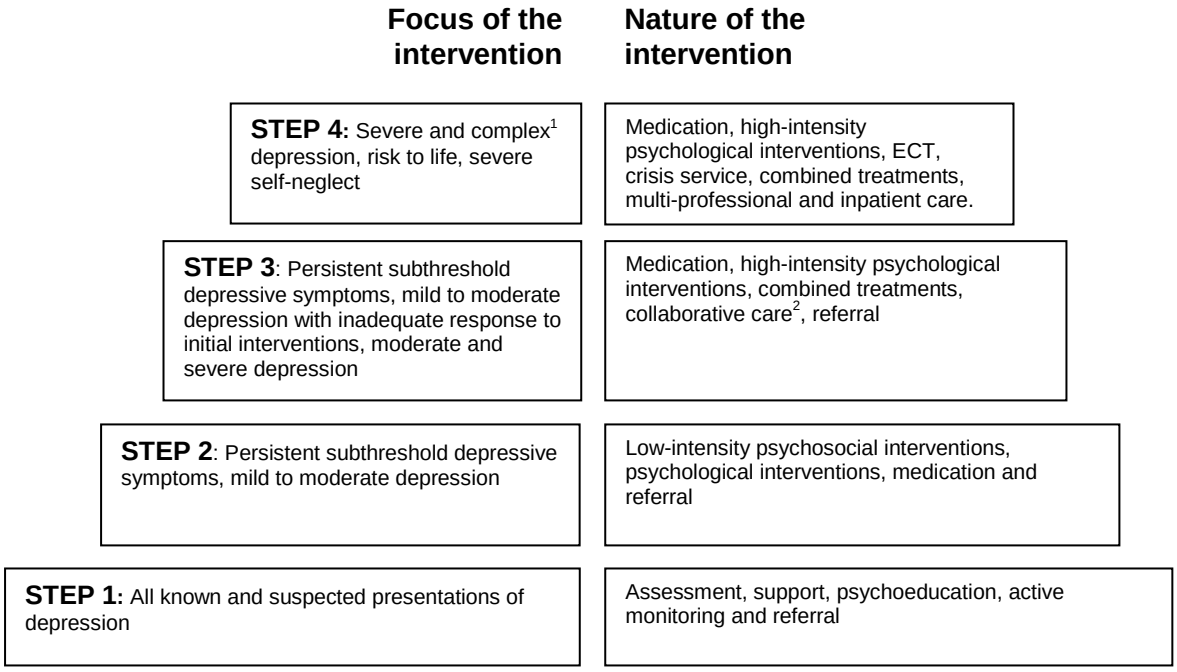
6.2.3 From evidence to recommendations

The 2004 depression guideline along with other NICE guidelines (for example, NICE 2004b) recommended the adoption of a stepped care model for the provision of psychological and pharmacological interventions for depression. Since that time there has been further but limited evidence providing direct support for the model (van Stratten *et al.*, 2006; Hakkaart-van

Rooijen *et al.*, 2006; Clark *et al.,* 2008) along with its increasing use in a number of collaborative care interventions particularly for people with physical health problems. Further evidence, albeit predominantly US-based, has indicated the efficacy of stepped care approaches in improving outcomes in the management of a range of chronic illness. Within the UK, stepped care has also been adopted by the IAPT programme (DH, 2007) as the framework for the delivery of the service. Given the lack of evidence to change the existing recommendation regarding the provision of stepped care, it is the view of the GDG that this model remains the best developed system for ensuring access to cost-effective interventions for a wide range of people suffering from depression and chronic physical health problems, particularly if supported by systems for routine outcome monitoring which enable prompt stepping up for those who have not benefited from a low intensity intervention. It is important that the treatments offered at each step be cost effective for the individual patient entering the stepped-care model at a particular level. Furthermore, the identification and referral of people to each step plays an important role on the overall cost-effectiveness. As an incorrectly identified patient may go on to consume health care that is not suitable for their condition. An intervention is only considered to be cost effective if it is prescribed to the relevant correctly identified patient.

In light of this the GDG, in collaboration and consultation with the Depression update GDG adopted the stepped care model set out in Figure 1.

Figure 4: Stepped care model



[1] **Complex includes depression with an inadequate response to multiple treatments, complicated by psychotic symptoms, and/or significant psychiatric comorbidity or psychosocial factors**
[2] **Only for depression associated with chronic physical illness and associated functional impairment**

Current models are in development (for example, Richards & Suckling, 2009) which will allow service delivery systems to monitor and review the effectiveness of stepped care models. Further research however is clearly needed to address the issues of efficacy, efficiency and acceptability of stepped care for people with depression and chronic physical health problems.

6.3 Service-level interventions

6.3.1 Studies considered[9]

The review team conducted a new systematic search for RCTs that assessed the efficacy of other service-level interventions and related health economic evidence. Information about the databases searched and the inclusion/ exclusion criteria used for this section of the guideline can be found in Table

[9] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

12. Further information about the search for health economic evidence can be found in Appendix 13.

Table 12: Databases searched and inclusion/exclusion criteria for clinical evidence.

Electronic databases	CINAHL, CENTRAL, EMBASE, MEDLINE, PSYCINFO
Date searched	Database inception to March 2008
Study design	RCT
Patient population	People with a chronic physical health problem and depression (sample either recruited for depression or had a mean baseline score above clinical cut-off on a recognised depression scale)
Interventions	Any service-level intervention aimed at reducing depression
Outcomes	Depression, treatment acceptability, mortality, quality of life, physical health outcomes, process of care

Seventeen trials relating to clinical evidence met the eligibility criteria set by the GDG, providing data on 4,997 participants. Of these, all were published in peer-reviewed journals between 1996 and 2008. In addition, 19 studies were excluded from the analysis. The most common reason for exclusion was that the population did not meet criteria for depression, or the paper failed to provide any usable data for the analysis (further information about both included and excluded studies can be found in Appendix 18).

Of the 17 included trials, 15 assessed the efficacy of collaborative care; one assessed psychiatric liaison and one assessed a case management intervention (conducted within a secondary mental health service). The review did not identify any trials meeting the inclusion criteria for the other service interventions. All trials were compared to some form of standard care (either standard or enhanced by additional features[10]).

6.3.2 Clinical evidence for collaborative care

Study information table for the trials of collaborative care are presented in Table 13. Evidence from the GRADE profiles are summarised in Table 14. The full evidence profiles and associated forest plots can be found in Appendix 21, and Appendix 19, respectively.

[10] Although the term 'enhanced care' has been used as an over-arching term to refer to all service level interventions, 'enhanced standard care' refers to standard care or usual care that has been enhanced by supplementary elements such as patient education, for example.

Table 13: Evidence summary of collaborative care

	Collaborative care vs. any control	Collaborative care vs. standard care	Collaborative care vs. enhanced standard care
Total number of studies (number of participants)	15 (n=4,256)	10 (n=2,813)	5 (n=1,443)
Study ID	BOGNER2008 COLE2006 CULLUM2007 DWIGHTJOHNSON 2005 ELL2007 ELL2008 FORTNEY2007 KATON2004 KATZELNICK2000 LANDIS2007 LIN2003* OSLIN2003 STRONG2008 WILLIAMS2004* WILLIAMS2007	BOGNER2008 COLE2006 CULLUM2007 DWIGHTJOHNSON 2005 KATON2004 KATZELNICK2000 LANDIS2007 LIN2003* STRONG2008 WILLIAMS2004*	ELL2007 ELL2008 FORTNEY2007 OSLIN2003 WILLIAMS2007
Diagnostic tool	*DSM-IV:* COLE2006 DWIGHTJOHNSON 2005 KATZELNICK2000 LIN2003* STRONG2008 WILLIAMS2004* WILLIAMS2007 *Clinical diagnosis (not clearly stated as DSM/ICD):* BOGNER2008 LANDIS2008 *Depression scale:* CULLUM2007 ELL2007 ELL2008 FORTNEY2007 KATON2004 OSLIN2003	*DSM-IV:* COLE2006 DWIGHTJOHNSON 2005 KATZELNICK2000 LIN2003* STRONG2008 WILLIAMS2004* *Clinical diagnosis (not clearly stated as DSM/ICD):* BOGNER2008 LANDIS2008 *Depression scale:* CULLUM2007 KATON2004	*DSM -IV:* WILLIAMS2007 *Depression scale:* ELL2007 ELL2008 FORTNEY2007 OSLIN2003
Physical health problem	*Diabetes* KATON2004 WILLIAMS2004* *Asthma or diabetes* LANDIS2007 *Cancer* DWIGHTJOHNSON	*Diabetes* KATON2004 WILLIAMS2004* *Asthma or diabetes* LANDIS2007 *Cancer* DWIGHTJOHNSON	*Cancer* ELL2008 *General medical illness* FORTNEY2007 ELL2007 OSLIN2003 *Stroke*

	2005 ELL2008 STRONG2008 *General medical illness* COLE2006 CULLUM2007 ELL2007 FORTNEY2007 KATZELNICK2000 OSLIN2003 *Arthritis* LIN2003* *Stroke* WILLIAMS2007 *Hypertension* BOGNER2008	2005 STRONG2008 *General medical illness* COLE2006 CULLUM2007 KATZELNICK2000 *Arthritis* LIN2003* *Hypertension* BOGNER2008	WILLIAMS2007
Baseline severity: mean (SD)	*HDRS* COLE2006: Mean (SD) ~ 21(6) KATZELNICK2000: Mean ~ 19 OSLIN2003: Mean (SD) ~ 15(5) WILLIAMS2007: Mean (SD) ~ 19(5) *PHQ-9* DWIGHTJOHNSON 2005: Mean (SD) ~ 13(7) ELL2008: Mean (SD) ~ 13(3) FORTNEY: Mean (SD) ~ 16(3) LANDIS2008: Mean (SD) 16(5) *SCL-20 (depression score)* KATON2004: Mean (SD) ~ 1.7(0.5) SRONG2008: Mean(SD) ~ 2(2) WILLIAMS2004: Mean (SD) ~ 1.7(0.6) *GDS-15* CULLUM2007: Mean (SD) ~ 10(2) *CES-D* BOGNER2008 ~19(14)	*HDRS* COLE2006: Mean (SD) ~ 21(6) KATZELNICK2000: Mean ~ 19 *PHQ-9* DWIGHTJOHNSON2005: Mean (SD) ~ 13(7) LANDIS2008: Mean (SD) 16(5) *SCL-20 (depression score)* KATON2004: Mean (SD) ~ 1.7(0.5) SRONG2008: Mean(SD) ~ 2(2) WILLIAMS2004: Mean (SD) ~ 1.7(0.6) *GDS-15* CULLUM2007: Mean (SD) ~ 10(2) *CES-D* BOGNER2008 ~19(14)	*HDRS* OSLIN2003: Mean (SD) ~ 16(5) WILLIAMS2007: Mean (SD) ~ 19(5) *PHQ-9* ELL2008: Mean (SD) ~ 13(3) FORTNEY2007: Mean (SD) ~ 16(3)

Previous history of depression	Range: 12 - 71% Mean across papers: ~50%	15-71% Mean across papers: ~51%	Range: 12– 66% Mean across papers: ~47%
Range of mean age in years	45 - 80	45-80	59 - 62
Setting	Primary care BOGNER2008 FORTNEY2007 KATON2004 KATZELNICK2000 LANDIS2008 LIN2003* OSLIN2003^^ WILLIAMS2004* Secondary care*** COLE2006 CULLUM2007 ELL2007 Specialist physical health service DWIGHTJOHNSON 2005 ELL2008 OSLIN2003^^ STRONG2008 WILLIAMS2007	Primary care BOGNER2008 COLE2006 DWIGHTJOHNSON 2005*** KATON2004 KATZELNICK2000 LANDIS2008 LIN2003* WILLIAMS2004* Secondary care/ specialist physical health service CULLUM2007 STRONG2008	Primary care ELL2008*** FORTNEY2007 OSLIN2003^^ Secondary care/ specialist physical health service ELL2007 OSLIN2003^^ WILLIAMS2007
Country	*UK* CULLUM2007 STRONG2008 *US* BOGNER2008 DWIGHTJOHNSON 2005 ELL2007 ELL2008 FORTNEY2007 KATON2004 KATZELNICK2000 LANDIS2008 LIN2003* OSLIN2003 WILLIAMS2004* WILLIAMS2007 *Canada* COLE2006	*UK* CULLUM2007 STRONG2008 *US* BOGNER2008 DWIGHTJOHNSON 2005 KATON2004 KATZELNICK2000 LANDIS2008 LIN2003* WILLIAMS2004* WILLIAMS2007 *Canada* COLE2006	*US* ELL2007 ELL2008 FORTNEY2007 OSLIN2003 WILLIAMS2007
Level of intervention complexity^	*Collaborative care component score (out of 26)* BOGNER2008 - 15	*Collaborative care component score (out of 26)* BOGNER2008 - 15	*Collaborative care component score (out of 26)* ELL2007 - 19

	COLE2006 - 15 CULLUM2007 - 11 DWIGHTJOHNSON2005 - 18 ELL2007 - 19 ELL2008 - 20 FORTNEY2007 - 15 KATON2004 - 18 KATZELNICK2000 - 14 LANDIS2007 - 15 LIN2003* - 15 OSLIN2003 - 15 STRONG2008 - 16 WILLIAMS2004* - 15 WILLIAMS2007 - 12	COLE2006 - 15 CULLUM2007 - 11 DWIGHTJOHNSON2005 - 18 KATON2004 - 18 KATZELNICK2000 – 14 LANDIS2007 - 15 LIN2003* - 15 STRONG2008 - 16 WILLIAMS2004* - 15	ELL2008 - 20 FORTNEY2007 - 15 OSLIN2003 - 15 WILLIAMS2007 - 12
Treatment length (maximum length of planned intervention^^^)	*Up to 3 months* BOGNER2008 CULLUM2007 WILLIAMS2007 *>3 - 6 months* COLE206 LANDIS2008 OSLIN2003 STRONG2008 *>6-12 months* DWIGHTJOHNSON 2005 ELL2007 ELL2008 FORTNEY2007 KATON2004 KATZELNICK2000 LIN2003* WILLIAMS2004*	*Up to 3 months* BOGNER2008 CULLUM2007 *>3 - 6 months* COLE206 LANDIS2008 STRONG2008 *>6-12 months* DWIGHTJOHNSON 2005 KATON2004 KATZELNICK2000 LIN2003* WILLIAMS2004*	*Up to 3 months* WILLIAMS2007 *>3 - 6 months* OSLIN2003 *>6-12 months* ELL2007 ELL2008 FORTNEY2007

Notes:
* Sub-group analysis of larger IMPACT study
^ Based on the collaborative care component score, higher score indicates greater intervention complexity
^^ Conducted in a Veterans Affairs Medical Centre and in speciality cardiology and rheumatology clinics
^^^ Includes any planned follow-up which was part of the intervention protocol
*** Secondary care includes general medical services such as general non-specialist hospitals used for treating a range of conditions.

Population

The included studies covered a range of chronic physical health conditions (see Table 13 for further details). The severity of depression as measured on a range of recognised scales varied across studies from mild to severe, with indications that the depression was chronic in nature. In papers reporting the percentage of participants with a history of depression, the mean across

studies was approximately 50% (COLE2006, CULLUM2007, ELL2007, ELL2008, FORTNEY2007, KATON2004, LANDIS2008, LIN2003), with the majority of participants having a history of at least two to three previous depressive episodes. The proportion of participants receiving current depression treatment ranged from 6% (DWIGHTJOHNSON2005) to 66% (FORTNEY2007) with KATZELNICK2000 including 20% of participants who had failed to respond adequately to recent treatment.

Country and setting

Two of the included studies (CULLUM2007, STRONG2008) were conducted in the UK, with the majority of the non-UK studies conducted in the US. Although the setting of the collaborative care intervention varied across trials, over half were conducted within primary care (BOGNER2008, FORTNEY2007, KATON2004, KATZELNICK2000, LANDIS2008, LIN2003, and OSLIN2003 WILLIAMS2004). The remaining seven trials were based either in secondary care including general hospitals and home healthcare settings (COLE2006, CULLUM2007, ELL2007) or in a specialist physical health setting such as an oncology clinic (DWIGHTJOHNSON2005, ELL2008 OSLIN2003, STRONG2008, WILLIAMS2007).

Intervention

There was considerable variation between the different collaborative care interventions, with the complexity of the intervention and treatment components differing among studies[11]**.** However, there were a number of common features shared by the majority of trials. All but two (COLE2006, STRONG2008) had an identified case manager, who may or may not have been responsible for the delivery of treatment. The professions of the case managers varied, with GPs (KATZELNICK2000), specialist medical staff (LANDIS2000), psychologists (LIN2003, WILLIAMS2004), social workers (DWIGHTJOHNSON2005, ELL2008) and nurses (CULLUM2007, FORTNEY2007, LIN2003, WILLIAMS2004, WILLIAMS2007) all evident in the trials. Many of the interventions followed a stepped care approach (ELL2007, ELL2008, FORTNEY2007, KATON2004, LIN2003, OSLIN2003, WILLIAMS2004) with both WILLIAMS2007 and KATZELNICK2000 employing a structured medication algorithm. Typically in stepped care approaches participants were given the option of either antidepressant medication or a psychological intervention as first-line treatment. Although there was some variation, the most common psychological intervention was problem solving therapy (DWIGHTJOHNSON2005, ELL2007, ELL2008, KATON2004, LIN2003, WILLIAMS2004) with two trials (COLE2006, FORTNEY2007) offering supportive psychotherapy and OSLIN2003 offering low-intensity psychosocial support. Other common features of the trials included patient and physician education, monitoring of progress, supervision of staff by a psychiatrist, and a focus on medication adherence.

[11] A checklist was developed to assess the components of the intervention in an attempt to more reliably characterise the complexity of the intervention in each trial, please seen appendix X for further details.

The length of planned follow up conducted by the case manager or equivalent varied among trials. In some trials, participants entered a maintenance or continuation phase for up to 6 to 12 months (ELL2007, ELL2008, FORTNEY2007, KATON2004, LIN2003, WILLIAMS2004), while others were only followed up briefly after the end of an active psychological or acute pharmacological intervention (BOGNER2008, CULLUM2007, WILLIAMS2007).

Comparison

The control condition in all of the studies was standard care. It is noteworthy, however, that the level of standard care differed among trials. In addition to the usual care provided, supplementary elements were added to enhance the care received by the control group in five of the included studies (ELL2007, ELL2008, FORTNEY2007, OSLIN2003, WILLIAMS2005). In four of the trials (ELL2007, ELL2008, FORTNEY2007, OSLIN2003) standard care was enhanced by a combination of the following components: structured depression screening protocols that included prompting for initial screening and reminders regarding follow-up screens; GP notification if the participant screened positive for depression; treatment decision aids; progress checklists; and patient and physician education. In these trials, collaborative care typically differed from the enhanced standard care condition in that the intervention was more structured and often implemented a specific depression treatment algorithm. In the other enhanced standard care trial (WILLIAMS2007), usual care was supplemented with an increased follow up of the physical health condition with the aim of controlling for any non-specific effects of the collaborative care intervention such as physician time. The differences in standard and enhanced standard care were explored in a subgroup comparison.

Outcomes

Data was reported on a wide range of outcome including depression, treatment acceptability, satisfaction with care and process of care. All data was reported for end of treatment, with a paucity of post-intervention follow-up data available.

Table 14: GRADE evidence profile for collaborative care versus any standard care

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
Mortality	RR 0.94 (0.74 to 1.19)	2999 (9)	⊕⊕⊕O moderate[12]
Depression: non-response (<50% improvement)	RR 0.82 (0.76 to 0.89)	3592 (11)	⊕⊕OO low[3,4,5]
Depression: non-response - removing papers with >50% drop out	RR 0.79 (0.73 to 0.85)	2652 (8)	⊕⊕⊕⊕ high
Depression: non-remission (scoring above cut-off)	RR 0.84 (0.73 to 0.96)	2348 (6)	⊕⊕OO low[4,5,6]
Depression outcome 2. Non-remission (scoring above cut off) - >50% drop out removed	RR 0.81 (0.73 to 0.9)	2191 (5)	⊕⊕⊕O moderate[4]
Depression diagnosis	RR 0.77 (0.54 to 1.1)	321 (2)	⊕⊕OO low[4,7]
Depression: change score	SMD -0.31 (-0.4 to -0.22)	1969 (10)	⊕⊕⊕⊕ high
Pain intensity	SMD -0.15 (-0.25 to -0.04)	1418 (3)	⊕⊕⊕O moderate[7]
General physical wellbeing/ functioning (SF-12 physical subscale)	SMD -0.26 (-0.35 to -0.17)	1856 (5)	⊕⊕⊕O moderate[1]
General physical wellbeing/ functioning (change scores)	SMD -0.12 (-0.24 to -0.01)	1150 (6)	⊕⊕⊕O moderate[6]
General QoL scales (Euroqol)	SMD -0.14 (-0.27 to -0.01)	964 (1)	⊕⊕⊕O moderate[7]
General QoL scales (Euroqol - change score)	SMD -0.08 (-0.29 to 0.14)	335 (1)	⊕⊕⊕O moderate[2,7]
Process of care: did not receive a consultation	RR 0.83 (0.67 to 1.02)	833 (3)	⊕⊕OO low[4,5]
Process of care: did not receive any psychosocial or pharmacological intervention	RR 0.5 (0.37 to 0.69)	1807 (5)	⊕⊕⊕O moderate[4]
Leaving the study early for any reason	RR 0.96 (0.85 to 1.08)	3742 (11)	⊕⊕OO low[1,2]
Not satisfied with treatment/care	RR 0.78 (0.67 to 0.91)	845 (3)	⊕⊕⊕O moderate[8]

[1] 2 trials are pre-planned sub-group analyses of a larger RCT
[2] Compatible with benefit and no benefit
[3] 3 trials with >50% drop out not accounted for in the analysis
[4] I-squared >50%
[5] 2 trials did not recruit specifically for co morbid chronic physical health problems
[6] 1 trial with >50% drop out not accounted for in the analysis
[7] Sparse data
[8] 1 trial did not recruit specifically for co morbid chronic physical health problems

There was consistent evidence that collaborative care had benefits on a range of depression outcomes including response (RR = 0.82, CI 0.76, 0.89) and remission (RR = 0.84, CI 0.73, 0.96) when compared with any form of standard care. When a sensitivity analysis removed trials in which more than 50% of the participants had dropped out of the study and had not been included in the trial's data analysis, there was an increase in effect size and a reduction in

heterogeneity (response RR = 0.79, CI 0.73, 0.85 and remission RR = 0.81, CI 0.73, 0.90). Similar modest findings were also demonstrated for change scores on continuous scale based measures of depression (SMD = -0.31, CI -0.40, -0.22).

There was no conclusive evidence that collaborative care reduced the numbers leaving the study for any reason (RR = 0.96, CI 0.85, 1.08). However, more participants receiving collaborative care were satisfied with the treatment and care received (RR = 0.78, CI 0.67, 0.91). Consistent evidence was also demonstrated for process of care variables, which indicated that collaborative care was more likely to increase the number of participants receiving some form of psychological and/or pharmacological treatment (RR = 0.50, CI 0.37, 0.69). However, the results for the process of care outcomes are hard to interpret because of high levels of heterogeneity (I^2 = 85.3%). Removal of a potential outlier (KATZELNICK2000) reduced the heterogeneity to an acceptable level (I^2 = 18.5%), but also slightly attenuated the effect size (RR = 0.59, CI, 0.51, 0.68).

Few conclusions can be drawn regarding the efficacy of collaborative care on improving physical health outcomes. With the exception of pain intensity and general physical functioning, there was a lack of comparable data on physical health outcomes. Trials differed in their physical illnesses, both within and between studies, and the reporting of physical health outcomes was sparse, with different papers reporting a diverse range of outcomes. The limited evidence for pain intensity indicated that collaborative care had a significant but small effect on pain reduction (SMD = -0.15, CI -0.24, -0.04)**.** Similar findings were demonstrated for physical well-being, where small effect sizes were evident for both end point data (SMD = -0.26, CI -0.35, -0.17) and mean change scores (SMD = -0.12, CI -0.24, -0.01). There was some limited data indicating that collaborative care improved adherence to medication for the physical health problem (RR = 0.33, CI, 0.18, 0.60). However, data for this outcome comprised only two small studies.

In order to reduce the possible confounding crossover effects in which the implementation of collaborative care changes the standard care for all patients in the practice, a number of trials employed a cluster randomised design. In these trials, the unit of randomisation was either the individual physician or clinic (FORTNEY2007, KATZELNICK2000, OSLIN2003). The design effect[12] was applied to the analysis of studies that had not accounted for the clustering in their analysis. Where papers reported the intracluster correlation coefficient (ICC) this was used in the calculations, with the empirically derived value of 0.02 used where the ICC was not reported. A sensitivity analysis was conducted to compare the results of the meta-analysis with and

[12] N (effective) = (k x m) / (1+ (m - 1) * ICC, where k indicates the number of clusters, m the number of observations per cluster and ICC the intracluster correlation coefficient

without the application of the design effect. Applying the transformation had little to no impact on any of the results reported, thus strengthening the robustness of the original analysis.

6.3.3 Sensitivity and sub-group analyses on collaborative care versus any standard care

While there was reasonable consistency among studies assessing collaborative care versus any form of standard care, there were a number of differences in terms of the level of complexity of standard care and the way in which participants were recruited for the trials, for example, whether or not they were recruited specifically for a co morbid physical health condition. The impact of these differences needs to be examined in order to test whether the results of the meta-analyses above are robust.

For all depression outcomes, there was a demonstrable increase in benefits when collaborative care was compared with standard care as opposed to enhanced standard care. Both response and remission rates increased in the standard care condition (standard care response: RR = 0.76, CI 0.71, 0.81; enhanced standard care response: RR = 0.86, CI 0.81, 0.92; standard care remission: RR = 0.75, CI, 0.68, 0.83; enhanced standard care remission: RR = 0.87, CI 0.80, 0.95) with the heterogeneity within each subgroup reducing to a low level. These findings were consistent with the scale-based data, which also indicated larger effects when collaborative care was compared with standard care (standard care: SMD = -0.33, CI, -0.43, -0.22; enhanced standard care: SMD = -0.24, CI, -0.42, -0.07). The findings regarding other outcomes such as general physical functioning and treatment acceptability were less conclusive, with effect sizes varying across different outcomes.

Although all participants had a chronic physical health problem, three trials (ELL2007, FORTNEY2007 and OSLIN2003) did not specifically recruit for this co morbidity. A sensitivity analysis was therefore conducted to test the effect of removing these three trials from the analysis. Removing the trials increased the effect sizes for both remission (RR = 0.78, CI, 0.71, 0.86) and response (RR = 0.76, CI 0.71, 0.80) but failed to have any impact on continuous scale-based measures when compared with any form of standard care (SMD = -0.30, CI, -0.39, -0.21). Further to this, a separate exploratory subgroup comparison was conducted on three cancer trials in which the intervention was specifically targeted and tailored towards the physical health condition (DWIGHTJOHNSON2005, ELL2008 and STRONG2008). Although there were no differences in the depression outcomes, with modest findings for remission and response rates**,** significant reductions in both mortality (RR = 0.67 CI, 0.46, 0.98) and leaving the study early for any reason (RR = 0.80, CI, 0.67, 0.96) were evident. However, it must be noted that the dataset is very limited and further confounded by the population and setting as two of the three trials were targeted at low-income Latino participants in the US.

6.3.4 Clinical evidence for other service level interventions

Study information table for the trials of other service level interventions are presented in Table 15. Evidence from the GRADE profiles are summarised in Table 16 and Table 17 . The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Table 15: Evidence summary of other service-level interventions

	Psychiatric liaison versus standard care	Case management versus standard care
Total number of studies (number of participants)	1 (n=669)	1 (n=69)
Study ID	SCHRADER2005	BANERJEE1996
Diagnostic tool	DSM-IV	Geriatric Mental State/ AGECAT
Physical health problem	Cardiovascular disease	General medical illness
Baseline severity	*CES-D:* Mild depression: 55% Moderate to severe depression: 45%	*MADRS:* Mean (SD) ~ 26(6)
Previous history of depression	Not reported	33%
Age	Not reported	Mean (SD) ~ 81(7)
Setting	Secondary care– cardiology unit	Secondary care
Country	Australia	UK
Treatment length (maximum length of planned intervention^^^)	Unclear: initial consultation with last follow-up data collection at 12 months	Unclear: last follow up at 6 months

There was sparse data for other service-level interventions, with only two studies meeting the inclusion criteria. Both trials were conducted in secondary care with participants with a diagnosis of major depression. Participants in the SCHRADER2005 trial all had cardiovascular disease, whereas in BANERJEE1996, participants were described as 'frail elderly' all requiring home healthcare. In both trials, control participants continued to receive standard care for their depression and medical condition(s).

Table 16: GRADE evidence profile for psychiatric liaison versus standard care

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
Mortality	RR 1.18 (0.65 to 2.14)	669 (1)	⊕⊕⊕O moderate[1,2]
Depression: diagnosis	RR 1.02 (0.93 to 1.12)	669 (1)	⊕⊕⊕O moderate[1,2]
General physical well-being/ functioning SF-36 physical subscale	SMD -0.06 (-0.25 to 0.12)	450 (1)	⊕⊕⊕O moderate[1,2]
Leaving the study early for any reason	RR 1.46 (1 to 2.12)	669 (1)	⊕⊕⊕O moderate[1,2]

[1] sparse data
[2] compatible with benefit and no benefit

There was no consistent evidence to suggest that psychiatric liaison when compared with standard care had any robust effect on depression or physical well-being. In both cases the small effect sizes in the study were not statistically significant.

Table 17: GRADE evidence profile for case management versus standard care

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
Mortality	RR 1.45 (0.35 to 6.02)	69 (1)	⊕⊕OO low[1,2,3]
Depression diagnosis (at follow up)	RR 0.61 (0.39 to 0.96)	69 (1)	⊕⊕OO low[1,2]
Depression (change score) MADRS	SMD -1.03 (-1.53 to -0.52)	69 (1)	⊕⊕OO low[1,2]
Leaving the study early for any reason	RR 1.09 (0.3 to 4.01)	69 (1)	⊕⊕OO low[1,2,3]

[1] Participants were not specifically recruited for a co morbid physical health problem
[2] Sparse data
[3] compatible with benefit and no benefit

There was some limited evidence that case management conducted in secondary mental healthcare had a positive impact on measures of depression. The number of participants with a diagnosis of major depression was significantly reduced by the intervention (RR = 0.61, CI, 0.39, 0.96)**.** This finding was consistent with the mean change in depression, with a large and significant effect demonstrated on the MADRS rating scale (SMD = -1.03, CI, -1.53, -0.52; WMD = -6.70, CI -9.75, -3.65). Despite these large effect sizes however, the data was sparse and comprised only one small UK-based study. Furthermore, although all participants had a chronic physical health problem requiring home healthcare, the participants were not specifically recruited for

this co morbidity, thus the generalisability of these results is likely to be confounded.

6.3.5 Clinical evidence summary

The review of collaborative care provided consistent and robust evidence for the efficacy of the intervention on improving a range of depression outcomes, particularly remission and response. The effect sizes for both response and remission were greater still when collaborative care was compared with standard care as opposed to enhanced standard care. There was only limited data for the efficacy of collaborative care on other outcomes, including physical health outcomes such as pain and general well-being. Although statistically significant, the effect sizes for these outcomes were small. The paucity of data and inconsistent reporting across collaborative care trials prevented the analysis of other physical health outcomes, including weight gain and blood-glucose measures. Overall, the analysis indicated that where collaborative care interventions recruited participants specifically for a co morbid physical health condition, effect sizes for all outcomes were more robust with reduced heterogeneity. Furthermore, where the collaborative care intervention was tailored to a particular condition, limited evidence was demonstrated for other outcomes including mortality and treatment acceptability. However, the data for tailoring interventions to specific conditions is very limited and predominantly comprises US-based studies.

There was no clear evidence for any other service -level intervention, including psychiatric liaison and case management, in treating depression in people with chronic physical health problems. This was primarily due to a lack of available data, with only one included study for each of the interventions.

6.3.6 Health economic evidence

Systematic review of the economic literature

The systematic literature search identified three studies that dealt with the cost effectiveness of service configurations in people with depression and chronic physical health problems (Simon *et al.,* 2001; Katon *et al.,* 2006; Simon *et al*., 2007*).*

Simon and colleagues (2001) looked at systematic depression treatment for high utilisers of general medical care. This study compared the costs and effects of a depression management programme (DMP) with those of usual care delivered in primary care in the US. The programme delivered education and telephonic care management, antidepressant pharmacotherapy (sertraline 50 mg/d as first-line therapy and nortriptyline 25 mg/d as second-line therapy) if deemed appropriate by the physician, and psychiatric consultation for those whose symptoms failed to respond. Treatment coordinators monitored all patients and scheduled phone contacts for monitoring of treatment response, treatment adherence, and medication adverse effects at regular intervals additional contacts occurred depending on clinical need.

Treating physicians received written feedback reports following each telephone monitoring call, as well as notification of any apparent treatment dropout. The usual care group did not receive any additional services other than those normally available (eg, antidepressant medication, referral to specialty mental health care). The usual care physicans received no information regarding patients' participation. The study population comprised of adult patients with outpatient medical visit rates above the 85th percentile for 2 consecutive years. A two-step screening process was undertaken to identify those patients with current depressive disorder (17-HDRS =>15) and not in active treatment. The RCT (n=407), provided the effectiveness data. Clinical outcomes were reported using the Hamilton Depression Rating Scale. These were converted to measures of 'depression-free days.' The evaluation adopted the third-party payer perspective and costs and resource use were calculated using health-plan standardised claims. Total health service costs included screening costs, treatment coordinator costs, and outpatient and inpatient costs.

Over the 12-month study period the DMP led to an increase of 47.7 2 depression-free days throughout 12 months (95% CI, 28.2-67.8 days). Estimated cost increases were $1,974 per year for total health services costs (95% CI, $848- $3171) and the estimated incremental cost per depression-free day was 41.34 (16.04-81.03. The study concluded that in the treatment of depression in a population of high utilisers of general medical care, an organized DMP produced gains in time free of depression, as well as increases in estimated health services costs.

When interpreting these results it should be considered that they may not generalise to other populations, for example, those people with depression who are not high utilisers of medical services, or to other health care systems, for example, usual care in the UK NHS is different to that provided in the US. Although it must be noted that usual care patients were notified of the diagnoses of depression not their physicians and this may have led to them receiving depression treatment, and potentially reduced differences between groups in clinical effectiveness and cost.

The cost effectiveness of enhanced treatment of depression for older adults with diabetes and depression compared with usual care was assessed by Katon and colleagues (2006). This study was based on the Improving Mood-Promoting Access to Collaborative (IMPACT) RCT set in the US. The population included in the study had to meet the following criteria: diabetics aged greater 60 years, meeting criteria for major depression and/or dysthymia on the Structured Clinical Interview for the DSM-IV (17), and a plan to continue to use the same primary care clinic over the next year.The IMPACT intervention consisted of a stepped collaborative care programme delivered by a depression care manager who was typically a nurse. He/she provided behavioural activation (that is, structured activities such as exercise) and an initial choice of problem solving treatment developed for primary care

or enhanced treatment with antidepressants prescribed by a primary care physician. In the usual care arm, primary care physicians were made aware of the depressive diagnosis and they could provide antidepressants and/or refer to mental health speciality care. The primary health outcome was the Hopkins Symptom Checklist 20 Depression Scale (HSCL-20). The authors adapted the method developed by Lave and colleagues (1998), to estimate the number of depression free days during the 24 month follow up period using the HSCL-20 depression scores from baseline and follow-up assessments. QALYS were estimated using data from a range of published sources. The data showed that going from fully symptomatic to full remission of depression was associated with an increase in quality of life from 0.2 to 0.4 on a scale of 0 (no quality) to 1 (full quality). To determine the incremental QALYs associated with the intervention, they divided the 2-year difference in depression-free days by 365 and then multiplied by the lower (0.2) and upper (0.4) bound increases in QALYs associated with full remission of depression. The resulting range of QALYs was then divided into the point estimate for incremental total outpatient costs to estimate costs per QALY associated with the intervention versus usual care. Direct health care costs were calculated from the third-party payer perspective. The costs evaluated were the total outpatient costs that were incurred i.e. both mental and medical health care related resource use.

Relative to usual care, intervention patients experienced 115 (95% CI 72–159) more depression-free days over 24 months. The mean number of additional depression-free days associated with the intervention in the first 12 months was 59.4 (95% CI 37.3– 81.4) and in the second 12 months was 56.1 (31.8–80.4). Total outpatient costs were $25 higher during the 2 year period. The incremental cost per QALY ranged from $198 (144–316) to $397 (287– 641). Increased mental health costs in the intervention group were balanced by lower ambulatory medical costs. Healthcare plan investments of $665 in outpatient costs in the first year were balanced by cost savings of a similar amount in the second year.

The study concluded that for adults with diabetes, systematic depression treatment significantly increased time free of depression and appeared to have some economic benefits from the health plan perspective. It also recommended that depression screening and systematic depression treatment should become routine components of diabetes care.

This trial was conducted in 18 primary care clinics belonging to eight diverse health care organizations in five states. Healthcare data from these diverse health care organisations were combined. Each used somewhat different methods to capture such data for the analysis. Detailed information on the trial methodology was not described. A final limitation was that the estimate of QALYs from HSCL-20–based depression-free days has not been independently validated against other measures of QALYs (i.e., time trade-off or standard gamble).

Finally, Simon and colleagues (2007) looked at the cost effectiveness of systematic depression treatment among people with diabetes mellitus in the US. The study aimed to evaluate the incremental cost and effectiveness of a systematic depression treatment programme among outpatients with diabetes from a third-party payer perspective. Specialised nurses delivered a 12-month stepped-care depression treatment programme beginning with either problem solving treatment, psychotherapy or a structured antidepressant pharmacotherapy programme. This was compared with usual care in the PATHWAYS RCT (Katon, *et al.,* 2004) alongside which this economic evaluation was conducted. A two-stage screening process identified 329 adults with diabetes and current depressive disorder (PHQ-9 =>10 at first screening and Hopkins Symptom Checklist (SCL) depression score of => 1.1 at the second screening) in primary care clinics of a US health plan. The measure of benefit used was the number of depression free days. Health service costs were assessed using health plan accounting records and included all outpatient services.

Over 24 months, patients assigned to the intervention accumulated a mean of 61 additional days free of depression (95% CI, 11 to 82 days) and had outpatient health services costs that averaged $314 less (95% CI, $1007 less to $379 more) compared with patients continuing in usual care. The depression treatment program dominated usual care.

The conclusion reached was that for adults with diabetes, systematic depression treatment significantly increased time free of depression and appeared to have some economic benefits from the health plan perspective. The authors recommended that depression screening and systematic depression treatment become routine components of diabetes care.

While the study estimated that the intervention program led to lower outpatient health services costs over 2 years, the sample was not large enough to exclude the possibility of the costs increasing. Replication of these findings in other patient samples and other healthcare systems is clearly needed. Also the healthcare use patterns in this sample might differ from those in a healthcare system with different financing mechanisms and financial incentives such as the UK.

Summary

The economic studies on service configurations were limited to settings outside the UK health setting. Some of these interventions assessed for cost effectiveness were not considered to be purely collaborative care in terms of the definition adopted by the GDG. However the evidence presented supports intervention in adults with depression and diabetes and in high utilisers of general medical care. Diabetes may or may not be considered to be a suitable representative of other chronic physical health conditions. The GDG were of the opinion that in the UK health care setting, diabetes may prove to

be a suitable proxy condition in the spectrum of chronic physical illnesses considered. This is because diabetes requires ongoing treatment that can be quite costly; it can also result in serious complications in the long-term and is associated with significant impact on quality of life. Moreover, if collaborative care is considered to be a primary care level intervention, diabetes can be considered an appropriate choice as it is now predominantly treated in the primary care setting.

The economic evidence presented is all conducted in the US health care setting and adopts the perspective of the 3rd party payer. Healthcare in the US is provided predominantly by separate private entities such as health maintenance organisations and to receive care patients often require private health insurance. This is very different to the UK where health care is predominantly publicly funded and there is free universal coverage. Therefore, this results in differences in access to healthcare and the resultant health care use patterns may differ too. The treatments received and cost of the treatments may also differ as health care providers may face different financial incentives. Cost estimates used in the studies would also vary greatly not only across different countries but also across different healthcare providers in the US alone, as prices for larger institutional purchasers may be lower than average wholesale prices due to their ability to negotiate lower prices. For the reasons stated above, the results of the economic studies reviewed have limited generalisability to the UK setting.

The clinical review aimed to assess the efficacy of any service level intervention directed at treating depression in people with chronic physical health problems. There was a lack of evidence for most of the interventions considered. However, the evidence for collaborative care has grown considerably and was the exception. This growth in evidence has led some experts to call for the widespread implementation of collaborative care. For many people depression is a chronic and disabling disorder and has been linked to an increase in healthcare utilisation, disability and work absenteeism in people with chronic physical illness. Therefore, there has been growing interest in the development of systems of care for managing depression in people with chronic physical health problems.

The clinical evidence review conducted supported that intervention in the form of collaborative care in this population would be clinically worthwhile. The review showed that a collaborative care intervention is effective when compared with usual care, unlike the review conducted in the depression-alone population, which showed a smaller clinical effect.

It was considered important to assess whether this intervention was cost effective in the UK setting when compared with usual care in this population. An economic analysis was conducted the details of which follow.

6.4 Economic modelling: cost effectiveness of collaborative care service configuration for people with depression and chronic physical health problems

6.4.1 Rationale for economic modelling – objectives

The systematic search of economic literature failed to identify any studies on the cost effectiveness of the collaborative care service configuration in the management of depression in the UK setting. The clinical evidence suggests that collaborative care interventions may be associated with improved depression outcomes in people with depression and chronic physical health problems. The limited economic data from UK-based studies pointed to the need for economic modelling for this guideline. The objective of economic modelling was to explore the relative cost effectiveness between collaborative care and usual care for people with depression and chronic physical health problems in the current UK clinical setting, using up-to-date appropriate information on costs and clinical outcomes. Details on the guideline systematic review of economic literature on service-level interventions for people with depression and chronic physical health problems are provided in section 6.3.6.

6.4.2 Economic modelling methods

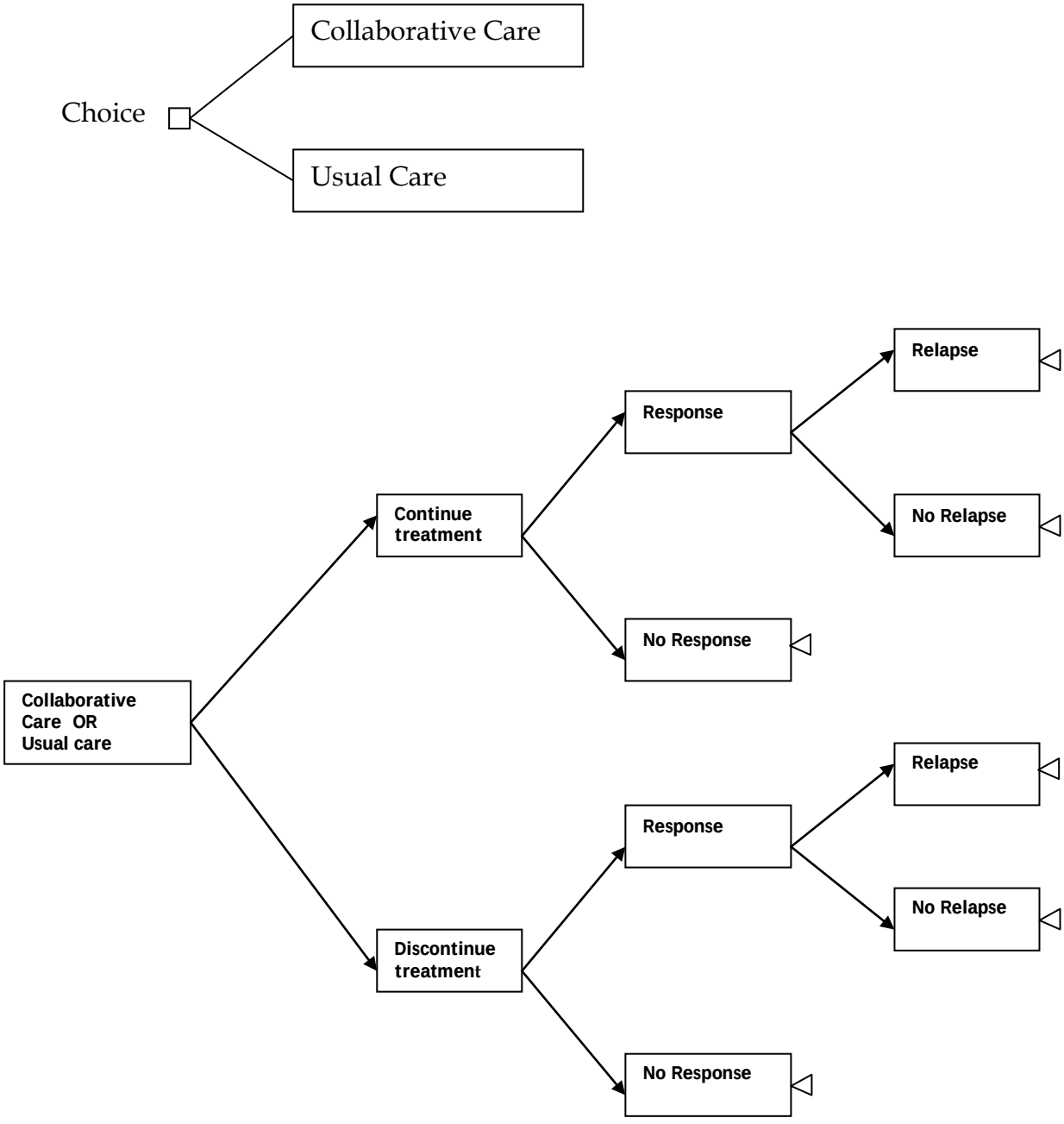
Interventions assessed

Collaborative care was compared with usual care. Collaborative care was considered to include usual care as delivered in the UK health care setting with the addition of the services of a case manager.

Model structure

A pragmatic decision analytical model was constructed using Microsoft Excel 2007. Within the model, patients entered collaborative care and either continued or discontinued treatment. People that remained in collaborative care responded or did not respond. Patients who responded to initial treatment received 6-months maintenance therapy and then were assumed to either relapse or not. People who discontinued from collaborative care treatment were assumed to receive various levels of care for their depression, including no care. Some of these people were assumed to clinically improve, and then either relapse or enter remission. The time horizon of the analysis was 18 months; this consisted of 6 months of treatment, reflecting the time point at which the clinical efficacy parameters reported in the studies included in the guideline meta-analysis were measured, plus 12 months follow-up, for which relapse data was available. Maintenance therapy was considered to occur for 6 months into the 12 month period. A schematic diagram of the economic model is presented in Figure 5.

Figure 5: Schematic diagram of the economic model structure.



Costs and outcomes considered in the analysis

The analysis adopted the NHS and Personal Social Services (PSS) perspective. The measure of outcome was the Quality Adjusted Life Year (QALY).

Clinical outcomes and event probabilities

In order to populate the model, the baseline absolute rates of non-response and treatment discontinuation associated with usual care, as well as the

respective relative risk estimates for treatment discontinuation and non-response of collaborative care versus usual care were derived from the relevant guideline systematic review and meta-analysis.

Non-Response was defined as the proportion of patients who had a less than 50% improvent from the from the baseline score. Treatment discontinuation was defined as the number of patients who terminated early for any reason.

The guideline meta-analysis of non-response rates was based on intention-to-treat analysis, with non-completers being considered as "unfavourable" outcome (that is, as non-responders). This meant that non-response rates included people who completed treatment but did not respond to it plus people who did not complete treatment. For the economic analysis, the rate proportion of non-responders out of completers was estimated from the available data, and was subsequently incorporated in the respective branch of the decision tree.

Table 18: Data incorporated into the model

Data		**Range (95% CI)**	**Reference**
RR of not completing treatment/discontinuation (leaving study early for any reason):			
Collaborative care versus usual care(a)	0.98	0.84 – 1.15	Guideline meta-analysis based on ITT analysis
Baseline rate: Usual Care (b)	0.18		
Value applied in the model = a*b		0.18	
RR of non-response following treatment(<50% improvement on outcome scales included in review):			
Collaborative care versus usual care (c)	0.76	0.71 – 0.80	Guideline meta-analysis based on ITT analysis
Baseline rate: Usual Care (d)	0.77		
Value applied in the model = c* d		0.58	
Probability of relapse during follow up:			
Both arms	0.34 (absolute rate)	0.14 – 0.54 (assumption)	Lustman, 2006
Probability of spontaneous remission for patients who discontinue initial treatment:			
Both arms	0.20	0.10 – 0.30	GDG expert opinion
Probability of relapse for patients who discontinue initial treatment and in remission:			
Both arms	0.52	0.22 – 0.72	Lustman, 2006

The relative risk of non-response of collaborative care versus standard care was taken from the collaborative care meta-analysis. The baseline rate of response over 6 months was taken from the studies included in the meta-analysis that reported this outcome at 6 months. The absolute rate at baseline was taken from the control arm of the meta-analysis. The relative risk shown

in Table 18 was multiplied by the baseline absolute response rate. The resultant figure shows that the value for non-reponse in collaborative care is much lower than the baseline rate in usual care.

For patients who responded to the collaborative care intervention after 6 months, it was assumed that they would either relapse or not. The rate of relapse for these patients was taken from a 12 month pharmacological continuation study by Lustman and colleagues (2006). This study was conducted in a population of people with depression and chronic physical health problems and looked at the clinical effects of SSRIs. This estimate was conservatively used in both arms.

For patients who discontinued collaborative care it was assumed that rather than remaining depressed, a proportion (20%) would improve from their baseline health state, either spontaneously or following treatment. Of those patients who improved following discontinuation, again it was assumed that a proportion would relapse and the remaining patients would enter remission. The rate of relapse for these patients was assumed to be 0.52 based on the placebo arm of the pharmacological continuation study by Lustman and colleagues (2006). Again, these rates were applied to both arms.

Utility data and estimation of QALYs

In order to express outcomes in the form of QALYs, the health states of the economic model needed to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on, and perceptions of, HRQoL in the health states under consideration.

Systematic review of published utility scores for adults with depression

Among the studies already assessed for eligibility, eight publications were identified that reported utility scores relating to specific health states and events associated with depression (Bennett *et al*., 2000; King *et al*., 2000; Lenert *et al*., 2000; Peveler *et al*., 2005; Pyne *et al*., 2003; Revicki & Wood, 1998; Sapin *et al*., 2004; Schaffer *et al*., 2002). Seven of these studies were solely despression focused with the study by Lenert and colleagues 2000 being the only paper distinguishing between diferent levels of physical impairment.

Three studies used the EQ-5D Index instrument, currently recommended by NICE as a measure of patient HRQoL for use in cost-utility analyses (King *et al*., 2000; Peveler *et al*., 2005; Sapin *et al*., 2004). In all three studies, preference values elicited from the UK population sample were used (Dolan & Williams, 1995). King and colleagues (2000) collected patient EQ-5D utility data over 12 months follow-up in a RCT comparing usual GP care with two types of brief psychological therapy (non-directive counselling and CBT) among patients with depressive or mixed anxiety/depressive symptoms (BDI > 14). Patient utility, reported as median scores, improved from baseline in all three

treatment groups at 4 and 12 months. However, no differences in median scores were detected between the three patient groups. The study by Peveler and colleagues (2000) was another HTA based on a RCT comparing the cost-utility of TCAs, SSRIs and lofepramine among UK patients with a new episode of depressive illness (based on GP diagnosis). Patients completed the EQ-5D questionnaire on a monthly basis over 12 months. Again, utility scores improved from baseline at 12 months in all three treatment groups with no differences were detected between groups.

The study by Sapin and colleagues (2004) was based on a multicentre, prospective cohort of patients with a new episode of MDD recruited in the French primary care setting assessed at 8 weeks follow-up. EQ-5D utility scores were stratified according to depression severity, defined by CGI scores, and by clinical response, defined by MADRS scores, at follow-up. At 8 weeks, patients with MADRS scores lower or equal to 12 were considered as "Remitters" and others considered as "Non-remitters". Patients with a decrease of at least 50% in relation to baseline score were considered as "Responder" and others as "Non-responders". These two patient groupings also led to the creation of three mutually exclusive groups: "Responder remitters", "Responder non-remitters" and "Non-responders".

The other five studies used a variety of instruments to measure patient utility (Bennett *et al*., 2000; Lenert *et al*., 2000; Pyne *et al*., 2003; Revicki & Wood, 1998; Schaffer *et al*., 2002). The study by Bennett and colleagues (2000) used a disease-specific measure, the McSad instrument, to estimate utility scores for a cross-sectional sample of patients who had experienced at least one episode of major, unipolar depression in the previous 2 years. McSad is a direct utility measure in which rating scale (RS) and standard gamble (SG) techniques were used to obtain utilities for specific health states. The health state classification system contains six dimensions (emotion/self-appraisal/cognition/physiology/behaviour/role-function) each with four levels of dysfunction (none/mild/moderate/severe). Utility scores were generated for three temporary clinical marker states of six-month duration (mild/moderate/severe depression) and chronic states of lifetime duration (self-reported and severe depression).

Lenert and colleagues (2000) estimated utility scores among depressed US primary care patients based on six health states according to level of depression severity (mild/severe) and physical impairment (mild/moderate/severe). Cluster analysis was applied to the SF-12 HRQoL instrument to generate the six health states. Utilities applied to the six health states were elicited through the use of visual analogue scale (VAS) and SG methods. The resulting 6-state health index model was then applied to HRQoL data taken from a longitudinal cohort study of patients with current major depression or dysthymia.

Pyne and colleagues (2003) used the self-administered Quality of Well-Being scale (QWB-SA) in a prospective cohort of US patients treated with antidepressants to measure change in patient HRQoL scores over 4 month follow-up. The scoring function of the QWB-SA was based on rating scale measurements taken from a random sample of the US population. QWB-SA scores improved during follow-up for treatment responders (defined by a 50% reduction in HRSD-17 scores) but did not improve for non-responders.

Revicki and Wood (1998) used standard gamble (SG) techniques in US and Canadian patients with major depressive disorder (MDD) in order to generate utility scores for 11 hypothetical depression-related and current health states according to depression severity and antidepressant treatment. The depression-related health states varied depression severity (mild/moderate/severe) and medication (nefazodone/fluoxetine/imipramine) and were framed in terms of 1 month duration and described symptom severity, functioning and well-being, and medication therapy including side-effects.

Similarly, the study by Schaffer and colleagues (2002) used SG techniques to elicit utility scores for 10 individual symptom profiles of major depression plus three 'clinical marker' depression profiles (mild/moderate/severe) amongst patients with current or past depression. The individual symptoms profiles each consisted of five statements describing a particular aspect of a symptom of depression, incorporating the content of several depression scales and interviews (HDRS; BDI; MADRS; DSM-IV and SCID-IV).

Summary

Table 19 summarises the methods used to derive health states and estimate utility scores associated with various levels of depression severity and treatments for depression as well as utility scores from each study. Overall, the studies reviewed here reported significant impact of depression on the health-related quality-of-life (HRQoL) of patients with depression. A number of studies indicated that patients valued the state of severe depression as being close to zero or death (Bennett *et al*., 2000; Revicki & Wood, 1998). There was some limited evidence to suggest that generic utility measures such as the EQ-5D may be less sensitive than disease-specific measures such as the McSad health state classification system.

NICE currently recommends the EQ-5D as the preferred measure of HRQoL in adults for use in cost-utility analyses. The institute also suggests that the measurement of changes in HRQoL sould be reported directly from people with the condition examined, and the valuation of health states be based on public preferences elicited using a choice-based method such as time trade-off (TTO) or SG, in a representative sample of the UK population (NICE, 2008). Therefore, based on these recommendations, the EQ-5D utility scores estimated by Sapin and colleagues (2004) were deemed to be the most suitable for use in calculating QALYs in the guideline economic models. Despite being

based on a cohort of French patients, which may limit their generisability to the UK setting, preference values assigned to health states were elicited from the UK population sample. Furthermore, utility scores were stratified according to disease severity and clinical response which is useful when modelling health states in economic analysis.

The data by Sapin and colleagues (2004) was selected for the base-case analysis for a number of reasons: they covered a range of health states of varying severity of depression; the methodology was described in detail; the valuations were made by members of the UK general population using TTO; utility data for health states associated with treatment were also reported; and the study provided sufficient data for linking specific health states to EQ-5D scores and subsequently to utility scores, thereby proving suitable for modelling exercises. Although the people examined in the study were not reported to have chronic physical illness, it was still deemed appropriate to use in the economic analysis, given that none but one of the studies (Lenert *et al.*, 2000) included in the utility review included or mentioned the presence of chronic illness with depression in the populations described. Full details of the utility scores are presented in Table 19 and Table 20.

The paper by Lenert and colleagues (2000) proved difficult to use in the model. The measure of outcome in the clinical review was response, which referred to depression only. Studies used did not report combined outcomes, that is, changes in depression and physical improvement or deterioration. The values reported in the above-mentioned utility paper were linked to combined physical and depression related states. Nevertheless, the values reported in the paper by Lenert and colleagues (2000) paper were adapted for sensitivity analysis as follows: The physical improvements were assumed due to the lack of combined depression and physical condition effectiveness evidence.

Qol weights (Lenert *et al.*, 2000)	
@ Baseline	0.781 (Severe mental and moderate physical impairment)
Response	0.944 (near normal health)
Relapse ffg. Response	0.871 (Mild mental with mild physical impairment)
Non-response	0.781 (Severe mental and moderate physical impairment)
@ Baseline	0.781 (Severe mental and moderate physical impairment)

It was assumed that a linear increase in QALYs occurred, for example, from initiation of treatment till response was achieved over the 6 month treatment

period. Furthermore, it was also assumed that a linear deterioration in QALYs occurred when, for example, relapse occurred over 12 months after a response was achieved

For those who dropped out and spontaneously improved it was assumed that their utility improved from baseline to that of response over 6 months. If a relapse was avoided then the utility value increased linearly to that of response with no relapse over the ensuing 12 months. While those who did not spontaneously improve remained at baseline.

QALYs were not discounted.

Table 19: Summary of studies reporting utility scores relating to specific health states and events associated with Depression

Study	Definition of health states	Valuation method	Population valuing	Results (95% CI/SD)
Bennett *et al.*, 2000	Utility values were elicited using the McSad health state classification system. The health state descriptions referred to untreated depression.	SG	105 patients with history of major, unipolar depression in the previous 2 years.	Temporary states (6-mo): - mild depression 0.59 (0.55-0.62) - moderate depression 0.32 (0.29-0.34) - severe depression 0.09 (0.05-0.13) Clinical States (lifetime): - self reported health state 0.79 (0.74-0.83) - severe depression 0.04 (0.01-0.07)
King *et al.*, 2000	RCT comparing three treatments: usual GP care and two types of brief psychological therapy (non-directive counselling and CBT) over 12 months follow-up	EQ-5D (TTO)	464 eligible patients with depressive symptoms,	CBT / ND Counselling / GP care Baseline 0.73 / 0.73 / 0.73 4 months 0.85 / 0.85 / 0.81 12 months 0.85 / 0.85 / 0.85
Lenert *et al.*, 2000	Cluster analysis used to obtain 6 health states from SF-12. The utility change scores over longitudinal study period were calculated using estimated health state utilities for those with remission, responder-non-remitters and those with no response.	VAS, SG	104 U.S. depressed primary care patients	Near-normal health (no depression): 0.94 (0.21) Mild mental with mild physical impairment: 0.87 (0.18) Severe physical health impairment: 0.83 (0.20) Severe mental health impairment (severe depression): 0.81 (0.21) Severe mental and moderate physical impairment: 0.78 (0.22) Severe mental and physical impairment: 0.66 (0.27)
Peveler *et al.*, 2005.	Pragmatic RCT of three classes of antidepressant: TCAs, SSRIs and lofepramine (LOF) over 12 months follow-up.	EQ-5D (TTO)	261 UK primary care patients with new episode of depression	TCA / SSRI / LOF Baseline 0.58 (0.27) / 0.61 (0.28) / 0.57 (0.27) 12 Months 0.78 (0.19) / 0.78 (0.19) / 0.77 (0.21)
Pyne *et al.* , 2003	Prospective observational study conducted over 16 weeks. Treatment with antidepressant &/or mood stabiliser. Depression response data (50% reduction in HRSD-17) collected at baseline, 4 weeks and 4 months.	QWB-SA (Category scaling)	58 US patients treated for MDD	Baseline (HRSD-17: 20.7-21.0) QWB-SA: 0.41-0.43 Responders: / Non-responders: 4-week: 0.54 / 0.46 4-month: 0.63 / 0.43

Revicki & Wood, 1998	11 hypothetical depression related states, varying depression severity and antidepressant treatment, and the patient's current health status.	SG	70 patients with MDD from primary care practices in USA & Canada	Severe depression, untreated: 0.30 (0.22) Moderate depression - Nefazadone: 0.63 (0.23) - Fluoxetine: 0.63 (0.19) - Imipramine: 0.55 (0.03) Mild depression: - Nefazadone: 0.73 (0.21) - Fluoxetine: 0.70 (0.20) - Imipramine: 0.64 (.20) Depression remission, maintenance treatment - Nefazadone: 0.83 (0.13) - Fluoxetine: 0.80 (0.15) - Imipramine: 0.72 (0.17) Remission, no treatment: 0.86 (0.16)
Sapin *et al*., 2004	Multicentre, prospective, non-comparative cohort study, 8 weeks follow-up. Impact on quality of life measured with EQ-5D instrument Clinical response, defined by MADRS scores. 'remitters': MADRS <=12 'responder': at least 50% decrease in baseline score	EQ-5D (TTO)	250 patients with new episode MDD not treated with AD before inclusion, from French primary care	Baseline Mild Depression: 0.45 (0.22) Moderate Depression: 0.33 (0.24) Severe Depression: 0.15 (0.21) 8 weeks No Depression: 0.86 (0.13) Mild Depression: 0.74 (0.19) Moderate depression: 0.44 (0.27) Severe Depression: 0.30 (0.27) Responder – remitter : 0.85 (0.13) Responder - non-remitter: 0.72 (0.20) Non-responders: 0.58 (0.28)
Schaffer *et al*., 2002	Utility scores for 10 individual symptoms of depression, and 3 depression severity profiles (mild/mod/severe).	SG	75 Canadian subjects (19 current depression, 21 past depression, 35 healthy controls)	Mild / Moderate / Severe Current: 0.59(0.33) / 0.51 (0.34) / 0.31(0.31) Past: 0.79(0.28) / 0.67 (0.36) / 0.47 (0.34) Controls: 0.80 (0.21) / 0.69 (0.29) / 0.46 (0.28) Psychological symptoms (low mood, anhedonia, poor concentration, guilt, suicidal ideation): 0.72 (0.24)

	Somatic (decreased appetite, energy, sleep, psychomotor agitation, retardation): 0.82 (0.19)

Table 20:HRQoL data

QoL weights	Base case value (mean)	Range (95% CI)	Reference
@ Baseline	0.33	(0.29 to 0.37)	Sapin *et al.* (2004)
Response– no relapse	0.85	(0.83 – 0.87)	
Response – with relapse	0.72	(0.65 to 0.79)	
Non Response	0.58	(0.50 to 0.66)	

Cost data

An NHS and personal social services (PSS) perspective was taken for the analysis based on current NICE guidance (NICE, 2008b). Therefore, only direct health and social care costs were considered in the model. Costs included drug acquisition costs, monitoring costs relating to consultations with a case manger, psychologists and GP visits, as well as other health and social care costs associated with the care of people with depression who discontinued treatment, or did not respond to treatment, or responded to treatment but relapsed at a later stage. Resource utilisation data were collected as part of the literature review or from GDG expert opinion. Unit costs were obtained from a variety of sources including the British Medical Association and the Royal Pharmaceutical Society of Great Britain (2008) and the Personal Social Services Research Unit (Netten & Curtis 2007; Netten & Curtis, 2009). All costs were reported in UK pound sterling and based on 2007/08 prices. They were inflated where necessary using Hospital and Community Health Service indices (Netten & Curtis, 2009). As in the case of outcomes, no discounting was applied. Specifically those costs and benefits incurred from the 12 to 18 month were not discounted as it was assumed that this omission would have no significant changes to the results, as it is a relatively short time period.

Drug acquisition costs

Drug acquisition costs were taken from BNF 56 (British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2008). The choice of antidepressant was based on the guideline recommendations for pharmacological interventions. Citalopram, a SSRI, was chosen as the representative antidepressant and according to prescribing data it is currently one of the most widely prescribed antidepressants in the NHS (Prescription Costing Analysis, 2008). Citalopram would be administered over the maintenance period as well.

Table 21: Acquisition costs of antidepressant medication included in the economic model

Drug	*Dosage*	*Unit cost (BNF 56, September 2008)*
Citalopram	40 mg/day	£0.07 /day 28-tab = £1.87

Usual care costs

Estimates on resource use associated with usual care was based on GDG expert opinion. No up-to-date data, appropriate to inform the economic analysis, was identified in the literature.

The RCTs included in the clinical effectiveness review were looked at to provide resource use estimates, however they failed to describe usual care resource use adequately, if at all. Therefore usual care, on advice from the GDG, was described as follows:

- All patients would receive antidepressant treatment (as described above).
- The GP co-ordinates care; over the 6-month treatment period a patient visits the GP six times and a further 2 times over the 6-month maintenance period.
- 6% of all patients are referred to a clinical psychologist; they would receive 12 CBT sessions over the treatment period and two booster sessions over the maintenance period.
- Costs associated with specialist psychiatric care were omitted from the analysis because they were deemed to be very low in both arms because only a small number of patients would be referred onto specialist services.
- The resource use related to chronic physical illness was also excluded as it was also estimated to be the same for both usual care and collaborative care. The costs are likely to differ widely across different chronic illnesses. This analysis focuses on the intervention for depression in a population of varied chronic illnesses.

Collaborative care costs

Estimates on resource use associated with collaborative care were based on resource use patterns described in the studies included in the clinical effectiveness review, as well as on GDG expert opinion.

It was assumed that collaborative care in a UK setting would entail elements of usual care (described above) and the addition of a case manager. Therefore, collaborative care was determined to consist of the following resource use:

- Patients would receive antidepressant treatment (as described above)
- The GP works in collaboration with the case manager. Patients make the same number of visits to the GP as in usual care.
- 8% of all patients are referred to a clinical psychologist. Where they receive 12 CBT sessions over the treatment period and two booster sessions over the maintenance period. This estimate was higher than usual care as it was assumed that the

referral rate would be expected to increase following the intervention of a case manager.

- The case manager in the collaborative care approach co-ordinates care of the person with depression and chronic physical health problems. The case manager is in face-to face and telephonic contact with the service user ten times over the treatment period and 3 contacts over the maintenance period.
- Costing a case manager posed a challenge as this role does not exist in this context in the NHS. The GDG assisted in describing the expected salary per annum, time in patient contact and qualification requirements of a case manager. Comparisons were drawn between low-intensity IAPT workers and a case manager because in the opinion of the GDG, the expected unit costs of both were considered to be similar. The NHS IAPT workforce capacity tool (DH, 2008c) described the annual salary (£29k/annum) and the number of contacts expected of a low intensity IAPT worker. The GDG considered these to be similar to what a case manager would provide. The reported salary and patient contacts were then matched to an existing position in the NHS (Netten & Curtis, 2009) to provide the unit cost of a case manager.

Table 22: Resource use related to case management

Case manager		Unit cost	Reference
Face-to-face contact	One 60-minute session One 30-minute session	£33/hour of client contact	Netten, A. & Curtis, L. (2008) *Unit Costs of Health and Social Care.* PSSRU Netten, A. & Curtis, L., (2007) *Unit Costs of Health and Social Care.* PSSRU
Telephonic contact	Eight 20-minute sessions	£28/hour of other client contact and activity	
Liaison with GP	Average 8 minutes over 3 months	£0.47 /minute	
Supervision by a psychiatrist	Fortnightly 2 minutes/patient	£0.47 /minute	

The Case manager was estimated to have face-to-face contacts with the service user as well as telephone them. They are also expected to liaise with the GP involved in delivering care. The liaison time for both GP and case manager was costed. An assumption about the time spent in liaison was made in collaboration with the GDG. Case managers were also expected to undergo supervision by a senior mental health professional. In the RCTs included in the clinical review, a psychiatrist fulfilled the supervision needs either weekly or fortnightly. Supervision was assumed to occur fortnightly in the economic

model. The time spent in supervision was costed for the psychiatrist as well. The duration of 2 minutes per patient is dependent on the assumption that a case manager has a 30 to 35 patient caseload. If 1 hour is spent in supervision then that results in 2 minutes of discussion time per patient.

Costs associated with discontinuation of treatment, non response to treatment and relapse following response

Patients who discontinued initial treatment did not incur the full costs of treatment. To revise costs downwards, it was assumed that patients who discontinued initial treatment would drop out after 4 weeks of treatment, irrespective of intervention group (Rush *et al*., 2006; GDG expert opinion). For patients who responded and did not relapse during follow-up, it was assumed that no further additional treatment or mental health care resources beyond the 6-month maintenance period were required.

However, for those with unsuccessful treatment outcomes i.e. patients who either a) discontinued their initial intervention b) did not respond to their initial intervention or c) responded to therapy but relapsed at a later stage, it was assumed that they would continue to consume additional mental health care resources over the 18-month time horizon. Cost data for subsequent mental health care were taken from a study published by the King's Fund which estimated annual mental health care costs for respondents with mild, moderate and severe depressive disorder based on the UK psychiatric morbidity survey (McCrone *et al*., 2008). As such, these annual mental health care costs may be an under estimate of the actual costs incurred by patients with moderate and severe depression, as one would expect respondents with mild depression to use less mental health care on average. These mental health care costs included hospital and outpatient care, social services, residential care, GP visits and medication costs. These annual costs were divided into monthly cost estimates and then projected for the periods during which unsuccessfully treated patients would consume subsequent mental health care estimated in the model. According to the survey, only 65% of people with depression were in contact or receipt of mental health services. Therefore, these subsequent mental health care costs were weighted downwards based on the assumption that 35% of patients would not incur any further health care costs. These costs were also inflated to the current financial year (2008).

Patients who did not respond following therapy incurred full 6-month treatment costs followed by subsequent mental health care thereafter. For patients who relapsed over the 12 months following response, it was assumed that they relapse in the middle of this period, that is, at 6 months (GDG expert opinion). Therefore they were assumed to incur these mental health and social care costs for 6 months, that is, right after the end of the maintenance therapy period. More unit cost parameters are presented in Table 23.

Table 23: Unit costs incorporated into the model

Unit costs (2007/2008)		Reference
GP surgery consultation	£36	Curtis (2009)
GP telephonic liaison with case manager	£3.10 per minute	Curtis (2009)
Psychiatrist supervision	£3.98 per minute	Curtis (2009)
CBT session	£58	Curtis (2009)
Subsequent care costs per month	£180	McCrone *et al.* (2008) Hospital and Community Health Service indices (Curtis, 2009)
Percentage of people receiving mental health treatment after discontinuation	65%	McCrone *et al.*, 2008

The full cost of 6 months of collaborative care in the treatment phase and 6 months in the maintenance phase was £782. The full cost of 6 months of usual care in the treatment phase and 6 months in the maintenance phase was £361. See Table 24. The expected healthcare costs over 18 months for patients who dropped out of collaborative care and did not go on to complete the initial treatment intervention was £2177. The expected healthcare costs over 18 months for patients who did not respond to the 6-month collaborative care intervention was £1976, while the expected cost of healthcare following relapse was £1480.

Table 24: Resource use and cost estimates applied in the economic model

Resource use estimate	Cost (£)	Source of Unit Costs
Collaborative Care(CC) complete treatment costs including maintenance		
- Case Manager	331	Table 21, Table 22, Table 23
- GP care incl. cost of liaison with CM	362	
- Psychological Therapy (8%)	65	
- Citalopram (40mg/day): 3 months plus 6 months maintenance	24	
Total	782	
Usual Care(UC) complete treatment costs including maintenance		
- GP care	288	Table 21, Table 23
- Psychological Therapy (6%)	49	
- Citalopram (40mg/day): 3 months plus 6 months maintenance	24	

Total	361	
Patients who discontinue treatment		
Collaborative care		
1 month treatment costs incl. all components of CC	188	Table 21, Table 22, Table 23
Subsequent mental health care: 17 months	1989	
Total	2177	
Usual Care		
1 month treatment costs incl. all components of UC	88	Table 21, Table 23
Subsequent mental health care: 17 months	1989	
Total	2077	
Patients who fail to respond		
Collaborative care		
6 month treatment costs incl. all components of CC	572	Table 21, Table 22, Table 23
Subsequent mental health care: 12 months	1404	
Total	1976	
Usual Care		
6 month treatment costs incl. all components of UC	270	Table 21, Table 23
Subsequent mental health care: 12 months	1404	
Total	1674	
Patients who relapse		
Collaborative care		
12 months treatment costs incl. all components of CC	778	Table 21, Table 22, Table 23
Subsequent mental health care: 6 months	702	
Total	1480	
Usual Care		
12 month treatment costs incl. all components of UC	361	Table 21, Table 23
Subsequent mental health care: 6 months	702	
Total	1063	

Data analysis and presentation of the results

An incremental cost effectiveness ratio (ICER) was calculated for collaborative care versus usual care. ICERs express the additional cost per additional unit of benefit associated with one treatment option relative to its comparator. Estimation of such a ratio allows consideration of whether the additional benefit is worth the additional cost when choosing one treatment option over another.

One-way sensitivity analysis was undertaken to explore the impact of the uncertainty characterising model input parameters on the base-case results. This involved varying a single parameter between its plausible minimum and

maximum values or upper and lower confidence interval estimates in some instances, while maintaining all remaining parameters in the model at their base case value. Uncertainty around the various transition probabilities, QoL weights as well as the cost implications of different levels of resource use involved in patient clinical management were all explored.

In order to demonstrate the joint uncertainty between the different parameters probabilistic analysis was attempted. This analysis utilised the mean point estimates and the 95% confidence intervals around them, appropriate distributions were assigned for each parameter estimate, that is, lognormal distributions were applied to relative risk estimates, gamma distributions to cost estimates and beta distributions to utility estimates and absolute rates. For cost estimates that did not have 95% confidence intervals, a standard error based on 30% of the mean estimate was applied in order to reflect any potential uncertainty around these estimates. Effectiveness and cost estimates were then recalculated 10,000 times using Monte Carlo simulation. Whether an intervention is cost-effective or not is dependant on how decision-makers value the additional health gain achieved by the intervention. The probability that collaborative care is cost-effective compared with usual care as a function of the decision-makers' maximum willingness-to-pay for an additional successfully treated patient or QALY was illustrated by cost-effectiveness acceptability curves (CEACs) (Briggs, 2000).

6.4.3 Results of economic analysis

The decision model resulted in an average of 0.83 QALYs per patient in the collaborative care pathway and 0.80 QALYs per patient in the usual care pathway. Therefore, the average gain in QALYs over the 15 month time horizon in collaborative care was 0.03 per patient.

Overall, collaborative care was estimated to be more effective and more costly than usual care for people with moderate or severe depression and chronic physical health problems. On average, collaborative care was £116 more expensive per patient than usual care. The resulting base case ICER was £4043 per QALY gained. This is below the NICE threshold of £20,000 per QALY gained and therefore collaborative care is a cost-effective intervention.

Table 25: Base case results

Results	**per patient**		
	Costs	**QALYs**	**ICER**
Collaborative care	£1614	0.83	
Usual care	£1498	0.80	**4043**
Difference	£116	0.03	

Sensitivity Analyses

Deterministic Sensitivity Analysis

The parameter values used in the sensitivity analyses and the relevant ICERs are presented in Table 26. Resource use estimates, quality of life weights and effectiveness data inputs were subject to sensitivity analysis. For the sensitivity analyses, 95% confidence intervals around the relevant inputs of collaborative care versus usual care were used. If these were not available a high and low estimate was chosen in consultation with the GDG.

The results of the deterministic sensitivity analysis indicated that the results were fairly robust when single parameters are varied over their uncertainty ranges. None of the parameters that were varied had a significant impact on the results as collaborative care remained more cost effective than usual care.

When the relative risk of discontinuation and non-response were varied they ICERs achieved were well below the NICE threshold. The results were similarly well below the threshold when the absolute rate of relapse and probability of spontaneous remission following discontinuation were tested.

The utility values were also subject to sensitivity analysis. At both high and low utility estimates as determined from Sapin and colleagues (2004), collaborative care remained more cost-effective than usual care. Collaborative care remained more cost-effective than usual care when the utility values from the paper by Lenert and colleagues (2000) paper were used. The physical improvements were assumed due to the lack of combined depression and physical condition effectiveness evidence.

Resource use and cost sensitivity analysis mainly focused on the case manager costs and those related to psychological therapy.

If the cost of case-manger was increased to £ 35 000 per annum the ICER increased to £8220 per QALY gained. Combined increases in case manager contacts, increased supervision time with a senior mental health professional and increased liaison time with the GP resulted in an ICER of £11 628 per QALY gained.

When the number of psychological contacts was increased to 16 session's collaborative care remained more cost effective than usual care. However if all patient in collaborative care receive psychological intervention and half of those in usual care receive psychological intervention the ICER is £15 214 per QALY gained.

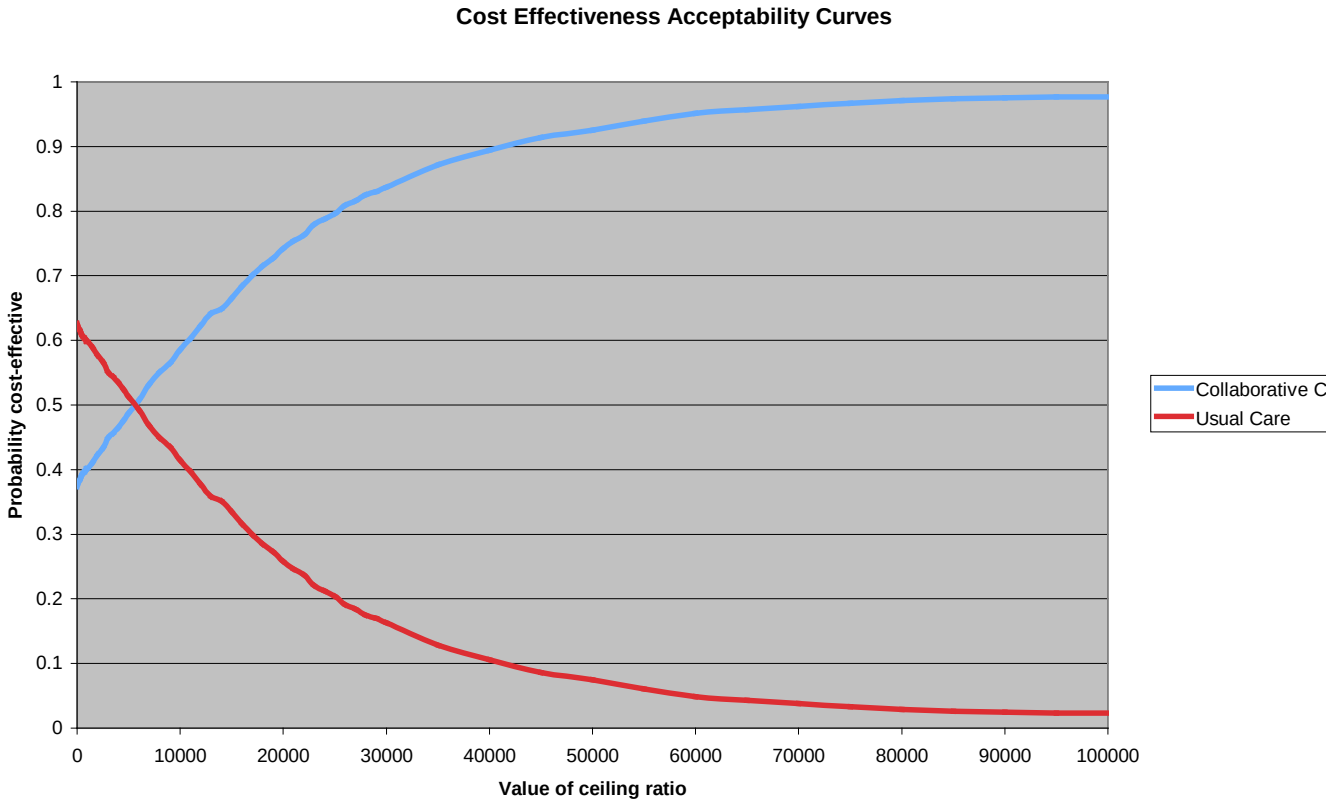
Table 26: Results of deterministic sensitivity analysis		
Analysis	Uncertainty range	ICER per QALY (£)
Base case analysis	-	**4043**
Clinical efficacy (Collaborative care (CC) versus usual care)		
Relative risk of discontinuation	0.84 – 1.15	3225 – 5617
Relative risk of non-response	0.71 – 0.8	2299-6045
Absolute rate of relapse	0.14 – 0.54	2535 – 7364
Probability of spontaneous remission following discontinuation	0.10 - 0.50	4023 - 4107
Probability of relapse after spontaneous remission following discontinuation	0.22 – 0.72	4051 – 4038
QoL weights		
@ Baseline	(0.29 to 0.37)	4206 - 3893
Response	(0.83 – 0.87)	6091 - 3026
Relapse ffg. Response	(0.65 to 0.79)	4221 - 3880
Non-response	(0.50 to 0.66)	2480 – 10 938
Qol weights (Lenert *et al.* 2000)		
@ Baseline	0.781 (Severe mental and moderate physical impairment)	
Response	0.944 (near normal health)	
Relapse ffg. Response	0.871 (Mild mental with mild physical impairment)	
Non-response	0.781 (Severe mental and moderate physical impairment)	5210
Resource use and costs		
% receiving psychosocial interventions	Collaborative care versus usual care	
50% versus 6%	13 619	
50% versus 10%	12 728	
50% versus 25%	9 385	
100% versus 50%	15 214	
Cost of case manager (Curtis, 2009):		
Salary of 35k/annum £50/hour of patient-related activity £62/hour of face-to-face contact	8 220	
Subsequent monthly healthcare costs = 0	11 599	
No. of CBT sessions	8 – 16	4000 – 4087
Increased case manager contact*, Increased GP—case manager liaison time and Increased supervision time 5 minutes/patient	11 628	

Probabilistic sensitivity analysis

In order to present the results of the probabilistic sensitivity analysis, cost-effectiveness acceptability curves (CEACs) were constructed (Figure 6). The CEAC indicates the probability of collaborative care being cost-effective for a range of threshold values. The threshold value represents the maximum a decision maker would be willing to pay for a unit of effect, in this case a QALY.

Current NICE guidance sets a threshold range of £20,000 to £30,000 per QALY (NICE, 2008a). Within this threshold range, the probability of collaborative care being cost-effective for patients with moderate to severe depression was 74 - 83% .

Figure 6: Cost effectiveness acceptability curves (CEACs)



Discussion

The results of the economic analysis suggest that collaborative care is more cost effective than usual care in the delivery of services to people with chronic physical health problems.

The cost results for patients receiving collaborative care suggests that although the initial treatment cost of collaborative care is higher than usual care, these costs were partially offset by savings due to lower subsequent

treatment costs. The main driver for this is the difference in the response rate between interventions. The higher response rate for collaborative care compared with usual care results in future cost savings.
Data on relapse rates were limited, and utility data was sourced from a population with possibly no chronic physical health problems (co-morbidities were not reported). However, when subject to one-way sensitivity analysis, collaborative care remained cost effective. This highlights the robustness of the results. Furthermore, probabilistic sensitivity analysis showed that within the current NICE threshold range, the probability of collaborative care being cost-effective for patients with depression and chronic physical health problems was 76-85% .

Three studies on service-level interventions were identified for the guideline economic evidence review. The study by Simon and colleagues (2007) supported that intervention in adults with diabetes significantly increases time free of depression and appears to have some economic benefits from the health plan perspective. While Katon and colleagues (2006) reported that the incremental cost per depression-free day was 25 cents (-$14 to $15) and the incremental cost per QALY ranged from $198 (144 –316) to $397 (287– 641). This ICER is quite low and may well fall below the NICE cost-effectiveness thresholds. This study supports the results attained in this evaluation. However this is a single study conducted in a non-UK health setting. Furthermore, this study alone reported results in terms of cost per QALY. The majority of the studies reviewed predominantly reported results in depression-specific terms that is cost effectiveness was reported in terms of 'cost per depression-free day.' This proves difficult in making comparisons with economic studies reporting QALYs.

The clinical evidence on service configurations potentially had several limitations (see Appendix 18). Only two studies included were conducted in the UK, with the majority of the non-UK studies conducted in the US. This raises questions about the degree to which effectiveness estimates of collaborative care can be translated to the UK healthcare system. A reason to be cautious about this is the fact that the collaborative care interventions evaluated within the clinical review have been designed within a private US managed-care system (Gilbody *et al.*, 2006b). As discussed earlier the UK healthcare setting is significantly different to that in the US. Healthcare in the US is predominantly privatised. UK healthcare is predominantly publicly funded and offers universal coverage. It is expected there may be differences in access to healthcare and the resultant health care use patterns. The treatments offered and their costs may also differ as health care providers may face different financial incentives. Usual care in the UK may be more intensive and possibly more effective than usual care offered in such a setting. Therefore, the use of such efficacy data may result in a possible over-estimation of successful outcomes for the intervention. However, even when compared to an 'enhanced' form of standard care collaborative care was still found to be clinically effective.

There was also marked variation between the different collaborative care interventions, with the complexity of the intervention and treatment components differing among studies**.** However, there were a number of common features shared by the majority of trials. All but two had an identified case manager. Many of the interventions followed a stepped care approach. Participants were given the option of either antidepressant medication or a psychological intervention as first-line treatment. Other common features of the trials included, monitoring of progress and supervision of staff by a psychiatrist. These features were shared in the components of collaborative care costed in the economic evaluation.

Gilbody and colleagues (2006b) point to an emergence of evidence that shows the clinical benefits of this method of organising care in European healthcare systems and in less well-financed systems. They also point out the usefulness of decision modelling in allowing examination of the cost effectiveness of this intervention between different healthcare systems that is by combining clinical effectiveness estimates from these US-based trials with routine service use and cost data from other healthcare settings. This was the aim of the present cost-effectiveness analysis.

Another limitation of this evaluation is the narrow focus on the outcomes of depression – only utility gains related to improvements in mood were evaluated, furthermore this was done in a depression only population The utility values used in this analysis may not reflect, for example, the negative effects of limited mobility that may occur in a certain chronic illnesses. Improved depression care is thought to produce other health benefits such as improved functioning and physical outcomes (Katon *et al.*, 2006); there was also some indication from the clinical evidence review that interventions for depression ultimately improved physical outcomes as well; this may be particularly significant for people with depression and chronic physical health problems. The paper by Lenert and colleagues 2000 showed that depression with associated severe physical impairment had very low utility values at baseline. This means that interventions that also improve physical health should result in substantial increases in utility and subsequently result in QALY gains. Therefore, the utilities for response used in this analysis may actually be an underestimate for this population. Furthermore, the potential to achieve such health gains can potentially reduce the population burden of illness and morbidity within healthcare budgets. There is an association between depression and increased use of medical services, therefore it follows that improved depression treatment could reduce medical expenditures, partially or fully offsetting costs of depression treatment (Simon *et al.*, 2001). This evaluation may have been more comprehensive if suitable data was available to link the utility gains or losses related to improvements/deterioration in physical outcomes following treatment of depression.

Another issue concerns the time horizon used for the analysis. An 18-month time horizon was used, with response rates applied at the end of the initial 6-month treatment and relapse rates applied during the 12-month follow-up period. This short time horizon does not allow for estimation of long-term costs which may be significant. Only one study in the entire clinical evidence review of interventions in this population provided relapse data at 12 months. It would have been preferable to evaluate the interventions over a longer follow-up period, for example, over a lifetime, but the lack of direct clinical evidence beyond 18 months precluded this.

Emerging RCT evidence has been cited that points to reductions in unemployment and increases in economic productivity as a consequence of case management approaches (Gilbody *et al.,* 2006a). Therefore, it is likely that including such costs would have further supported that collaborative care is more cost-effective than usual care.

Conclusion

The economic analysis undertaken for this guideline showed that collaborative care is more cost effective than usual care for people with depression and chronic physical health problems. Results were characterised by an ICER well below the NICE cost-effectiveness threshold of £20,000 per QALY and deterministic sensitivity analysis showed that collaborative care remained more cost effective when compared with usual care under all the scenarios explored. Probabilistic sensitivity analysis showed that within the NICE threshold range it is quite probable that collaborative care is more cost-effective than usual care for patients with moderate to severe depression and chronic physical illness .

Taking account of the limitations of this evaluation, economic and clinical evidence supports the recommendation of this intervention in people with depression and chronic physical health problems.

Further UK-based research is needed on the benefits and patterns of service use of collaborative care versus usual care in people with depression alone and in those with depression and co morbidities. Moreover, clinical data in the area of relapse prevention is also needed to enable a more comprehensive assessment of the relative cost effectiveness of collaborative care versus usual care.

6.4.4 From evidence to recommendations

The systematic review of clinical evidence demonstrated the efficacy of collaborative care when compared with standard care alone in improving depression outcomes in people with depression and chronic physical health problems. There was robust evidence across a number of depression outcomes including response, remission and continuous scale-based data. The clinical evidence was further supported by the health economic evaluation,

which indicated that collaborative care for people with depression and chronic physical health problems is a cost-effective intervention within UK settings. The results of sensitivity analyses, which varied the parameters in the health economic evaluation, continued to indicate that collaborative care was cost effective. Although the GDG noted that one limitation of the evidence base is that a significant number of studies have been conducted outside the UK, and predominantly within the US, it was concluded that the health economic evidence coupled with the clinical evidence warranted the inclusion of a specific recommendation.

It was the consensus of the GDG that collaborative care should form part of a well-developed stepped care approach for people with depression and chronic physical health problems. In particular, the GDG thought that collaborative care should be implemented where there is evidence of a relationship between a patient's depression and physical health problem and/or where a patient's depression has not adequately responded to initial treatment(s).

Although there were robust findings for the efficacy of collaborative care in improving depression outcomes, there was a paucity of data concerning the effects on the physical health conditions. In particular, very few studies reported measures of physical health outcomes, and where studies did report outcomes, the data were sparse. Given the interaction between depression and chronic physical health problems, the GDG considered this to be an important area for further research.

Recommendations

Effective delivery of interventions for depression

6.4.4.1 Where a patient's management is shared between primary and secondary care, there should be clear agreement between practitioners (especially the patient's GP) on the responsibility for the monitoring and treatment of that patient. The treatment plan should be shared with the patient and, where appropriate, with their family or carer.

6.4.4.2 If a patient's chronic physical health problem restricts their ability to engage with a preferred psychosocial or psychological treatment for depression(see recommendations 7.4.1.6 - 7.4.1.18),, consider alternatives in discussion with the patient, such as antidepressants (see recommendations 8.5.2.3 – 8.5.2.31) or delivery of psychosocial or psychological interventions by telephone if mobility or other difficulties prevent face-to face contact.

Step 3: Collaborative care

6.4.4.3 Consider collaborative care for patients with moderate to severe depression and a chronic physical health problem with associated functional impairment whose depression has not responded to initial high-intensity psychological interventions, pharmacological treatment or a combination of psychological and pharmacological interventions. **[KP]**

6.4.4.4 Collaborative care for patients with depression and a chronic physical health problem should normally include:

- case management which is supervised and has support from a senior mental health professional
- close collaboration between primary and secondary physical health services and specialist mental health services
- a range of interventions consistent with those recommended in this guideline, including patient education, psychological and pharmacological interventions, and medication management
- long-term coordination of care and follow-up.

Step 4: complex and severe depression

6.4.4.5 Practitioners providing treatment in specialist mental health services for patients with complex or severe depression and a chronic physical health problem should:

- refer to the NICE guideline on the treatment of depression[13]
- be aware of the additional drug interactions associated with the treatment of patients with both depression and a chronic physical health problem (see recommendations 8.5.2.8 to 8.5.2.17)
- work closely and collaboratively with the physical health services.

6.5 Research Recommendations

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

6.5.1 The effects of collaborative care on physical health outcomes for patients with moderate to severe depression and a chronic physical health problem

What is the clinical and cost effectiveness of collaborative care with regard to physical health outcomes for people with moderate to severe depression and a chronic physical health problem?

Why this is important

There is a reasonable evidence base to support the use of collaborative care in people with moderate to severe depression and a chronic physical health problem. However, the evidence base regarding the effects of collaborative care on physical health outcomes is more limited. Improved depression care is thought to produce other health benefits, such as improved functioning and physical outcomes[14]; this may be particularly significant for people with depression and a chronic physical health problem. This means that interventions that also improve physical health should result in substantial increases in utility and subsequently result in quality-adjusted life year (QALY) gains. Furthermore, the ability to achieve such health gains can potentially reduce the population burden of illness and morbidity within

[13] 'Depression: the treatment and management of depression in adults (update)' (NICE clinical guideline XX; to be published alongside this guideline)

[14] Katon, W., Unutzer, J., Fan, M.Y. *et al* (2006) Cost-effectiveness and net benefit of enhanced treatment for depression for older adults with diabetes and depression. *Diabetes Care*, *29*, 265–270

healthcare budgets. There is an association between depression and increased use of medical services, and so it follows that improved treatment of depression could reduce medical expenditure, partially or fully offsetting the costs of treating the depression[15]. The answer to this question has important practical implications for service delivery and resource allocation within the NHS.

This question should be answered using a randomised controlled trial design that includes people with moderate to severe depression and a chronic physical health problem. In addition to depression-related outcomes, physical health outcomes such as general physical functioning and pain, as well as outcomes specifically related to the condition (such as HbA1c for diabetes), should be assessed. These outcomes should reflect both observer-rated and patient-rated assessments of medium-term and long-term outcomes for at least 18 months. The study should also include an assessment of the acceptability and burden of treatment options and the impact of the intervention on the overall care system. It should be large enough to determine the presence or absence of clinically important effects using a non-inferiority design together with robust health outcome measures.

6.5.2 The effectiveness of physical rehabilitation programmes for patients with a chronic physical health problem and depression

What is the effectiveness of rehabilitation programmes for patients with depression and a chronic physical health problem in terms of improved mood?

Why this is important

Many patients with a chronic physical health problem undergo rehabilitation programmes. There is some suggestion in the literature that these have a beneficial effect on mental health. Understanding and/or enhancing the psychological benefits of these interventions has potentially important cost and service-design implications for the NHS. Given the large data set that already exists, it is important to determine the potential effects of these programmes to date before embarking on any individual studies. The answer to this question has important practical implications for service delivery and resource allocation within the NHS.

This question should be answered by an individual patient meta-analysis. There is an existing evidence base showing that programmes specifically designed to treat depression (for example, psychosocial and pharmacological interventions in patients with a chronic physical health problem) are effective.

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[15] Simon, G.E., Manning, W.G., Katzelnick, D.J., *et al.*, (2001). Cost-effectiveness of Systematic Depression Treatment for High Utilizers of General Medical Care. *Archives of General Psychiatry*, *58*, 181-187.

However, many patients with a chronic physical health problem are also undertaking specifically designed rehabilitation programmes (for example, cardiac rehabilitation programmes after myocardial infarction). These interventions are multi-modal and reports indicate that they can have an impact on mental health outcomes, in particular depression. However, it is unclear what the size of this effect may be, which components of the intervention are effective and which specific patient populations may benefit. Therefore an individual patient meta-analysis to examine the impact of rehabilitation programmes on symptoms of depression in patients with a chronic physical health problem should be undertaken before any further research is conducted.

7 Psychosocial interventions for people with depression and chronic physical health problems

7.1 Introduction

Depression is one of several problems faced by people with chronic physical health problems. The other problems include the symptoms of the physical illness itself (for example, pain and weakness), the consequent impairment of social and occupational functioning (for example, restricted mobility and prevention of valued activities), the changes in lifestyle necessitated by the illness or its treatment (for example, dietary restrictions and renal dialysis) and the side effects of medication.

Depression in this context is important because it can exacerbate the symptoms and disabling effects of the physical illness, but it is also potentially treatable. Successful treatment of depression may offer one of the few ways in which the health-related quality of life of people with chronic physical health problems can be improved.

Non-pharmacological interventions are important for several reasons. Many people who are already taking medication for their physical illness are reluctant to take further drugs for depression. Some people are averse to the idea of taking antidepressant drugs in any case and would prefer to be offered a treatment that helps them cope better with the effects of their illness and in which they can actively participate.

This chapter reviews the efficacy for psychosocial interventions to treat depression in people with chronic physical health problems. In addition, combination treatments (that is, psychosocial and pharmacological interventions) are also reviewed.

A range of psychological and related psychosocial treatments for depression (including depression with an associated chronic physical health problem) have been shown to relieve the symptoms of depression and there is growing evidence that psychosocial therapies can help people recover from depression in the longer-term (NICE, 2004a). People suffering depression typically prefer psychological and psychosocial treatments to medication (Prins *et al.*, 2008) and value outcomes beyond symptom reduction that include positive mental health and a return to usual functioning (Zimmerman *et al.*, 2006). This chapter sets out how these therapies have emerged as evidence-based approaches and some of the contextual issues that are important in translating recommendations based on clinical research on groups of people to particular care plans for individuals presenting to the health service with depression

with chronic physical health problems. It is important to note the limitations of this available data for making recommendations about treatments, particularly when many have been developed for people with depression but not with an accompanying physical health problem. (see Pilling, 2008 for a fuller discussion of these issues).

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

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

It is also important to note that such patients with relapsing and persistent problems constitute a significant proportion of the work of psychological treatment services. In the research recommendations (Section 7.4.2) we suggest priorities for further research to establish more definitively what therapies work for what people, especially in enabling people's longer term recovery, a pressing concern for many people who suffer recurrent depression.

7.1.1 Increasing the availability of psychosocial therapies in health care settings

The 2004 NICE Guideline (NICE, 2004a) has been influential in reshaping the sorts of psychosocial depression treatments available to people suffering

depression but it did not focus specifically on the needs of people with depression and chronic physical health problems. Most notably there has been a recent increase in the accessibility of evidence-based therapies, mainly for patients with less complex or enduring disorders at the level of primary care. Alongside the NICE Guideline and evidence base a number of factors determine whether a psychosocial therapy becomes accessible in the NHS. First, public demand and expectation influences service commissioners. User groups have long advocated the need for psychosocial approaches and this has influenced commissioning at a national and regional level. The high direct and indirect costs associated with depression, and the tremendous human suffering for people who experience depression and their friends and families have also been drivers. Psychosocial therapies, particularly high intensity therapies that involve one-to-one therapy over longer periods of time, are resource intensive. The NHS has limited resources and there are therefore drivers to find therapies that are as cost-effective as possible. This has been one of the drivers for the development of less intensive therapies as well as innovative delivery formats such as group based work. Finally, there is greater understanding of how depression presents in the NHS and models of care and service delivery have been shaped accordingly (See Chapter 5).

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

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

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

but also help with the prevention of relapse. The IAPT programme has also recently produced guidance in relation to depression in adults with chronic physical health problems. In 2009 it is expected that other interventions such as IPT will form part of the treatments offered by IAPT.

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

7.1.3 Contextual factors that impact on clinical practice

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

Client factors

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

Therapist factors

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

The therapeutic alliance

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

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

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

Therapist Competence

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

There is evidence that more competent therapists produce better outcomes (Barber *et al.,* 1996; Barber *et al.,* 2006; Kuyken & Tsivrikos, 2009). A number of studies have also sought to examine more precisely therapist competence and its relation to outcomes; that is what it is that therapists do in order to achieve good outcomes. A number of studies are briefly reviewed here; this section, which focuses mainly on CBT and depression, draws on a more extensive review of the area by Roth and Pilling (2009). In an early study Shaw and colleagues (1999a) examined competence in the treatment of 36 patients treated by 8 therapists offering CBT as part of the NIMH trial of depression (Elkin *et al.,* 1989). Ratings of competence were made the Cognitive Therapy Scale (CTS). Although simple correlation of the CTS with outcome suggested that it contributed little to outcome variance, regression analyses indicated a more specific set of associations. Specifically, when controlling for pre-therapy depression scores, adherence and the alliance the overall CTS score accounted for 15% of the variance in outcome. However, a subset of items on the CTS account for most of this association. Some understanding of what may account for this association emerges from three studies by DeRubeis's research group (DeRubeis and Feeley, 1990; Feeley *et al.,* 1999). All the studies made use of the Collaborative Study Psychotherapy Rating Scale (CSPRS: Hollon *et al.*, 1988), subscales of which contained items specific to CBT. On the basis of factor analysis the CBT items were separated into two subscales, labelled 'Cognitive therapy – Concrete' and 'Cognitive therapy – Abstract'. (Concrete techniques can be thought of as pragmatic aspects of therapy (such as establishing the session agenda, setting homework tasks, or helping clients identify and modify negative automatic thoughts). Both DeRubeis and Feeley (1990) and Feeley and colleagues (1999) found some evidence for a significant association between the use of 'concrete' CBT techniques and better outcomes.

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

Agreeing and monitoring homework is one of the set of 'concrete' CBT skills identified by researchers reviewed above. All forms of CBT place an emphasis

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

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

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

7.2 Psychosocial interventions: review of clinical evidence

7.2.1 Introduction

This review includes all RCTs identified by a systematic search pertaining to the non-pharmacological treatment of depression in people with chronic physical health problems. What distinguishes it from other, apparently similar, reviews is that its focus is solely on people with depression and, in most cases, an intervention that aims to relieve depression. Other systematic reviews have included RCTs of psychosocial interventions that aimed to

prevent onset or complications of physical illness, improve adherence to medication and improve health-related quality of life (for example, Fekete, Antoni & Schneiderman, 2007).

Current practice

At present there are several limitations to the treatment of depression in people with chronic physical problems. First, depression is not sufficiently recognised in such people and therefore no treatment is offered. This may be a particular problem in a number of physical health settings and is reviewed in the Introduction and addressed more fully in Chapter 5 on case identification. Second, specialist treatment, such as that used in the treatments reviewed in this section, may not be available in some primary and particularly secondary acute care settings which have not traditionally offered such treatments although even here the position is changing (RCP&RCPsych, 2003). Third, some people are unwilling to agree to specific treatment for depression because they do not believe that it can be effective.

Definition and aim of review

This review considered any psychosocial intervention (either alone or in combination with pharmacotherapy) aimed at treating depression for people with chronic physical health problems. The review also considered interventions aimed at treating psychosocial stressors to ensure that all interventions aimed at treating people with depression and chronic physical health problems were covered. The effects of focusing the intervention on depression, modifying the intervention to account for the chronic physical health problem and broadly targeting psychosocial stressors were explored *a priori* in a sub-group analysis. The review did not consider interventions with a primary aim of managing the chronic physical health problem as this is outside the scope of this guideline.

Studies met criteria for depression if participants had a diagnosis of depression or if they screened positive for depression on a recognised depression scale. Studies that did not report a diagnosis of depression or were not screened for depression but the treatment and control groups had a mean baseline depression score above the clinical cut-off on a recognised depression scale were also considered (see Table 27 for cut-offs used for each scale). However, studies were also included if they scored just below the cut-off criteria for mild depression because the GDG considered that these represented the category of subthreshold depressive symptoms that is associated with impaired health-related quality of life and increased healthcare costs in people with chronic physical health (This is set out in Appendix 12). Previous reviews highlight that the majority of studies of psychosocial interventions for people with chronic physical health problems do not use a sample with an established diagnosis of depression and focus on other factors such as quality of life (for example Fekete *et al.,* 2007). In order to include this potentially important evidence (and because of the evidence of increased poor functioning people with subthreshold depressive symptoms

and chronic physical health problems) studies of interventions for subthreshold depressive symptoms and chronic physical health problems were also considered. A sensitivity analysis was performed removing the studies that did not recruit participants for depression.

Table 27 Cut off points used for each of the identification tools (adapted from, for example, Pignone *et al*., 2002; Gilbody *et al*., 2007)

Table 27 Cut off points for depression scales

Scale	Cut off points
BDI 21 items	 13
PHQ-9 9 items	 10
GHQ 28 items 12 items	 5 3
HADS-D	10
CES-D	16
GDS 30 item 15 items	 10 5
Zung	50

This review considered all comparisons, including other psychosocial or pharmacological interventions and control conditions such as standard care and waitlist control. The outcomes of interest were depression, quality of life and physical health outcomes.

Definition of interventions
The following definitions of psychosocial interventions were adopted for the guideline.

Guided self-help

Guided self-help (GSH) is defined as a self-administered intervention designed to treat depression, which makes use of a range of books or other self-help manuals based on an evidence-based intervention and designed specifically for the purpose. A healthcare professional (or para-professional) facilitates the use of this material by introducing, monitoring and reviewing the outcome of such treatment. This intervention would have no other therapeutic goal, and would be limited in nature, usually no less than three contacts and no more than six. (One study in this guideline *pure self-help* in which self help materials are given to a patient but there is very limited or not support in the sue of the materials other that that contained in the material itself).

Peer (self-help) support

Peer (self-help) support is defined as any intervention where an individual (in groups or pairs) with a common condition (e.g. a mental or physical disorder)

or the relatives or carers of individual with a common condition meet to provide emotional or practical support to each other. Typically there is no direct professional input to the group although there may be some limited psycho-educational input. Support can be individual or group based although most interventions fall into the later category. Meetings can be opened ended or time limited and generally follow a structure provide by a professional or patient support organisation.

Computerised cognitive behaviour therapy

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

Physical activity

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

Cognitive behavioural therapies

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

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

We have also included trials based looking at group CBT which emerged from the "Coping With Depression" model (Lewinsohn *et al.*, 1984). This approach often has a strong psycho-educational component focused on

teaching people techniques and strategies to cope with the problems that are assumed to be related to their depression.

Couple-focused therapies

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

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

Problem-solving therapy

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

Interpersonal therapy

Interpersonal therapy (IPT) was defined as a discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where the therapist and patient:

- Work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems.
- Seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

Counselling

The definition used in this guideline followed that of the British Association for Counselling and Psychotherapy (BACP) which defined counselling as 'a systematic process which gives individuals an opportunity to explore, discover and clarify ways of living more resourcefully, with a greater sense of well-being.

Psychodynamic interventions

Psychodynamic interventions were defined as psychological interventions, derived from a psychodynamic/psychoanalytic model, and:

- which seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

- where therapist and patient explore and gain insight into conflicts and howthese are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference).
- where patients are given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with a technical focus on interpreting and working though conflicts.
- which is non-directive and recipients are not taught specific skills (e.g. thought monitoring, re-evaluating, or problem-solving).

Group existential therapy

Group existential therapy is a model of group therapy which draws on both supportive expressive and existential theory. It is a fixed term or open-ended form of therapy usually for 6 to 8 people. Groups tend to be disorder specific (e.g. cancer) and focus on the development of a supportive network, grief, improve problem solving e coping, enhance a sense of mastery over life and re-evaluate priorities for the future

7.2.2 Databases searched and inclusion/exclusion criteria[16]

Study information for the databases searched and the inclusion/ exclusion criteria can be found in Table 28. The search took a very inclusive approach setting filters only for RCTs and the depression population. Therefore no limits were contained in the search strategy concerning psychosocial interventions in order to minimise the risk of missing relevant references.

Table 28: Databases searched and inclusion/exclusion criteria for clinical evidence.

Electronic databases	CINAHL, CENTRAL, EMBASE, MEDLINE, PSYCINFO
Date searched	Database inception to March 2008
Study design	RCT
Patient population	People with a chronic physical health problem and depression (sample either recruited for depression or the sample had a mean baseline score above clinical cut-off on a recognised depression scale)
Interventions	Any psychosocial intervention aimed at depression or psychosocial stressors
Outcomes	Depression, quality of life, physical health outcomes

7.2.3 Studies considered[1]

Forty-two trials met the eligibility criteria set by the GDG, providing data on 3,636 participants. Of these, all were published in peer-reviewed journals between 1984 and 2008. Fifty-three studies were excluded from the analysis. The most common reason for exclusion was that the population did not meet

[16] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

criteria for depression (further information about both included and excluded studies can be found in Appendix 18).

Of the 42 included trials, 24 recruited participants for depression and chronic physical health problems; 18 did not recruit for depression but the treatment and control arms had a mean baseline depression score above the clinical cut-off on a recognised scale.

Regarding low intensity psychosocial interventions there were: four trials on physical activity met the eligibility criteria of the review and were compared with standard care. Three trials were found on peer (self-help) support and were all compared with standard care, of these three trials, two were also compared with group based cognitive and behavioural interventions. There were three trials on self-help interventions that used cognitive and behavioural principles (two were individual-based and one was group-based). In addition, there was a self-help intervention based on a McMaster model of family functioning. There were three trials on health education versus standard care. Of these, two studies had additional psychosocial components added to the health education intervention. The review also found one trial on social support and one trial on relaxation training. These interventions were compared with standard care. The review did not find any included studies on CCBT. A full review of CCBT in depression can be found in section 7.1 of the Depression Update Guideline (NCCMH, forthcoming), which updated the NICE Technology Appraisal 51 (2002).

For high intensity interventions, there were eight trials in total on individual-based cognitive and behavioural intervention. Of these trials, five were compared with standard care, three were compared with counselling and one was compared with supportive psychotherapy. In total there were 11 trials on group-based cognitive and behavioural interventions. Of these trials, ten were compared with standard care and five were compared with other psychosocial interventions. Of these, three were compared with health education and two were compared with peer (self-help) support. Four trials on interpersonal therapy (IPT) were included: two comparing IPT with standard care and one comparing IPT with enhanced standard care. A further one study compared IPT with individual based-cognitive and behavioural intervention and supportive psychotherapy. One trial looked at counselling versus standard. There was one trial on problem solving, one trial on supportive psychotherapy and three trials on group existential therapy.

In addition, the review found a total of four studies that looked at psychosocial interventions in combination with pharmacological treatment compared with psychosocial interventions alone. Of these studies one also looked at psychosocial interventions in combination with pharmacological treatment compared with medication alone. The same study also explored psychology alone versus medication alone.

7.2.4 Clinical evidence for physical activity

Study information table for the trials of physical activity are presented in Table 29. Evidence from the GRADE profiles are summarised in Table 30. The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Table 29. Study information table for trials of physical activity

	Physical activity versus standard care
Total no. of trials (total no. of participants)	4 RCTs (N = 167)
Study ID	COURNEYA2007* KOUKOUVOU2004 LAI2006* SIMS2009
Physical health problem	Cancer COURNEYA2007* Cardiovascular disease (KOUKOUVOU2004) Stroke (LAI2006*, SIMS2009)
Baseline severity (mean)	BDI KOUKOUVOU2004: M ~ 18.4; S.D. ~ 4.88 GDS LAI2006*: M ~ 3.6; S.D. ~ 2.75 CES-D overall: M ~ 16.43; S.D. ~ 9.03 SIMS2009: M ~ 19.35; S.D. ~ 8.18 COURNEYA2007*: M ~ 13.50; S.D. ~ 9.87
Average age	53 years
Treatment length	10-weeks (SIMS2009) 12-weeks (LAI2006*) 12-weeks (COURNEYA2007*) 6-months (KOUKOUVOU2004)
Frequency of session	2-4 sessions per week (all studies)
Duration of sessions	Up to 1 hour (KOUKOUVOU2004, COURNEYA2007*) LAI2006*, SIMS2009: no information
Length of follow up	6 months (COURNEYA2007*, SIMS2009)
Note. *Below clinical cut-off on a depression scale	

Population

One study in the review recruited participants for depression and chronic physical health problems (SIMS2009). The treatment and comparison arm in one study met minimal clinical cut-off for depression on a recognised scale at baseline (KOUKOUVOU2004). Two studies were just below the clinical cut-off for depression (LAI2006, COURNEYA2007).

Intervention

Three of the interventions were primarily aimed at reducing depression (COURNEYA2007, LAI2006, SIMS2009) and one focused on reducing psychosocial stressors and improving quality of life (KOUKOUVOU2004). All interventions included supervised physical activity; two involved both aerobic physical activity and resistance training (KOUKOUVOU2004, SIMS2009) and one involved aerobic physical activity only (LAI2006). In COURNEYA2007 there were two physical activity intervention arms, one of which involved aerobic training alone and the other involved resistance training alone; in this review the two groups were combined. The intervention in SIMS2009 involved group based physical activity and in KOUKOUVOU2004 the intervention involved bother group- and individual based physical activity. LAI2006 was delivered in individual based physical activity and it was not clear what the mode of delivery was in COURNEYA2007.

Comparison

The three physical activity interventions were compared with standard care for the physical health problem where there was potential for referral to, or treatment by a mental health service (LAI2006, COURNEYA2007, SIMS2009). For KOUKOUVOU2004 no further information was provided other than the study used a control condition.

Outcomes

The outcomes included were self-report outcomes on depression, including the BDI (KOUKOUVOU2004,), CES-D (COURNEYA2007, SIMS2009) and the GDS (LAI2006); quality of life (COURNEYA2007, LAI2006, KOUKOUVOU2004) and physical health outcomes (KOUKOUVOU2004).

Table 30. Evidence summary for trials of physical activity versus standard care

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	361 (3)	⊕⊕OO low[1,2]	SMD -0.58 (-1.2 to 0.05)
Depression (end of treatment: change score)	164 (3)	⊕⊕OO low[1,2]	SMD -0.29 (-0.6 to 0.03)
Non remission (below cut off)	139 (2)	⊕⊕OO low[1,2]	RR 0.64 (0.31 to 1.3)
Non remission (below cut off: 6 month follow-up)	125 (2)	⊕⊕⊕O moderate[2]	RR 0.4 (0.23 to 0.69)
Quality of life (end of treatment)	361 (3)	⊕⊕OO low[1,2]	SMD -0.62 (-1.28 to 0.03)
Physical health outcomes (end of treatment) - Resting HR (beats/min)	26 (1)	⊕⊕⊕O moderate[3]	SMD -0.58 (-1.39 to 0.23)

[1] I squared > 50%

[2] Population just below clinical cut-off for depression (for some studies)

[3] Sparse data

The review found physical activity to have a moderate effect compared with standard care (SMD = -0.58; -1.20 to 0.05) for depression at end of treatment. There was also a moderate effect on quality of life at end of treatment (SMD = -0.62;-1.28 to 0.03). The effect estimates for both outcomes were of borderline statistical significance.

7.2.5 Clinical evidence for peer (self-help) support

Study information table for the trials of peer (self-help) support are presented in Table 31. Evidence from the GRADE profiles are summarised in Table 32 and Table 33. The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Table 31. Study information table for trials of peer (self-help) support

	Peer (self-help) support versus standard care	Peer (self-help) support versus group based cognitive and behavioural therapy
Total no. of trials (total no. of participants)	3 RCTs (N = 191)	2 RCTs (N = 89)
Study ID	EVANS1995 KELLY1993 SIMONI2007	EVANS1995 KELLY1993
Physical health problem	HIV (KELLY1993, SIMONI2007) Cancer (EVANS1995)	HIV (KELLY1993) Cancer (EVANS1995)
Baseline severity: mean (S.D.)	CES-D overall: M ~ 25.92; S.D. ~ 9.02 EVANS1995: M ~ 28.45; S.D. ~ 7.70 KELLY1993: M ~ 29.55; S.D. ~ 7.55 SIMONI2007: M ~ 19.75; S.D. ~ 11.80	CES-D overall: M ~ 27..83; S.D. ~ 7.90 EVANS1995: M ~ 28.10; S.D. ~ 7.90 KELLY1993: M ~ 27.55; S.D. ~ 7.90
Average age	43.7 years	44.0 years
Treatment length	8 weeks (EVANS1995, KELLY1993) 12 weeks (SIMONI2007)	8 weeks (EVANS1995, KELLY1993)
Frequency of sessions	1 session per week (EVANS1995, KELLY1993) 1 session every 2 weeks (SIMONI2007)	1 session per week (all studies)
Duration of sessions	1 hour (EVANS1995, SIMONI2007) 1 ½ hours (KELLY1993)	1 hour (EVANS1995) 1 ½ hours (KELLY1993)
Longest length of follow up	3 months (SIMONI2007, KELLY1993) 6 months (EVANS1995)	3 months (KELLY1993) 6 months (EVANS1995)

Population

Two trials recruited participants for depression and chronic physical health problems (KELLY1993, EVANS1995). One trial did not recruit participants for depression but the treatment and comparison arms met minimal criteria for depression at baseline on a recognised scale (SIMONI2007).

Intervention

The peer (self-help) support interventions included in this review were primarily aimed at reducing the psychosocial stressors associated with the chronic physical health problem. Participants were encouraged to share their feelings associated with having a chronic physical health problem and members chose different topics to be discussed at group meetings. While KELLY1993 and EVANS1995 focused on the experience of sharing among the group as a whole, SIMONI2007 placed emphasis on assigning members to one peer.

Comparison

All the studies compared peer (self-help) support with standard care. In standard care there was potential for participants to be referred to or be treated by a mental health service (EVANS1995, KELLY1993, SIMONI2007). EVANS1995 and KELLY1993 also compared peer (self-help) support with group based cognitive and behavioural intervention.

Outcome

All studies used the CES-D self-report outcome as a measure of depression. Only one study reported physical health outcomes (SIMONI2007) and no study reported health-related quality of life measures.

Table 32. Evidence summary of peer (self-help) support versus standard care

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Effect estimate
CES-D (end of treatment)	191 (3)	⊕⊕⊕O moderate[1]	SMD -0.32 (-0.62 to -0.03)
CES-D (6 month follow-up)	202 (3)	⊕⊕⊕O moderate[1]	SMD -0.19 (-0.74 to 0.37)
Physical health outcomes: HIV-1 RNA viral load (end of treatment)	123 (1)	⊕⊕⊕O moderate[2,3]	SMD 0.26 (-0.09 to 0.62)
Physical health outcomes: HIV-1 RNA viral load (3 month follow-up)	118 (1)	⊕⊕⊕O moderate[2,3]	SMD 0.17 (-0.2 to 0.53)

[1] I squared > 50%
[2] Compatible with benefit and no benefit
[3] Sparse data

The review found peer (self-help) support to have a small and statistically significant effect on depression at end of treatment compared with standard care for people with depression and chronic physical health problems as measured by the CES-D (SMD = -0.32; -0.62 to -0.03; WMD = -4.50; -7.30 to -1.30).

A sensitivity analysis was performed removing one study (SIMONI2007) which not did recruit participants for depression and chronic physical health problems but which the treatment and comparison groups had a mean baseline depression score above the clinical cut-off on a recognised depression scale. The review found that for participants recruited for depression and chronic physical health problems, peer (self-help) support had a large effect on depression(as measured by the CES-D) at end of treatment (SMD = -0.93; -1.39 to -0.48 and WMD =-8.33; -11.94 to -4.78).

Table 33. Evidence summary of peer (self-help) support versus group based cognitive and behavioural intervention

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	89 (2)	⊕⊕⊕O moderate[1]	SMD -0.23 (-0.66 to 0.20)
Depression (6 month follow up)	92 (2)	⊕⊕⊕O moderate[1]	SMD -0.34 (-0.76 to 0.08)

[1] Compatible with benefit and no benefit

In the comparison of peer (self-help) support with group based cognitive and behaviour intervention there was a small effect on depression at end of treatment in favour of peer (self-help) support (SMD = -0.23, -0.66 to 0.20; WMD = -2.47, -6.46 to 1.53). However, this effect was statistically non-significant. The results at follow up were consistent with the results at end of treatment (SMD = -0.34, -0.76 to 0.08; WMD = -4.48, -10.11 to 1.14).

7.2.6 Clinical evidence for self-help intervention based on cognitive and behavioural principles

Study information table for the trials of self-help interventions based on cognitive and behavioural principles are presented in Table 34. Evidence from the GRADE profiles are summarised in Table 35. The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Table 34. Study information table for trials of self-help-based cognitive and behavioural interventions

	Self-help-based cognitive and behavioural interventions versus standard care
Total no. of trials (total no. of participants)	3RCTS (N =103)
Study ID	BARTH2005 BRODY 2006 LANDREVILLE1997
Physical health problem	Older adults with functional impairment (LANDREVILLE1997) Older adults with macular degeneration (BRODY2006) Cardiovascular disease (BARTH2005)
Baseline severity (mean)	BDI overall: M ~ 20.43; S.D. ~ 7.61 BARTH2005: M ~ 20.14; S.D. ~ 5.91 LANDREVILLE1997: M ~ 20.73; S.D. ~ 9.30 GDS-15 BRODY 2006: M~7.65, S.D. ~ 2.27
Average age	57 years
Treatment length	4 weeks (BARTH2005, LANDREVILLE1997) 6 weeks (BRODY2006)
Frequency of session	1 session per week (LANDREVILLE1997) Details not reported: BARTH2005, BRODY2006
Duration of sessions	15 minutes (LANDREVILLE1997) 50 minutes (BARTH2005) Details not reported: BRODY2006
Length of follow up	None

Three self-help interventions based on cognitive and behavioural principles were included in the review (BARTH2005, BRODY2006, LANDREVILLE1997), two were individual based self-help (BARTH2005, LANDREVILLE1997) and one was group based self-help (BRODY2006). Two were compared with standard care (BARTH2005, LANDREVILLE1997). The standard care arm provided the potential for participants to receive treatment from mental health services. In the third study, BRODY2006 collapsed standard care and an audiotape health education group as there were no differences between the groups. In two of the studies participants were recruited for depression (BARTH2005, LANDREVILLE1997). In BRODY2006, a subset of participants who completed treatment and who had depression at baseline were analyzed. The outcome of depression reported in the study was

the self-report measures of the BDI (BARTH2005 and LANDREVILLE1997) and the GDS (LANDREVILLE1997). The observer-rated HAM-D was also reported (BARTH2005). LANDREVILLE1997 also reported physical health outcomes.

In addition to the three cognitive and behavioural self help interventions, the review found one self-help intervention based on the McMaster model of family functioning (STEIN2007) which was compared with no further treatment for depression. This study recruited participants for depression. The chronic physical health problems included were: HIV (STEIN2007). The outcomes of depression reported in the study were the dichotomous outcomes of non-remission and non-response as assessed by the BDI (STEIN2007).

Table 35. Evidence summary of self-helped based cognitive and behavioural principles versus standard care

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	103 (3)	⊕⊕⊕O moderate[1]	SMD -0.40 (-0.79 to 0.00)
Physical health outcome - Visual Functioning Questionnaire	32 (1)	⊕⊕OO low[1,2,3]	SMD -0.44 (-1.16 to 0.29)

[1] Only looked at sub-group of depression (in one study) original sample not stratified for depression
[2] Sparse data
[3] Effect compatible with benefit and no benefit

Self-help interventions based on a cognitive and behavioural model compared with control had a moderate and marginally statistically non-significant effect on depression at end of treatment (SMD = -0.40; -0.79 to 0.00).

A self-help intervention based on the McMaster model of family functioning found no effect on depression as measured by non-response (RR = 1.03; 0.84 to 1.26) and non-remission (RR = 0.97; 0.79 to 1.19).

7.2.7 Clinical evidence for health education

Study information table for the trials of health education are presented in Table 36.

Table 36. Study information table for trials of health education

	Health education versus standard care	Health education plus additional psychosocial components versus standard care
Total no. of trials (total no. of participants)	1 RCT (N = 160)	2 RCTs (N = 89)
Study ID	HECKMAN2007	BALFOUR2006 CLARK2003*
Physical health problem	HIV	HIV (BALFOUR2006) Stroke (CLARK2003)
Baseline severity: mean	BDI: M ~ 22.10; S.D. 1.10	CES-D: M ~ 29.75; S.D. 7.90 (BALFOUR2006) GDS: M ~ 3.85; S.D. ~ 2.75 (CLARK2003)
Average age	43 years	56 years
Treatment length	8 weeks	4 weeks (BALFOUR2006) 20 weeks (CLARK2003)
Frequency of sessions	1 session per week	1 session per week (BALFOUR2006) 3 sessions over 5 months (CLARK2003)
Duration of sessions	1½ hours	Up to 1½ hours (all studies)
Longest length of follow up	8 months	None
Note: * Below clinical cut-off for depression		

The review found there three trials on health education. One trial compared health education with standard care for the physical health problem (HECKMAN2007) and two trials compared health education plus additional psychosocial components with standard care (BALFOUR2006, CLARK2003). HECKMAN2007 did not recruit participants for depression but the treatment and standard care arm had a mean baseline depression score that met clinical cut-off. BALFOUR2006 did not recruit participants for depression but reported outcomes for a sub-group with depression. The treatment and comparison arm in CLARK2003 scored just below the minimal cut-off for depression. The outcomes reported and extracted were self-report measures of depression including the BDI (CLARK2003, HECKMAN2007) and CES-D (BALFOUR2006); one study reported quality of life (CLARK2003).

Health education compared with standard care had a small but statistically non-significant effect on depression at end of treatment as measured by the BD1-21 item (SMD = -0.26; -0.58 to 0.06; WMD = -1.64; -3.60 to 0.32); this is based on one study. This effect was diminished at 8-month follow-up (SMD = 0.00;-0.34 to -0.35; WMD = 0.03; -2.34 to 2.40). Similarly health education with additional psychosocial components had a small and statistically non-

significant effect on depression at end of treatment (SMD = -0.24; -0.66 to 0.18).

7.2.8 Clinical evidence for relaxation training

The review found one study on relaxation training delivered over 12 weeks and was compared with an active control (YU2007). Participants were not recruited for depression but the treatment and control group has a mean baseline depression score above clinical cut-off on the HADS (M ~ 12.18; S.D. ~ 3.61). The chronic physical health problem included in the study was cardiovascular disease. Depression was measured using the HADS and quality of life was measured using Chronic Heart Failure Questionnaire. No other relevant outcomes reported.

The study found relaxation training to have a small and statistically significant effect on depression at end of treatment in comparison to an active control (SMD -0.37; -0.73 to -0.01). There was a similar effect for quality of life but were not statistically significant (SMD -0.24; -0.56 to 0.08).

7.2.9 Clinical evidence for social support

The review found one study on social support (DESR0SIERS2007). The intervention was compared with standard care for the physical health problem where participants were visited at home by a researcher for a similar number of visits as the treatment group. The participants were not recruited for depression but the treatment and standard care group had a mean baseline depression score that met clinical cut-off on the CES-D (M ~ 17.40). The physical health problem included in the review was stroke. The outcomes reviewed were the CES-D and quality of life.

Social support compared with a standard care had a moderate and statistically significant effect on depression at end of treatment as measured by the CES-D (SMD =-0.67; -.1.21 to -0.13; WMD = -4.90; -8.71 to -1.09).

7.2.10 Clinical evidence for high intensity cognitive and behavioural interventions

Study information for the trials of individual-based cognitive behavioural interventions Table 37 and group-based cognitive and behavioural interventions are presented in Table 40, respectively. Evidence from the GRADE profiles for individual-based cognitive behavioural interventions versus standard care are summarised in Table 38 and versus counselling are summarised in Table 39. Evidence from the GRADE profiles for group-based cognitive behavioural interventions versus standard care are summarised in Table 41 and versus other psychosocial interventions are summarised in Table 42. The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Individual-based cognitive and behavioural interventions

Table 37. Study information table for trials of individual-based cognitive and behavioural interventions

	Individual-based cognitive behavioural interventions versus standard care	Individual-based cognitive behavioural interventions versus counselling
Total number of studies (number of participants)	5 RCTs (N= 404)	3 RCTs (404)
Study ID	ADDOLORATO2004 FOLEY1987 MANNE2007 MOHR2000 SAVARD2006	BROWN1993 MANNE2007 MOHR2005
Baseline severity	BDI overall M ~ 18.89; S.D. ~ 9.58 FOLEY1987: M ~ 23.05; S.D. ~ 14.00 MANNE2007: M ~ 13.01; S.D. ~ 8.46 SAVARD2006: M ~ 20.62; S.D. ~ 6.27 POMS-D overall M ~ 30.5; S.D. = MOHR2000: M ~ 30.50; S.D. ~ 12.25 ADDOLORATO2004 did not report baseline Zung scores	BDI overall M ~ 14.33; S.D. ~ BROWN1993: M ~ 14.66; S.D. ~ 6.55 MANNE2007: M ~ 13.99; S.D. ~ 8.46 MOHR2005: M ~ 27.66; S.D. 7.85
Physical health problem	Multiple sclerosis (MOHR2000, FOLEY1987) Cancer (MANNE2007, SAVARD2006) Coeliac disease (ADDOLORATO2004).	Cardiovascular disease (BROWN1993) Cancer (MANNE2007) Multiple sclerosis (MOHR2005)
Age (average)	42.6 years	50 years
Treatment length	7 weeks (average)	12 weeks (average)
Frequency of session	1 session per week (FOLEY1987, MOHR2000, SAVARD2006) 1 session per fortnight: (ADDOLORATO2004) MANNE 2007 did not provide details	1 session per week (all studies)
Duration of sessions	Up to 1 hour (MANNE2007, MOHR2000) Up to 1 ½ hours (SAVARD2006) ADDOLORATO2004 and FOLEY1987 did not provide details	Up to 1 hour (all studies)
Length of follow up	6 months (MANNE2007)	6 months (MOHR2001) 12 months (MOHR2005) 15 months (BROWN1993)

Population

Of the seven trials on individual-based cognitive and behavioural interventions, five recruited participants for depression and chronic physical health problems (ADDOLORATO2004, BROWN1993, MOHR2000,MOHR2005, SAVARD2006); two did not recruit participants for depression but the treatment and comparison arm had a mean baseline score

that met clinical cut-off for depression on a recognised scale (FOLEY1987, MANNE2007).

Intervention

The interventions included in the review were aimed at treating depression (BROWN1993, MOHR2005), treating depression and modified for the chronic physical health problem (ADDOLORATO2004, MOHR2000, SAVARD2006) or aimed at reducing the impairment of psychosocial stressors (FOLEY1987, MANNE2007).

Comparison

For individual-based cognitive and behavioural interventions, five studies compared the treatment with standard care where participants could potentially be referred to mental health service and receive treatment for depression (ADDOLORATO2004, FOLEY1987, MANNE2007, MOHR2000, SAVARD2006). For example, the comparison group in MANNE2007 received standard psychosocial care, this could have involved a referral to a psychiatrist or psychologist by their physician. In MOHR2000 the comparison group involved standard care through their patient's health maintenance organisation; one patient was an antidepressant medication and another was in ongoing weekly psychotherapy.

Three studies compared individual-based cognitive and behavioural interventions with counselling (BROWN1993, MANNE2007, MOHR2005).

Outcomes

For individual-based cognitive and behavioural interventions, two studies reported depression outcomes using the HAM-D (SAVARD2006, MOHR2005). The remaining studies reported depression using self-report measures: five used the BDI (FOLEY1987, MANNE2007, SAVARD2006, BROWN1993, MOHR2005) and one used the POMS-D (MOHR2000).

One study reported physical health outcomes (SAVARD2006) and one study reported quality of life (SAVARD2006).

Table 38. Evidence summary of individual-based cognitive and behavioural interventions versus standard care

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Effect
Depression (end of treatment)	338 (4)	⊕⊕⊕O moderate[1]	SMD -0.55 (-0.97 to -0.13)
Non-remission (below cut-off)	66 (1)	⊕⊕⊕O moderate[2]	RR 0.63 (0.23 to 1.71)
Depression (6 month follow up)	233 (1)	⊕⊕⊕O moderate[2]	SMD -0.07 (-0.33 to 0.18)
Quality of life (end of treatment)	37 (1)	⊕⊕⊕O moderate[2, 3]	SMD 0.00 (-0.65 to 0.65)
Physical health outcome - CD4 cell count	37 (1)	⊕⊕⊕O moderate[2, 3]	-0.09 (-0.74 to 0.56)

[1] I squared = 56.4%
[2] Sparse data
[3] Compatible with benefit and no benefit

The review found that for people with depression and chronic physical health problems, individual-based cognitive and behavioural interventions had a moderate and statistically significant effect on depression at end of treatment when compared with standard care (SMD = -0.55; -0.97 to -0.13) for people for people who ranged from subthreshold depressive symptoms to mild depression. Similar results were found for non-remission but the results were not statistically significant and were based on one study (RR = 0.63; 0.23 to 1.71). The quality of evidence was moderate as the heterogeneity for the main outcome measure of depression was just above 50%.

A sensitivity analysis was performed removing those studies that did not recruit participants for depression. This increased the effect size for depression at end of treatment from a moderate to large effect (SMD = -0.84; -1.34 to -0.34).

Table 39. Evidence summary of individual-based cognitive and behavioural interventions versus counselling

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	364 (2)	⊕⊕⊕O moderate[1]	SMD -0.23 (-0.62 to 0.17)
Depression (change score: end of treatment)	40 (1)	⊕⊕⊕O moderate[2]	SMD 0.30 (-0.32 to 0.92)
Physical health - CD4 cell count	26 (1)	⊕⊕⊕O moderate[2]	SMD 0.34 (-0.44 to 1.11)

[1] Compatible with benefit and no benefit
[2] Sparse data

There was a small difference in effect size between individual-based cognitive and behavioural interventions and counselling for depression at end of treatment (SMD = -0.23; -0.62 to 0.17) in favour of individual-based cognitive and behavioural intervention; however this difference was statistically non-

significant. At a follow-up of up to six months, this difference was reduced (SMD = -0.01; 0.23 to 0.22) however it remained statistically non-significant.

In one study (BROWN1994), only a change score could be calculated because there were statistically significant differences in depression scores at baseline between the two intervention groups. This study was therefore analysed separately. In this study there was a small but statistically non-significant difference in effect size between the two interventions in favour of counselling (SMD = 0.34, -0.44 to 1.11; WMD = 2.70, -2.79 to 8.19).

In addition there was one trial on individual-based cognitive and behavioural intervention versus supportive psychotherapy (MARKOWITZ1998). This study found there to be no statistically significant differences between individual-based cognitive and behavioural interventions and supportive psychotherapy. However, the direction of benefit was slightly in favour of supportive psychotherapy for depression at end of treatment (SMD = 0.16; -0.39 to 0.71)

Group based cognitive and behavioural interventions

Table 40. Study information table for trials of group-based cognitive and behavioural interventions

	Group-based cognitive and behavioural interventions versus standard care	Group-based cognitive and behavioural interventions versus other psychosocial interventions
Total number of studies (number of participants)	10 RCTs (N = 632)	5 RCTs (N = 465)
Study ID	ANTONI2006* CHESNEY2003 DAVIS1984 EVANS1995 HECKMAN2007 HENRY1997* KELLY1993 LARCOMBE1984 LUSTMAN1998 LII2007	CHESNEY2003:health education EVANS1995:peer (self-help) support HECKMAN2007: health education KELLY1993: peer (self-help) support KUNIK2008: health education
Baseline severity	<u>BDI overall: M ~ 18.96; S.D. ~ 7.94</u> ANTONI2006*: M ~ 12.00; S.D. ~ 8.60 DAVIS1984: M ~ 20.75; S.D.s not reported HECKMAN2007: M ~ 22.51; S.D. ~ 10.30 HENRY1997*: M ~12.22; S.D. ~ 3.69 LARCOMBE1984: M ~ 28.22; S.D. ~ 7.16 LUSTMAN1998: M ~ 23.00; S.D. ~ 8.50 LII2007: M ~ 14.04; S.D. ~ 9.41 <u>CES-D overall: M ~ 24.90; S.D. ~ 8.35</u> CHESNEY2003:M ~ 17.40; S.D. ~ 9.40 EVANS1995: M ~ 28.10; S.D. ~ 7.90 KELLY1993: M ~ 29.20; S.D. ~ 7.75	<u>BDI overall: M ~ 22.61; S.D. ~ 11.51</u> HECKMAN2007: M = 22.94; S.D. = 10.81 KUNIK2008: M ~ 22.28; S.D. ~ 12.29 <u>CES-D overall M ~ 24.15; S.D. ~ 8.45</u> CHESNEY2003:M ~ 16.80; S.D. ~ 9.55 EVANS1995: M ~ 28.10; S.D. ~ 7.90 KELLY1993: M ~ 27.55; S.D. ~ 7.90
Physical health problem	HIV (ANTONI2006*, CHESNEY2003, HECKMAN2007, KELLY1993) EPILEPSY (DAVIS1984) CANCER	HIV (CHESNEY2003, HECKMAN2007, KELLY1993) CANCER (EVANS1995) CARDIOVASCULAR DISEASE

	(EVANS1995) DIABETES (HENRY1997*, LUSTMAN1998) MULTIPLE SCLEROSIS (LARCOMBE1984) RENAL DISEASE (LII2007).	(KUNIK2008)
Age (average)	43.5 years LII2007 did not report age at baseline	42.5 years
Treatment length	8 weeks (average)	8 weeks (average)
Frequency of session	1 session per week (all studies)	1 session per week (all studies)
Duration of sessions	1 hour (EVANS1995, LUSTMAN1998) 1 ½ to 2 hours (ANTONI2006*, CHESNEY2003, DAVIS1984, HECKMAN2007, HENRY1997, LARCOMBE1984, LII2007, KELLY1993)	1 hour (EVANS1995, KUNIK2008) 1 ½ to 2 hours (CHESNEY2003, HECKMAN2007, KELLY1993)
Length of follow up	3 months (KELLY1993) 6 months (EVANS1995, LUSTMAN1998) 8 months (HECKMAN2007) 12 months (ANTONI2006*)	3 months (KELLY1993) 6 months (EVANS1995) 8 months (HECKMAN2007) 12 months (KUNIK2008)
Note. *Below clinical cut-off for depression		

Population

Of the 11 studies of group based cognitive and behavioural interventions, eight recruited participants for depression and chronic physical health problems (CHESNEY2003, DAVIS1984, EVANS1995, HECKMAN2007, KUNIK2008, LARCOMBE1984, LUSTMAN1998, KELLY1993); in the other three studies the participants were not recruited for depression. In these studies, the treatment and control arms in LII2007 had a mean baseline depression score that met clinical cut-off on a recognised scale and in ANTONI2006 and HENRY2007 the groups scored just below the minimal cut-off for caseness on the BDI.

Intervention

Six of the studies included an intervention that was aimed at treating depression (DAVIS1984, EVANS1995, KELLY1993, KUNIK2008, LARCOMBE1984 and LUSTMAN1998). In one study the intervention was aimed at treating depression and was modified for the chronic physical health problem (LII2007). The remaining four studies included an intervention aimed more broadly at reducing psychosocial stressors (ANTONI2006, CHESNEY2003, HECKMAN2007 and HENRY2007).

Comparison

In eight studies, group-based cognitive and behaviour interventions were compared with standard care (CHESNEY2003, DAVIS1984, EVANS1995, HENRY1997, HECKMAN2007, KELLY1993, LARCOMBE1984, LII2007). One trial delivered medication adherence training to both the treatment and control condition (ANTONI2006) and another delivered diabetes education program to both conditions (LUSTMAN1998). In standard care participants had the potential to be referred to mental health services and to receive treatment from mental health services.

In addition, three studies compared group-based cognitive and behavioural intervention with health education (CHESNEY2003, HECKMAN200, KUNIK2008) and two with peer (self-help) support (EVANS1995, KELLY1993).

Outcomes

The majority of outcomes reported in the clinical evidence for group-based cognitive and behavioural interventions were self-report measures of depression at end of treatment such as the BDI (HECKMAN2007, DAVIS1984, KUNIK2008, LARCOMBE1984, HENRY1997, LII2007) and CES-D (CHESNEY2003, KELLY1993, EVANS1995). One study reported depression at end of treatment using the observer-rated HAM-D (LARCOME1984) and one study reported non-remission and non-response using the BDI (LUSTMAN1998). Two studies reported quality of life (KUNIK2008, LII2007). No studies reported usable data on physical health outcomes.

Table 41. Evidence summary of group-based cognitive and behavioural interventions versus standard care

	No. of participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	580 (9)	⊕⊕⊕O moderate[1]	SMD -0.54 (-0.86 to -0.21)
Depression (follow up)	262 (2)	⊕⊕⊕O moderate[3]	SMD -0.17 (-0.42 to 0.07)
Non-remission (below cut off)	52 (1)	⊕⊕⊕O moderate[2]	RR 0.41 (0.22 to 0.75)
Non-response (<50% reduction from baseline)	52 (1)	⊕⊕⊕O moderate[2]	RR 0.51 (0.29 to 0.91)
Quality of life (end of treatment)	48 (1)	⊕⊕⊕O moderate[2][3]	SMD -0.28 (-0.86 to 0.29)

1 Possible publication bias
2 Sparse data
3 Compatible with benefit and no benefit

For people with depression and chronic physical health problems, group-based cognitive and behavioural interventions had a moderate and statistically significant effect on depression at end of treatment in comparison to standard care (SMD = -0.54; -0.86 to -0.21) for people with mild to moderate depression. Similar results were found for non-remission (RR = 0.41; 0.22 to

0.75) and non-response (RR = 0.51; 0.29 to 0.91). The quality of evidence was moderate for depression at end of treatment because there was possible publication bias as indicated by the Egger's test (-3.89, -5.90 to -1.89; p<.05).

Due to the high heterogeneity found for depression at end of treatment (I^2 = 65.75%) a sensitivity analysis was performed removing an outlier (LARCOMBE1984), which had a large effect on depression at end of treatment (SMD = -3.07; -4.49 to -1.65). Removing this study reduced the effect of the intervention on depression from a moderate to a small effect at end of treatment (SMD -0.30; -0.47 to -0.13). Even after removing this study, and looking only at the standard delivery of the intervention (one study delivered the intervention entirely via teleconference), the review still found group-based cognitive and behavioural interventions to have a moderate and statistically significant effect on depression at end of treatment (SMD = -0.42; -0.63 to -0.21). LARCOMBE1984 was removed from all further analyses.

A second sensitivity analysis was performed removing those studies that did not recruit for depression and chronic physical health problems. This sensitivity analysis found a similar effect for group-based cognitive and behavioural interventions on depression at end of treatment compared with standard care for only those studies that recruited for depression and chronic physical health problems (SMD = -0.40; -0.68 to -0.12).

A sub-group analysis was performed to observe the effect of treatment for interventions targeted specifically at depression and for those targeting more broadly at reducing the psychosocial stressors experienced by people with chronic physical health problems. The review found a larger and statistically significant effect on depression at end of treatment for the interventions aimed at depression (SMD = -0.58; -0.95 to -0.21) and a smaller effect on depression that was not statistically significant at end of treatment for interventions that broadly targeted psychosocial stressors (SMD = -0.18; -0.40 to 0.03).

Table 42. Evidence summary of group-based cognitive and behavioural interventions versus other psychosocial interventions

Outcomes	No. of participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression (end of treatment)	465 (5)	⊕⊕⊕O moderate[1]	SMD 0.09 (-0.09 to 0.28)
Depression (follow up)	320 (4)	⊕⊕⊕O moderate[1]	SMD 0.15 (-0.08 to 0.37)

[1] Compatible with benefit and no benefit

Over all there was no difference between group-based cognitive and behavioural interventions and other psychosocial for depression at end of treatment (SMD = 0.09; 95% CI -0.09 to 0.28). In the comparison with peer

(self-help) the direction of effect was towards peer (self-help) support but the difference was not statistically significant (SMD = 0.23; -0.20 to 0.66).

Problem solving

This review found one eligible study on problem solving (Gellis *et al.*, 2008). The population (N = 62) included older adults with a range of medical conditions living in a care home. All participants met DSM-IV criteria for subthreshold depressive symptoms and scored 11 or higher on the HAM-D. The intervention comprised of six sessions of home-based problem solving that were adapted to meet the needs of older adults with a medical illness. Adaptations included the intervention to be brief and relevant to the specific life circumstances of each individual. The comparison used in this study was treatment as usual provided by the care home. Outcomes measured were depression (HAM-D, GDS-15) and quality of life (QoLI). For the purpose of this review the results were narratively reviewed.

Problem solving has a large effect on depression at end of treatment in comparison with treatment as usual for both the HAM-D (SMD = -2.78, -3.49 to -2.07; WMD -10.78, -12.68 to -8.88) and GDS-15 (SMD -1.09, -1.63 to -0.55; WMD -5.33, -8.01 to -3.05). The results were maintained at the six month follow-up, HAM-D (SMD = -2.52, -3.20 to -1.84; WMD = -10.32, 12.35 to -8.29) and GDS-15 (SMD = -0.97, -1.50 to -0.44; WMD = -5.05, -7.60 to -2.50). There was no effect of problem solving on quality of life in comparison to treatment as usual at end of treatment (SMD -0.01, -0.51 to 0.48) or at the six month follow-up (SMD = 0.12, -0.81 to 1.05).

7.2.11 Clinical evidence for interpersonal therapy (IPT)

Study information table for the trials of IPT are presented below and are summarised in Table 43.

Table 43. Study information table for trials of IPT

	IPT versus standard care	IPT versus supportive psychotherapy
Total no. of trials (total no. of participants)	3 RCTs (N = 288)	1 RCT (N = 75)
References	Lesperance *et al.* (2007) Mossey *et al.* (1996) Ransom *et al.* (2008)	Markowitz *et al.* (1998)
Physical health problem	Cardiovascular disease (Lesperance *et al,* 2007) General medical illness in older adults (Mossey *et al.*, 1996) HIV (Ransom *et al.*, 2008)	HIV
Baseline severity	Lesperance *et al.* (2007) HAM-D: M~ 30.02; S.D. ~ 7.04 Mossey *et al.* (1996) GDS: M = 15.6; S.D. = 3.7 Ransom *et al.* (2008) BDI: M = 27.4L S.D. = 11.0	HAM-D: M ~ 20.72; S.D. ~ 4.90
Average age	37 years (Lesperance *et al,* 2007) 44 years (Ransom *et al.*, 2008) 71 years (Mossey *et al.*, 1996)	55 years
Treatment length	12 weeks (Lesperance *et al,* 2007) 10 weeks (Mossey *et al.*, 1996)	12 weeks
Frequency of sessions	1 session per week (Lesperance *et al,* 2007; Mossey *et al.*, 1996) Ransom *et al.* (2008) did not provide details	1 session per week
Duration of sessions	Up to 1 hour (MOSSEY1996, RANSOM2008) Lesperance *et al.* (2007) did not provide details	50 minutes
Longest length of follow up	12 months (MOSSEY1996)	No follow up

Population

Of the three trials on IPT (Lesperance, *et al.,* 2007; Markowitz, *et al*., 1998 and Mossey *et al.,* 1996) all participants were recruited for depression. MOSSEY1996 included a population with subthreshold depressive symptoms and actively excluded major depression. Lesperance and colleagues (2007) and Markowitz and colleagues (1998) including a population with major

depression. Ransom and colleagues (2008) included participants with major depressive disorder or dysthymic disorder.

Intervention

In all of the studies, IPT was aimed at treating the depression. Three studies modified the intervention for the chronic physical health problem (Lesperance *et al.,* 2007, Markowitz *et al.,* 1998, Mossey *et al.,* 1996). Mossey and colleagues (1996) adapted the therapy by making it more intensive by increasing the number of sessions from a range of six to eight sessions to ten sessions and from 30 minutes to 60 minutes in duration. Lesperance and colleagues (2007) adapted the therapy by taking into account the possible constraints of attending intensive therapy for people with depression and chronic physical health problems by allowing up to four sessions to be conducted by telephone. Markowitz and colleagues (1998) adapted the content of the therapy to include psychosocial concerns that may be experienced by patients with depression and HIV. The IPT delivered by Ransom and colleagues (2008) was telephone-administered.

Comparison

Two of the studies compared interpersonal therapy with standard care (Mossey *et al.,* 1996, Ransom *et al.* 2008) or enhanced standard care: clinical management that was given to both the treatment and control group (Lesperance *et al.,* 2007). One study compared IPT with supportive psychotherapy and an individual-based cognitive and behavioural intervention (Markowitz *et al.* 1998).

Outcomes

The outcomes included in the review were the observer-rated depression scale, HAM-D (Lesperance *et al.,* 2007), the self-rated depression scale, GDS (Mossey *et al.,* 1996) and BDI (Ransom *et al.*, 2008) and non-response (Lesperance *et a,,.* 2007, Mossey *et al.,* 1996). Physical health outcomes (Lesperance *et al.,* 2007) were also reported.

A meta-analysis was not possible in the comparison of IPT with standard care because of the heterogeneity between the studies (I^2 = 76.5%). Mossey and colleagues (1996) found for the treatment of mild depression in older adults hospitalised for general medical illness that IPT showed an improvement in remission rates compared with standard care (RR = 0.80; 0.50 to 1.10). Ransom and colleagues (2008) found a small but statistically non-significant effect of IPT in comparison to standard care (SMD = -0.27; -0.72 to 0.17). Lesperance and colleagues (2007) did not find IPT to be superior to clinical management for the treatment of major depression in participants with cardiovascular disease (SMD = 0.21; -0.12 to 0.54),

One study (Markowitz *et al.*, 1998) compared IPT with two other psychosocial interventions: supportive psychotherapy and individual-based cognitive behavioural interventions, and found IPT to have a moderate and statistically

non-significant effect on depression at end of treatment compared with supportive psychotherapy (SMD = -0.54; -1.11 to 0.04) and a moderate and statistically significant effect on depression at end of treatment compared with an individual-based cognitive and behavioural intervention (SMD = -0.66; -1.23 to -0.10).

7.2.12 Clinical evidence for counselling

Study information table for the trials of counselling are presented below and are summarise in Table 44. Forest plots can be found in Appendix 19.

Table 44. Study information on counselling

	Counselling versus standard care
Total no. of trials (total no. of participants)	1 RCT (N = 231)
Study ID	MANNE2007
Physical health problem	HIV
Baseline severity	BDI = 13.49
Average age	50 years
Treatment length	6 weeks
Frequency of sessions	Details not provided
Duration of sessions	1 hour
Length of follow up	6 months

There was one trial on counselling versus standard care (MANNE2007). This study did not recruit participants for depression but the treatment and standard care group met clinical cut-off for depression at baseline.

Counselling versus standard care did not have an effect on depression as measured by the BDI at end of treatment (SMD = -0.14; 0.40 to 0.12 and WMD=-1.09; -3.08 to 0.90); this is based on one study.

There were addition trials on individual-based cognitive and behavioural interventions versus counselling. For the results of these comparisons please see section 1.2.10.

7.2.13 Clinical evidence for group existential therapy

Study information table for the trials of group existential therapy are presented in Table 45 and evidence summaries are presented in Table 46.

Table 45. Study information table for trials of group existential therapy

	Group existential therapy versus standard care or enhanced standard care
Total no. of trials (total no. of participants)	3 RCTS (N =157)
Study ID	KISSANE2007 SIMSON2008 WEISS2003*
Physical health problem	Cancer (KISSANE2007) HIV (WEISS2003) Diabetes (SIMSON2008)
Baseline severity: mean	BDI ~ 10.65 (WEISS2003) HADS: M ~ 11.15; S.D. ~ 2.8 (SIMSON2008) Diagnosis of depression (KISSANE2007)
Average age	45 years
Treatment length	5 weeks (SIMSON2008) 12 weeks (KISSANE2007) 17 weeks (WEISS2003)
Frequency of sessions	1 session per week (all studies)
Duration of sessions	½ hour (SIMSON2008) 1½ hours (KISSANE2007) 2½ hours (WEISS2003)
Length of follow up	None
Note. *Below clinical cut-off for depression	

The included trials on group existential therapy compared the intervention with standard care for the physical health problem where participants could have been referred to or receive treatment from mental health services (SIMSON2008) or enhanced standard care (KISSANE2007, WEISS2003). Enhanced standard care was standard care and in addition, KISSANE2007delivered relaxation training to both the treatment and comparison arm and WEISS2003 also delivered written health education material to both the treatment and standard care group. KISSANE2007 reports outcomes for a sub-group with depression at baseline. The treatment and comparison group in WEISS2003 was below clinical cut-off for depression as measured by the BDI. All participants in SIMSON2008 were screened for depression according to the depression scale, HADS-D. The outcomes of

depression reported were non-remission (KISSANE2003), self-report BDI (WEIS2003), POMS-D (WEISS2003) and HADS-D (SIMSON2008). No other outcomes were reported.

Table 46. Evidence summary for trials for group existential therapy

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect estimate
Depression - BDI-21 (end of treatment)	73 (1)	⊕⊕OO low[1,2,3]	SMD 0.03 (-0.43 to 0.49)
Depression - HADS (change score - end of treatment)	30 (1)	⊕⊕⊕O moderate[2,3]	SMD -0.42 (-1.14 to 0.31)
Non-remission (still meeting diagnosis of depression) - end of treatment	54 (1)	⊕⊕OO low[2,3,4]	RR 0.64 (0.37 to 1.11)

[1] Subthreshold depressive symptoms
[2] Sparse data
[3] Effect compatible with benefit and no benefit
[4] Outcomes reported for a subgroup

The review found no effect on depression (as measured by the BDI) at end of treatment for group existential therapy compared enhanced standard care (SMD = 0.03; -0.43 to 0.49; WMD = 0.20; 3.01 to 3.41); this was based on one study (WEISS2003). One study reported a change score using the HADS and showed similar results (SMD = -0.42; -1.14 to 0.31) WMD -1.90; -5.05 to 1.25) (SIMSON2008). In addition there was a moderate effect for non-remission but this effect was statistically non-significant and based on low quality evidence (RR = 0.64; 0.37 to 1.11).

7.2.14 Clinical evidence from effectiveness trials of cognitive and behavioural interventions

There was one study that met criteria for an effectiveness trial of cognitive and behavioural interventions, Enhancing Recovery in Coronary Heart Disease (ENRICHD). This study used a different methodological approach from the efficacy studies reviewed above and therefore was not included in the meta-analysis.

The ENRICHD study

Population

The chronic physical health problem investigated in this study was myocardial infarction (MI). Participants were included in the study if they had an MI within 28 days before enrolment in the study. Participants were also selected if they had a DSM-IV diagnosis of current depressive episode measured using a semi-structured interview developed for ENRICHD. The sample also consisted of participants who had low perceived social support in addition to their depression or on its own. Of the 2,481 participants who were

randomised, 39% were depressed, 26% had low perceived social support and 34% had both. The results of the narrative review focuses only on the sub-group of participants with depression.

Intervention

For participants with depression, individual CBT was delivered according to Beck and colleagues (1979) and Beck (1995) and, where feasible, was also delivered in a group format. For participants with low perceived social support, CBT was adapted to meet their needs and was supplemented with techniques based on social learning theory. For these participants, detailed assessments were provided to tailor the intervention to the individual. The primary focus of this intervention was on strengthening network ties. Participants with both depression and low perceived social support received an intervention with elements from both treatments; therefore they did not receive a purely cognitive and behavioural intervention but had elements that encouraged developing social relationships.

The maximum duration of individual CBT was 6 months. Group CBT could extend to an additional 12 weeks. Group CBT was only delivered if practical after the participant completed at least three sessions of individual therapy. Some participants receiving group CBT discontinued individual therapy, perhaps demonstrating their preference for group-based CBT.

For those participants who scored more than 24 on the HAM-D or showed a less than 50% reduction in BDI scores after 5 weeks were also referred for pharmacotherapy. Participants received sertraline that was initiated at 50 mg per day and adjusted to a maximum of 200 mg per day if needed. Other SSRIs or nortriptyline were considered for participants where sertraline was not appropriate. Adjunctive pharmacotherapy was delivered for 12 months.

Comparison

Individual- and/or group-based CBT was compared with treatment as usual, which consisted of the standard care provided by the participant's physician. However, physicians were notified in writing if their patients were enrolled in the study with either depression or low perceived social support or both and were contacted immediately if their patients were suicidal or severely depressed. Informing physicians that patients in the usual care arm were depressed may have biased the results. With the physicians aware of their patient's depression status, they may have been more likely to treat their patient for depression providing more of an enhanced care comparison.

Outcomes

Outcomes were collected by researchers who were blinded to the participants' treatment group. Depression was measured 6 months after randomisation using the observer-rated measure, HAM-D, and the self-report measure, BDI.

Results

At 6 months after randomisation, CBT had a modest and statistically significant effect on depression at end of treatment compared with treatment as usual for a sub-group of participants with depression only (SMD = -0.35, -0.46 to -0.24). These results were similar for depression as measured by the HAM-D (SMD = -0.26, -0.37 to -0.16). These results are only slightly smaller than those found in the efficacy studies for both group based and individual based cognitive and behavioural interventions even when taking into consideration that the efficacy study was compared with enhanced care as physicians were told if their patients were depressed. A limitation of the study is that the intervention was not purely cognitive and behavioural but also included aspects of social networking and interacting.

7.2.15 Clinical evidence for psychosocial interventions in combination with pharmacological interventions

Study information table for the trials of psychosocial interventions in combination with pharmacological interventions are presented in Table 47. Forest plots can be found in Appendix 19.

Table 47. Study information table of trials for psychosocial interventions in combination with pharmacological interventions

	SSRIs + psychosocial intervention versus psychosocial intervention alone	TCA + psychosocial intervention versus psychosocial intervention alone	SSRI + psychosocial intervention versus SSRI
Total no. of trials (total no. of participants)	3 (N = 207)	1 (N = 50)	1 (N = 142)
Study ID	LESPERANCE2007 TARG1994 ZISOOK1998	MARKOWITZ1998	LESPERANCE2007
Physical health problem	Cardiovascular disease (LESPERANCE2007) HIV (TARG1994, ZISOOK1998)	HIV	Cardiovascular disease
Baseline severity: mean	HAM-D overall: M ~ 23.32; S.D. ~ 5.34 LESPERANCE2007: M ~ 29.40; S.D. ~ 6.41 TARG1994: M ~ 20.25; S.D. ~ 4.65 ZISOOK1998: M ~ 20.30; S.D. ~ 4.95	HAM-D: M ~ 20.45; S.D. ~ 5.05	HAM-D: M ~ 29.20; S.D. ~ 6.41 :
Age (mean)	42 years	37 years	58 years
Treatment length	7 weeks (ZISOOK1998) 12 weeks (LESPERANCE2007, TARG1994)	17 weeks	12 weeks
Frequency of sessions	1 session per week (LESPERANCE2007, TARG1994) Details not provided (ZISOOK1998)	16 sessions within 17 weeks	1 session per week
Duration of sessions	Details not provided	50 minutes	Details not provided
Longest length of follow up	None	None	None
Effect estimates	Depression (HAM-D): WMD =-3.73 (-6.19 to -	Depression (HAM-D): WMD = 0.20 (-3.63 to 4.03)	Depression (HAM-D): WMD 2.40 (-0.89 to 5.69)

	1.27) Depression (BDI): WMD -4.26 (-6.86 to -1.67) CD4 cell count: WMD -132.4 (-354.39 to 89.59)	Depression (BDI): WMD = -2.30 (-8.14 to 3.54) CD4 cell count: WMD = 77 (-16.62 to 170.62)	Depression (BDI): WMD -1.40 (-4.92 to 2.12)

Population

All trials recruited participants for depression and chronic physical health problems. The population ranged from moderate to severe depression as measured by the HAM-D.

Intervention

The psychosocial interventions included in the review were IPT (LESPERANCE2007, MARKOWITZ1998), a group-based cognitive and behavioural intervention (TARG1994) and peer (self-help) support (ZISOOK1998). The pharmacological interventions included in the analysis were SSRIs: citalopram (LESPERANCE2007) and fluoxetine (TARG1994, ZISOOK1998). One study looked at the TCA, imipramine (MARKOWITZ1998).

Comparison

All studies compared a psychosocial intervention in combination with medication to a psychosocial intervention alone (LESPERANCE2007, TARG1994, MARKOWITZ1998, ZISOOK1998). One also compared a psychosocial intervention in combination with medication to medication alone (LESPERANCE2007).

Outcome

The outcomes extracted for the review were observer-rated depression scales including the HAM-D (TARG1994, MARKOWITZ1998, LESPERANCE2007, ZISOOK1998) and self-report depression scales including the BDI (MARKOWITZ1998, LESPERANCE2007, ZISOOK1998). Two studies reported physical health outcomes (TARG1994 and MARKOWITZ1998). No study reported health related quality of life.

Results

There was a modest and statistically significant benefit on depression at end of treatment (as measured by the HAM-D) when SSRIs were offered in combination with a psychosocial intervention when compared to a psychosocial intervention alone (SMD = -0.39, -0.67 to -0.11; WMD = -3.73, -6.19 to -1.27). The results were similar when depression was measured at end of treatment using the BDI (SMD = -0.44, -0.73 to -0.15; WMD = -4.26, -6.86 to -1.67).

The added benefit for adding TCAs to a psychosocial intervention for people with depression and chronic physical health problems was less conclusive.

The review only included one study which had conflicting results depending on the measure of depression. When a TCA was added to interpersonal therapy in comparison to interpersonal therapy alone, there was no difference for depression at end of treatment, as measured by the HAM-D (SMD = 0.03, -0.53 to 0.58; WMD = 0.20, -3.63 to 4.03). When depression was measured with the BDI, the study found a small but statistically non-significant effect at end of treatment (SMD = -0.22, -0.77 to 0.34; WMD = -2.30, -8.14 to 3.54).

There was a small but statistically non-significant effect on depression at end of treatment when IPT was offered in addition to an SSRI compared to an SSRI alone as measured by the BDI (SMD = -0.13, -0.46, 0.20; WMD -1.40, -4.92 to 2.12). There was no added benefit when depression was measured with the HAM-D (SMD = 0.24, -0.09 to 0.57; WMD = 2.40, -0.89 to 5.69). This study did not find IPT to be more effective than clinical management.

7.2.16 Clinical evidence for psychosocial interventions compared with pharmacological interventions

Study information table for the trials of psychosocial interventions compared with medication are presented in Table 48. Forest plots can be found in Appendix 19.

Table 48 Study information for psychosocial intervention versus SSRI

	IPT versus SSRI
Total no. of trials (total no. of participants)	1 (N = 150)
Study ID	LESPERANCE2007
Physical health problem	Cardiovascular disease
Baseline severity: mean	HAM-D overall: M~ 29.80; S.D. ~ 6.43
Age (mean)	58 years
Treatment length	12 weeks
Frequency of sessions	1 session per week
Duration of sessions	Details not provided
Longest length of follow-up	None
Effect estimates	Depression (BDI): WMD 2.50 (-0.92 to 5.92) Depression (HAM-D): WMD 0.51 (0.19 to 0.84)

There was one study that directly compared a psychosocial intervention with medication that met the inclusion criteria for the review (LESPERANCE2007). The participants were recruited for depression and chronic physical health problems. The chronic physical health condition covered in this review was cardiovascular disease. The study compared IPT with citalopram and looked at depression at end of treatment measured by the HAM-D and BDI.

Citalopram had a moderate and statistically significant effect on depression as measured by the HAM-D at the end of treatment (SMD = 0.51, 0.19 to 0.84; WMD = 3.90, 1.47 to 6.33) as compared with IPT. There was a small but statistically non-significant effect on depression in favour of IPT for depression as measured by the BDI at end of treatment compared with citalopram (SMD = 0.23, -0.09 to 0.55; WMD = 2.50, -0.92 to 5.92). The study did not find IPT alone to be more effective than clinical management.

Clinical evidence summary

There are a number of significant limitations to the studies included in this review. First, most of the studies are small and do not present data to show whether the participants are representative of patients with the physical illness in question. Secondly, many of the studies included in this review used standard care. This means that the superiority of the intervention over the control group could, in theory, be because of the increased attention given to the participants in the active treatment groups compared with the control groups. Where the interventions have been compared with active comparison groups (that is, another psychosocial intervention or education), most have shown a marked reduction in the difference between the intervention and the comparator groups. Thirdly, most of the studies have tested relatively short periods of treatment—often one session per week for 6 to 8 weeks – which is in contrast to a number of interventions covered in the Depression Guideline (NICE, 2009) where group CBT duration typically runs to 12 week and individual CBT to 16 to 20 weeks . (It should also be noted that relatively little evidence for brief high intensity interventions was found in the NICE (2009) depression Guideline).

In spite of the limitations of the evidence, the pattern of response to various interventions is broadly in line with that identified for depression in individuals without a chronic physical health problems (NICE, 2009). In particular, the review found for low intensity psychosocial interventions, that physical activity, peer (self-help) support and individual guided self help (based on cognitive and behavioural principles) were effective than standard care. The evidence was of weaker quality for exercise. For high intensity interventions, individual- and group-based cognitive and behavioural interventions were more effective than standard care. In the relatively few studies available no clinically important differences were identified between these interventions and other psychosocial interventions. However the evidence base for the effectiveness of counselling and health education when compared to standard care failed to demonstrate a difference in contrast to that for individual- or group-based cognitive and behavioural interventions. There was some evidence for the benefit of combining medication with psychosocial interventions for people with moderate to severe depression. There was inconclusive evidence regarding IPT.

7.3 Psychosocial interventions: health economics evidence

The guideline systematic literature search identified no economic evidence on psychosocial interventions in this population. Cost analyses were performed to assist in decision making. The clinical review includes 11 different interventions. The economic analyses did not focus on all the interventions. Only those interventions for which evidence was sufficient to conduct a cost analyses and or indicate a recommendation were focused on. However, the GDG needed to and did consider resource implications for all possible interventions.

7.3.1 Cognitive Behaviour Therapy

It was anticipated that an economic model would be constructed in order to estimate the cost effectiveness of a combination of CBT and antidepressant therapy (combination therapy) versus antidepressant therapy alone for people with depression and chronic health problems. However, there was insufficient evidence from the systematic clinical review comparing the two treatment strategies in this patient population. Therefore, a brief summary of the results of the economic model of combination therapy versus antidepressant therapy for depression, taken from the concurrent Depression Update guideline (NCCMH, Forthcoming), is presented here.

In summary, a short-term decision analytic model was constructed to compare the cost-effectiveness of combination therapy versus antidepressant therapy for people with moderate and severe depression. The clinical evidence showed no overall superiority for CBT alone versus antidepressant therapy. Therefore, this treatment option was not considered in the analysis. The key clinical parameters taken from the guideline meta-analyses included rates of discontinuation, remission and relapse for the two treatments. Resource use and cost parameters included the two treatment protocols plus any subsequent mental health care whilst utility estimates taken from the study by Sapin and colleagues (2004) were used to calculate QALYs. Over the 15-month analysis period, combination therapy resulted in slightly higher costs (£620 to £650) and slightly higher QALY gains (0.09 to 0.11) in comparison with antidepressant therapy. The resulting ICERs were £7,000 for people with moderate depression and £5,500 for people with severe depression, both well below current NICE cost-effectiveness threshold range (NICE, 2008a).

Given that combination therapy is a cost-effective treatment for patients with moderate and severe depression, it is possible that it will also be a cost-effective treatment option for people with depression and chronic health problems. The systematic clinical review showed some limited evidence of the clinical benefit of combining psychosocial interventions (including CBT) with antidepressant medication for people with moderate to severe depression and chronic health problems. Furthermore, the results presented here may well be

conservative when applied to people with depression and chronic health problems, if the interventions can improve physical health in addition to mental health. The QALY improvements may be underestimated when applied to depressed people with chronic health problems since any possible physical improvements have not been considered in the QALY estimates undertaken for the guideline economic analysis. Obviously, such physical improvements are also dependent on the chronic health problem in question. Further research is necessary in order to establish whether combined CBT and antidepressant treatment is cost-effective for depressed patients across a range of chronic health conditions.

7.3.2 Low intensity psychosocial interventions

Physical Activity Programs

The RCTs included in the guideline systematic literature review of physical activity programs described interventions delivered either individually or in structured groups of 5-6 people under the supervision of a competent practitioner or exercise facilitator. The programme would typically involve 2 to 3 sessions per week of 45 minutes to 1 hour duration over a 10 to 14 week period.

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

Based on the estimated staff time associated with delivering and supervising a physical activity programme as described above and the cost of a community mental health nurse, the average cost of a physical activity programme when delivered at an individual level would range between £765 to £2,142 per person in 2007/08 prices. If a physical activity programme were delivered on a structured group basis, it is assumed that resources required to deliver the programme would be identical. Based on the assumption of 5-6 people per group, the average costs of the programme would fall to between £128 to £428 per person in 2007/08 prices.

The clinical evidence suggests that a mixture of both individual and structured group physical activity interventions is effective in reducing depression symptoms when compared to a no physical activity control. It is difficult to assess how these clinical improvements can be translated into overall improvements in patient HRQoL and the relative cost-effectiveness of

an individual or group-based physical activity programme also depends on the impact on downstream resource use and not just the service costs of delivering the interventions. However, given the lower costs of delivering a structured group-based physical activity programme, it is possible that this will be more cost-effective than an individual programme for patients with subthreshold depressive symptoms or mild to moderate depression. Furthermore, although no formal cost-effectiveness analysis was conducted, the GDG judged that the clinical benefit achieved justified the intervention cost.

Group Peer support

The clinical evidence in the guideline systematic literature review described interventions consisting of 1 session per week over an 8 week period. The intervention would be delivered by a mental health professional with each session lasting 1 – 1.5 hours.

Peer support groups can be set in the NHS or in a private health care setting. Furthermore, these groups could be facilitated by paid staff or by volunteers. The availability and costs of such groups is expected to vary significantly across the NHS in England and Wales, therefore a costing analysis was not attempted.

Therefore referral to such services would depend on the costs in a specific setting and availability.

Guided Self Help

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

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

Based on the estimated staff time associated with delivering an individual guided self-help programme as described above and the cost of a community mental health nurse, estimated average cost of the programme would ranges between £42 to £259 per person in 2007/08 prices.

Computerised Cognitive Behaviour Therapy

The systematic search of economic literature undertaken for this guideline identified 0 studies on computerised cognitive behavioural therapy. Evidence on this intervention was extrapolated from the Depression Update guideline. Therefore, the review of the economic literature identified in that guideline is presented here.

The systematic search of economic literature undertaken for the Depression guideline update identified 2 studies on computerised cognitive behavioural therapy for people with depression set in the UK (McCrone *et al.,* 2004, and Kaltenthaler *et al.,* 2006).

The paper by McCrone and colleagues (2004) compared the Beating the Blues (BtB) software package versus standard care in the care of people with a diagnosis of depression, mixed depression and anxiety or anxiety disorders treated in the UK primary care setting.

The study was conducted alongside a RCT PROUDFOOT2004 Costing was conducted prospectively on a sub-sample of the patients included in the RCT. The benefit measures used in the economic analysis were improvements in BDI scores, depression-free days, and quality-adjusted life-years (QALYs), these were estimated using the method described by Lave and colleagues (1998). The study adopted a societal perspective. Costs included contacts with mental health care staff (psychiatrists, psychologists, community mental health nurses, counselors and other therapists), contacts with primary care staff (GPs, practice nurses, district nurses, and health visitors), contacts with hospital services (inpatient care for psychiatric and physical health reasons, outpatient care, day surgery, and accident and emergency attendance), contacts with home helps, medications (antidepressants, anxiolytics and sedatives), and contacts with other services (chiropodists, physiotherapists and dieticians). The cost of buying the licence to use 'Beating the Blues' (plus overheads) was also considered. The price of the computer program license was obtained from the manufacturer. The time horizon of the analysis was 8 months.

Results were presented in the form of Cost-Effectiveness Acceptability Curves (CEACs), which demonstrate the probability of an intervention being cost-effective at different levels of willingness-to-pay per unit of effectiveness (that is, at different cost effectiveness thresholds the decision-maker may set). The CEAC showed that the probability of BtB being cost-effective over standard care was greater than 80% at a value of £40 per unit reduction in BDI score. In terms of depression-free days, the CEAC suggested that if society placed a value of £5 on a depression-free day, then there would be an 80% chance of the intervention being cost-effective. At a cost effectiveness of £15,000 per QALY, the probability of BtB being cost-effective was found to be 99%. At a

willingness-to-pay of £5,000 per QALY, the probability of the intervention being cost-effective was 85%

The authors concluded that BtB had a high probability of being cost effective. The following limitations of the study were noted: sensitivity analysis was conducted only on the cost of the CCBT programme, as this was deemed to be the most uncertain factor. This cost was determined using the throughput levels that were based on assumptions about the number of patients likely to be picked up from a general practice. These throughput levels are highly uncertain due to the novel nature of CCBT in the NHS. The study may benefit from more scrutiny into the uncertainty by more sensitivity analysis. The societal perspective was adopted; this is not recommended by NICE. The time horizon spanned 8 months and this may underestimate the potential costs and benefits of the intervention. The indirect method in which QALYs were estimated was deemed problematic. A utility value was selected from a study that combined the values from a number of different published studies, using a range of sources and methods.

The economic analysis for the health technology appraisal by Kaltenthaler and colleagues (2006) aimed to evaluate a range of CCBT packages for the treatment of depression, The software packages considered included BtB, Overcoming Depression and Cope. These packages were compared to treatment as usual in primary care over an 18 month time horizon. The study population consisted of patients with mild to moderate, moderate to severe or severe depression Variation in cost effectiveness by severity of depression was also explored with a subgroup analysis.

The same model structure was used to evaluate the three depression programmes. The decision tree model compared two arms, CCBT and standard care. CCBT was one of the depression products and this was compared to care received usually in primary care. Patients were given either CCBT or standard care over a 2-month period. A proportion of these were assumed to complete the treatment. Patients who complied with treatment were then assumed to be distributed across the four depression severity categories depending on the success of the intervention: minimal, mild to moderate, moderate to severe and severe. Those who did not complete CCBT were assumed to be offered standard care and this resulted in a set of transition probabilities between disease severity categories. Patients were assumed to spend 6 months in their new severity state following treatment. At the end of the 6-month period, which was 8 months after treatment began; patients who improved stayed the same or relapsed. If they relapsed, then at 10 months after initiating treatment they were offered either another course of CCBT or treatment as usual in the CCBT arm. At the second cycle, patients were assumed to transit between severity categories as before over the next 2 months and then stabilised for the remaining 6 months of the model. If they did not relapse they stayed in the post-retreatment severity category. If they

did not improve in the first place (they were in moderate or severe categories) they also stayed in the same severity category.

Effectiveness estimates in terms of transition probabilities were sourced from published and unpublished trials for each of the products, and further assumptions. BtB was the only product based on an RCT. The authors aimed to find utility values for depression linked to the BDI, the primary outcome in the CCBT studies. Utility values were obtained from a data set from a recently published UK based RCT of supervised self-help CBT in primary care by Richards and colleagues (2003). This study incorporated the EQ-5D and Core. Core is a depression-specific questionnaire that has also been mapped onto the BDI. The mapping function was fitted to these data to provide BDI data on each case. Based on the estimated BDI scores, Kaltenhaler and colleagues 2006 categorised patients in this dataset as having minimal (BDI score of ≤ 9), mild (BDI score 10–18), moderate (BDI score 19–29) and severe (BDI score 30–63) depression and then linked each category with an average EQ-5D score, based on people's responses in each category. The ranges of scores were reported to be comparable to those found in other studies.

The study adopted the perspective of the health service. Costs included intervention costs as well as other service costs depending on the level of severity of depression. The estimated costs of each intervention included licence fees, computer hardware, screening of patients, clinical support, capital overheads and training of support staff. Each product has a licence fee tariff, with all products offering a fixed fee for purchase at the level of general practice. The license fee is fixed, so the cost per patient depends on the number of patients likely to use each copy. The authors made assumptions about the throughput levels used to estimate the cost per patient using the program and about the number of patients likely to be picked up from a general practice. For example, for BtB it was estimated that 100 patients would come forward each year in practices of one to five GPs. This was based on the following assumptions: there are 10,000 patients per practice; 1000 of these suffer from depression; and 10% of these will be treated each year. There is considerable uncertainty surrounding these assumptions and this is one of the main drivers of cost.

BtB was found to be more effective and more costly than TAU. The incremental cost per QALY of BtB over TAU was £1801, for Cope it was £7139 and £5391 for Overcoming Depression. The probability of accepting BtB over TAU at 30,000 was 86.8%, 62.6% for Cope and 54.4% for Overcoming Depression. The subgroup analysis found no differences across the severity groupings.

All 3 packages for depression demonstrated an ICER well below the cost-effectiveness threshold of £20,000/QALY. However, BtB was the sole package to be evaluated in the context of an RCT with a control group; it was also the package that demonstrated the highest probability of being cost-effective at

£30 000/QALY. Subsequently, BtB was the only package recommended in the TA.

One of the limitations of the economic model was that a number of parameters such as compliance and relapse rates were based on assumptions due to lack of relevant data. For example, therapist- led CBT relapse rates were used as an estimate for CCBT relapse rates. The author's highlighted this as a strong assumption that needs validation.

Moreover, although the model assumed more realistic throughput levels there remains a large amount of uncertainty in the costs of the license per patient. This is due to uncertainty in the throughput of people receiving CCBT. There remains scant evidence on the likely take-up in practice.

QALYs were estimated from a population of patients receiving CBT. This study was based in the UK and therefore would be representative of those patients utilizing the NHS. However, primary data using generic preference-based measures in the relevant population would have been ideal.

Summary of Health Economic Evidence

BtB was found to be more cost-effective than standard care. Based on the clinical and cost-effectiveness findings of Kaltenthaler and colleagues (2006), BtB was recommended by NICE (2006) as suitable treatment for patients with depression.

Since the publication of the technology appraisal on CCBT no new BtB RCT data has become available and there have been no new published economic evaluations in the UK related to BtB or other CCBT packages. The problem of paucity of data mentioned in Kaltenhaler and colleagues (2006) remains, and no data on compliance, relapse rates and costings have been made available since. Therefore, the economic analysis of BtB cannot be updated and conclusions on its cost effectiveness versus TAU remain. The clinical effectiveness data reviewed for this guideline suggests that other CCBT packages (internet/web based) may be similarly effective with BtB. The results are based on indirect evidence as no head-to-head trials were identified. Moreover, the clinical trials used different comparators and outcome measures, which make inference on the relative effectiveness of CCBT packages problematic. Nevertheless, comparison of the effect sizes in each case indicates that the various CCBT packages may offer similar benefits to people with depression compared with a baseline treatment such as waitlist control and treatment as usual.

Regarding costs, other CCBT packages considered in the clinical review are likely to incur lower intervention costs compared with BtB. A major cost component of BtB was its licence fee, according to the TA economic analysis, the license fee for BtB comprised 73% of the total intervention cost (Appendix 11, table 58, p159 of the TA). On the other hand, free packages such as

MoodGym do not require a license fee and therefore intervention costs are greatly reduced. Moreover, where patients can access a CCBT program over the internet or at locations other than at a GP practice (e.g. at home or at a public library) the costs of providing this intervention are going to be further reduced, as they do not include hardware and overhead costs. If a web-based program were to be offered at a GP practice, providing this service would incur costs for hardware, overheads and supervision. Hardware and overheads are fixed costs and would be the same for both free and licensed programs. Furthermore, the RCTs of some web-based programs describe minimal supervision requirements e.g. Moodgym trialled by Christensen and colleagues (2007) described 6-10 minute telephonic contacts by lay interviewers to patients to assist in the use of the site.

In addition to intervention costs, other costs associated with care of people with depression needs to be assessed. However, if different packages result in similar improvements for people with depression, as suggested by the findings of the clinical review, it is possible that other service costs associated with provision of CCBT are similar across the packages. The technology appraisal has shown BtB to be more cost effective than treatment as usual using conservative estimates of the likely take up of the intervention. If other CCBT packages are similarly effective to BtB (as indicated in the clinical review) and incur lower intervention costs, then they could be also potentially more cost-effective than usual care.

Patient preference is important and little published information is available on their preferences regarding CCBT. Patients may prefer utilising CCBT in the privacy of their homes or some may prefer visiting their GP practice for CCBT. By offering a range of CCBT options this may fulfil the range of patient preference.

7.4 From evidence to recommendations[17]

As has been noted in the various clinical summaries above, the evidence base on psychosocial interventions for people with depression and chronic physical health problems is more limited than that identified for depression in the absence of chronic physical health problems. However, the broad pattern of evidence is similar with evidence for low intensity interventions in subthreshold depressive symptoms and mild depression and evidence for high intensity interventions for moderate to severe depression. Given that the GDGs view was that the nature of depression in chronic physical health problems is not fundamentally different from depression in the absence of

[17] In drawing up the recommendations in this guideline the GDG had access to the evidence and recommendations of the NICE Depression Update Guideline (NCCMH, 2009), indeed on some issues such as case identification and collaborative care the groups worked together. The evidence of the depression update was then considered in drawing up these recommendations.

such problems the group considered it appropriate to draw on the evidence base for depression more generally in drawing up its recommendations.

The GDG drew on a number of principles when extrapolating from the general depression evidence base. These included: 1) supplementing the evidence in this guideline where indications from the general depression guideline supported it (for example, guided self-help and physical activity); 2) not supplementing the evidence base when studies reviewed for this guideline demonstrated no evidence of effect (for example, interpersonal therapy); 3) extrapolating from the other guideline where there was no available evidence but the GDG considered the recommendation to be of importance (for example, the recommendation of the delivery of psychological interventions, CCBT and couples therapy); 4) where there was inconsistent evidence in the general depression guideline and in the present guideline no extrapolation took place (for example, counselling). For further details concerning the methods used for extrapolating from the general depression guideline see Chapter 3.

One difference the GDG noted was the increased proportion of the evidence for various group-based psychosocial interventions including group-based cognitive and behavioural interventions, peer (self-help) support for people with depression and chronic physical health problems (In some instances, physical activity was also delivered in group based settings). The evidence on group existential therapy was however inconclusive and did not support the development of a recommendation. The GDG took into account that interventions delivered in groups were not only more cost effective than individual-based interventions but that they may have further non-specific benefits such as installation of hope and a forum for informal psycho-education about the disorder (when sharing the same physical health problem).

For low intensity interventions, the GDG concluded from the review on people with chronic physical health problems that the evidence supported the development of recommendations for physical activity and group based peer (self-help) support. In addition the GDG extrapolated from the depression update evidence and made recommendations for individual guided self-help and computerised cognitive behavioural therapy. Factors influencing this extrapolation included the increased accessibilty associated with both guided self-help (delverable over the telephone) and computerised cognitive behavioural therapy (deliverable in the home over the internet) which was considered important in populations where mobility may often be limited.

For high intensity interventions, the evidence base was strongest for group and individual cognitive and behavioural interventions. On cost-effectiveness grounds, the GDG concluded that group-based cognitive and behavioural interventions should be the first option in moderate depression. This is because group-based interventions will be more cost-effective in these

patients if both individual and group-based interventions are similarly effective but group-based interventions require less intensive resource use.

Following the principles of extrapolation summarised above (that is, no evidence identified for people with depression and chronic physical health problems but supportive evidence in people with depression in general) the GDG recommended cognitive behavioural therapy in people with severe depression (because of the strong evidecen base for cognitive behavioural therapyin the depression guideline) and couples therapy in people with moderate depression (for couples therapy the recommendation was influenced by the knowledge that a chronic phycial illness may also have a significant impact on a partner (se Chapter 5)).

However, the GDG did not extrapolate from the depression guideline (following the principles of extrapolation summarised above and in Chapter 3) concerning counselling interventions as there was no evidence of benefit reported in trials comparing counselling with treatment as usual in the present guideline. When considering the evidence in people with chronic physical health problems in addition to the limited evidence found in the general depression guideline the GDG did not consider it reasonable to make recommendations concerning counselling in this guideline.

7.4.1 Recommendations

Effective delivery of interventions for depression

7.4.1.1 All interventions for depression should be delivered by competent practitioners. Psychological and psychosocial interventions should be based on the relevant treatment manual(s) *, which should guide the structure and duration of the intervention. Practitioners should consider using competence frameworks developed from the relevant treatment manual(s)* and should:

- receive regular high-quality supervision
- use routine outcome measures and ensure that the patient with depression is involved in reviewing the efficacy of the treatment
- engage in monitoring and evaluation of adherence and competence – for example, by using video and audio tapes, and external audit and scrutiny where appropriate. [KP]

* Treatment manuals describe the structure and content of a complex intervention (including psychological interventions. They also describe the process by which the treament should be delivered. There purpose is to support fidelity and adherence to the intervention.

7.4.1.2 Consider providing all interventions in the preferred language of the patient with depression and a chronic physical health problem where possible.

Step 2: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression

General measures

Sleep hygiene

7.4.1.3 Offer patients with depression and a chronic physical health problem advice on sleep hygiene if needed, including:

- establishing regular sleep and wake times
- avoiding excess eating, smoking or drinking alcohol before sleep
- creating a proper environment for sleep
- taking regular physical exercise where this is possible for the patient.

Active monitoring

7.4.1.4 For patients who, in the judgement of the practitioner, may recover with no formal intervention, or patients with mild depression who do not want an intervention, or patients with persistent subthreshold depressive symptoms who request an intervention:

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

Low-intensity psychosocial interventions

7.4.1.5 For patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem, consider offering one or more of the following interventions, guided by the patient's preference:

- a structured group physical activity programme
- a group-based peer support (self-help) programme
- individual guided self-help based on the principles of cognitive behavioural therapy (CBT)
- computerised cognitive behavioural therapy (CCBT).

Delivery of low-intensity psychosocial interventions

7.4.1.6 Physical activity programmes for patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem, should:

- be modified (in terms of the duration of the programme and frequency and length of the sessions) for different levels of physical ability as a result of the particular chronic physical health problem, in liaison with the team providing care for the physical health problem
- be delivered in groups with support from a competent practitioner
- consist typically of two or three sessions per week of moderate duration (45 minutes to 1 hour) over 10 to 14 weeks (average 12 weeks)
- be coordinated or integrated with any rehabilitation programme for the chronic physical health problem.

7.4.1.7 Group-based peer support (self-help) programmes for patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem, should be:

- delivered to groups of patients with a shared chronic physical health problem
- focused on sharing experiences and feelings associated with having a chronic physical health problem
- supported by practitioners who should:
  - facilitate attendance at the meetings
  - have knowledge of the patients' chronic physical health problem and its relationship to depression
  - review the outcomes of the intervention with the individual patients
- delivered over a period of 8 to 12 weeks.

7.4.1.8 Individual guided self-help programmes based on the principles of CBT (and including behavioural activation and problem-solving techniques) for patients with persistent subthreshold depressive symptoms or mild to moderate

depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem, should:

- include the provision of written materials of an appropriate reading age (or alternative media to support access)
- be supported by a trained practitioner, who typically facilitates the self-help programme and reviews progress and outcome
- consist of up to six to eight sessions (face-to-face and via telephone) normally taking place over 9 to 12 weeks, including follow-up.

7.4.1.9 CCBT for patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem, and for patients with subthreshold depressive symptoms that complicate the care of the chronic physical health problem, should:

- be provided via a stand-alone computer-based or web-based programme
- include an explanation of the CBT model, encourage tasks between sessions, and use thought-challenging and active monitoring of behaviour, thought patterns and outcomes
- be supported by a trained practitioner, who typically provides limited facilitation of the programme and reviews progress and outcome
- typically take place over 9 to 12 weeks, including follow-up.

Step 3: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression

Treatment options

7.4.1.10 For patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the patient and provide:

- an antidepressant (normally a selective serotonin reuptake inhibitor [SSRI]) **or**
- one of the following high-intensity psychological interventions:
  - group-based CBT **or**

- individual CBT for patients who decline group-based CBT or for whom it is not appropriate, or where a group is not available **or**
- couples therapy for people who have a regular partner and where the relationship may contribute to the development or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit.[18]

7.4.1.11 For patients with initial presentation of moderate depression and a chronic physical health problem, offer the following choice of psychological interventions:

- group-based CBT **or**
- individual CBT for patients who decline group-based CBT or for whom it is not appropriate, or where a group is not available **or**
- couples therapy for people who have a regular partner and where the relationship may contribute to the development or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit. **[KP]**

7.4.1.12 For patients with initial presentation of severe depression and a chronic physical health problem, consider offering a combination of individual CBT and an antidepressant.[19]

7.4.1.13 The choice of intervention should be influenced by the:

- duration of the episode of depression and the trajectory of symptoms
- previous course of depression and response to treatment
- likelihood of adherence to treatment and any potential adverse effects
- course and treatment of the chronic physical health problem
- patient's treatment preference and priorities.[20]

Delivering high-intensity psychological interventions

7.4.1.14 For all high-intensity psychological interventions, the duration of treatment should normally be within the limits indicated in this guideline. As the aim of treatment is to obtain

[18] This recommendation also appears in section 8.5.2 where the pharmalogical data is presented.
[19] This recommendation also appears in section 8.5.2 where the pharmalogical data is presented.
[20] This recommendation also appears in section 8.5.2 where the pharmalogical data is presented.

significant improvement or remission the duration of treatment may be:

- reduced if remission has been achieved
- increased if progress is being made, and there is agreement between the practitioner and the patient with depression that further sessions would be beneficial (for example, if there is a comorbid personality disorder or psychosocial factors that impact on the patient's ability to benefit from treatment).

7.4.1.15 Group-based CBT for patients with depression and a chronic physical health problem should be:

- delivered in groups (typically of between six and eight patients) with a common chronic physical health problem
- typically delivered over a period of 6 to 8 weeks.

7.4.1.16 Individual CBT for patients with moderate depression and a chronic physical health problem should be:

- delivered until the symptoms of depression have remitted (over a period that is typically 6 to 8 weeks and should not normally exceed 16 to 18 weeks)
- followed up by two further sessions in the 6 months after the end of treatment, especially if treatment was extended.

7.4.1.17 Individual CBT for patients with severe depression and a chronic physical health problem should be:

- delivered until the symptoms of depression have remitted (over a period that is typically 16 to 18 weeks)
- focused in the initial sessions (which typically should take place twice weekly for the first 2 to 3 weeks) on behavioural activation
- followed up by two or three further sessions in the 12 months after the end of treatment.

7.4.1.18 Couples therapy for depression should normally be based on behavioural principles, and an adequate course of therapy should be 15 to 20 sessions over 5 to 6 months.

7.5 Research Recommendations

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

7.5.1 Combined medication and CBT for patients with moderate to severe depression and a chronic physical health problem

What is the clinical and cost effectiveness of combined medication and CBT compared with antidepressants or CBT alone for patients with moderate to severe depression and a chronic physical health problem?

Why this is important

There is limited evidence for the effectiveness of combined antidepressant treatment and CBT for patients with moderate to severe depression and a chronic physical health problem. Data from studies in patients with depression in the absence of a chronic physical health problem suggest that combined treatment may bring real benefit. However, uncertainty about medium-term outcomes for these patients remains. In addition to uncertainty about the effectiveness of the interventions, the potential for interactions between medication prescribed for depression and for chronic physical health problems is a concern. This needs to be considered in terms of both the difficulties that may arise from drug interactions and the anxieties of individual patients about this, which may reduce the likelihood of them complying with antidepressant medication. The answer to this question has practical implications for service delivery and resource allocation in the NHS.

The outcomes for this proposed study should involve both observer-rated and patient-rated assessments of acute and medium-term outcomes for at least 6 months and an assessment of the acceptability and potential burden of the various treatment options. The study should be large enough to determine the presence or absence of any clinically important effects using a non-inferiority design together with robust health economic measures.

7.5.2 Peer support interventions compared with group-based exercise and treatment as usual for patients with mild to moderate depression and a chronic physical health problem

What is the clinical and cost effectiveness of group peer support and group-based exercise when compared with treatment as usual for patients with mild to moderate depression and a chronic physical health problem?

Why this is important

There is limited evidence for the effectiveness of peer support and exercise in the treatment of patients with depression and a chronic physical health problem. Although the available data suggest that both are practical and potentially acceptable treatments that may bring real benefit, uncertainty

remains about medium-term outcomes. The answer to this question has practical implications for service delivery and resource allocation in the NHS.

This question should be answered in an adequately powered three-arm randomised controlled trial that examines medium-term outcomes, including cost effectiveness. The outcomes should reflect both observer-rated and patient-rated assessments for acute and medium-term outcomes for 12 months, and an assessment of the acceptability and potential burden of treatment options. The study should be large enough to determine the presence or absence of clinically important effects using a non-inferiority design with robust health economic measures.

7.5.3 Behavioural activation compared with antidepressant medication for patients with moderate to severe depression and a chronic physical health problem

What is the clinical and cost effectiveness of behavioural activation compared with antidepressant medication in the treatment of moderate to severe depression in patients with a chronic physical health problem?

Why this is important

There is limited evidence for the effectiveness of high-intensity psychological interventions in the treatment of moderate to severe depression in patients with a chronic physical health problem; the most substantial evidence base is for CBT. Recent developments suggest that behavioural activation may be an effective intervention for depression. In principle, this may be a more feasible treatment to deliver in routine care than CBT and could potentially contribute to increased treatment choice for patients. The answer to this question would have practical implications for service delivery and resource allocation within the NHS.

This question should be answered using a randomised controlled trial in which patients with moderate to severe depression and a chronic physical health problem receive either behavioural activation or antidepressant medication. The outcomes should be chosen to reflect both observer-rated and patient-rated assessments for acute and medium-term outcomes for at least 12 months and also 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 and robust health economic measures.

7.5.4 The efficacy of counselling compared with low-intensity cognitive and behavioural interventions and treatment as usual in the treatment of depression in patients with a chronic physical health problem

What is the relative efficacy of counselling compared with low-intensity cognitive and behavioural interventions and treatment as usual in patients with depression and a chronic physical health problem?

Why this is important

There is a limited evidence base for counselling compared with treatment as usual in the treatment of patients with depression and chronic physical health problems. High-intensity cognitive and behavioural interventions have the best evidence base for efficacy but there is limited evidence on low-intensity cognitive and behavioural interventions. The evidence on low-intensity cognitive and behavioural interventions for people with chronic physical health problems was largely supplemented by the evidence base in the Depression update guideline (CGXX). It is therefore important to establish whether either counselling or low-intensity cognitive and behavioural intervention is an effective alternative to treatment as usual for patients with chronic physical health problems and should be provided in the NHS. The answer to this question 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 the training and supervision of the practitioners providing interventions in order to ensure that the treatments are both robust and generalisable. The outcomes chosen should reflect both observer-rated and patient-rated assessments of improvement and an assessment of the acceptability of the treatment options. Particular attention should be given to physical health and quality-of-life outcomes in addition to depression outcomes. 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.

8 Pharmacological interventions in the treatment and management of depression and chronic health problems

8.1 Introduction

Since the introduction of the monoamine oxidase inhibitors (MAOIs) and the first tricyclic antidepressant (TCA), imipramine, in the late 1950s, many new antidepressants have been introduced and currently approximately 30 different antidepressants in a number of classes are available worldwide. Over the succeeding 50 years there has been intensive research on the effects of drug therapy on depression and how drugs might alter the natural history of the disorder. A large number of reviews and meta-analyses have been conducted that sought to synthesize this vast literature this includes those conducted for the previous NICE guideline on depression (NCCMH, 2004) and the update of that guideline (see NCCMH forthcoming).

There have been rather fewer studies of antidepressants for people with depression and chronic physical health problems. Many of the meta-analyses of antidepressants exclude people with physical health problems (for example, NCCMH (2004)) therefore it is difficult to assess the safety and efficacy of these medications in people with ill health.

However, it should also be noted that treating depression in people with physical health problems is potentially more challenging in terms of adverse effects of medication (as the physical illness may make physical adverse effects of much greater consequence). In addition, people in this population are likely to be taking a number of different medications related to their physical condition and so there is a greater likelihood of potential interactions with antidepressants.

8.2 Efficacy of pharmacological interventions

8.2.1 Introduction

There have been systematic reviews assessing antidepressants in various populations of people with chronic physical health problems including stroke (for example, Hackett *et al.,* 2004), heart disease, cancer (for example, Rodin *et al.,* 2007) and HIV. It appears from these reviews that antidepressants are effective in a range of physically ill populations.

Definition and aim of review

The purpose of this review was to assess the efficacy of antidepressants for the treatment of depression in people with chronic physical health problems. The search took the most inclusive approach setting filters only for RCTs and depression. Therefore no limits were placed on pharmacological interventions in order to minimise the risk of missing relevant references. The inclusion criteria of the review was limited to RCTs on the most commonly used antidepressants in clinical practice including SSRIs, TCAs, MAOIs, duloxetine, venlafaxine, buproprion, reboxetine, mirtazapine, trazodone, mianserin, and psychostimulants (see Table 49for further details). Outcomes were focused on depression, physical health and quality of life.

8.2.2 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/ exclusion criteria used for this section of the guideline can be found in Table 49 (further information about the search for health economic evidence can be found in section 8.4).

Table 49. Databases searched and inclusion/exclusion criteria for clinical evidence.

Electronic databases	MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Library
Date searched	Database inception to January 2009
Study design	RCT
Patient population	People with depression and chronic physical health problems
Interventions	SSRIs, Third generation antidepressants, TCAs, MAOIs, Trazadone, Psychostimulants
Outcomes	Mean depression score, Non-remission, Non-response, Physical health outcomes, tolerability

8.2.3 Studies considered[21]

The review team conducted a new systematic search for RCTs that assessed the efficacy and safety of antidepressants (and related health economic evidence (see section 8.4).

Sixty-one trials relating to clinical evidence met the eligibility criteria set by the GDG, providing data on 5794 participants. Of these, 1 (SCT-MD-24) was unpublished and 60 were published in peer-reviewed journals between 1984 and 2008. In addition, 80 studies were excluded from the analysis. The most common reason for exclusion was insufficient evidence of depression in participants (further information about both included and excluded studies can be found in Appendix 18).

[21] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

Of the 61 included trials, 49 trials compared antidepressants with placebo: 35 involving a comparison of SSRIs with placebo, nine of TCAs with placebo, two of third generation antidepressants with placebo, two of mianserin with placebo, one of trazodone with placebo. In addition, trials were head-to-head comparisons of antidepressants: 14 compared SSRIs with TCAs, one compared an SSRI with another SSRI, one compared a tetracyclic with mianserin, and one compared a TCA with Nomifesene.

No studies were identified concerning switching and sequencing of antidepressants in patients with chronic physical health problems. However, when forming recommendations the GDG considered evidence reviewed in Chapter 10 of the update of the Depression in Adults guideline (see NCCMH, forthcoming).

8.2.4 Clinical evidence on antidepressants versus placebo

Table 50 summarises study information for the included trials of antidepressants versus placebo.

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
Total no. of trials (total no. of participants)	35 RCTs (N = 3758)	9 RCTs (N=445)	1 RCT (N=311)	2 RCTs (N=128)	1 RCT (N=22)	1 RCT (N=94)
Study ID	ANDERSEN1994 BLUMENFIELD1997 BROWN2005A CHEN2002 DEVOS2008 EHDE2008 EISER2005 EVANS1997 FISCH2003 FRUEHWALD2003 GLASSMAN2002 GOTTLIEB2007 LACASSE2004 LEENTJENS2003 LESPERANCE2007 LUSTMAN2000 LUSTMAN2006 MAURI1994 MCFARLANE2001 MENZA2008 MORROW2003 MURRAY2005A MUSSELMAN2006 PAILEHYVARINEN2003 PAILEHYVARINEN2007 RABKIN1999 RABKIN2004 RAZAVI1996 ROBINSON2000 SCT-MD-24 STRIK2000 TOLLEFSON1993 WERMUTH1998 WIART2000	ANDERSEN1980 BORSON1992 KIMURA2000 LAKSHMANAN1986 LIPSEY1984 LUSTMAN1997A RABKIN1994 ROBINSON2000 TAN1994	WISE2007	COSTA1985 VANHEERINGEN1996	RAFFAELE 1996	VAN DEN BRINK2002

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	YANG2002					
Diagnostic tool	*DSM-III-R/DSM-IV:* BLUMENFIELD 1997 BROWN2005A DEVOS2008 EHDE2008 EISER2005 FISCH2003 GLASSMAN2002 LACASSE2004 LEENTJENS2003 LESPERANCE2007 LUSTMAN2006 MAURI1994 MENZA2008 MURRAY2005A MUSSELMAN2006 PAILEHYVARINEN 2003 PAILEHYVARINEN 2007 RABKIN1999 RABKIN2004 RAZAVI1996 ROBINSON2000 SCT-MD-24 STRIK2000 TOLLEFSON1993 WERMUTH1998 WIART2000 *ICD-10:* WIART2000 *Geriatric Mental State / AGECAT:*	*DSM-III-R/DSM-IV* BORSON1992 LUSTMAN1997A RABKIN1994 ROBINSON2000 *Clinical Diagnosis (not clearly stated as DSM/ICD):* ANDERSEN1980 LIPSEY1984 *Depression scale* KIMURA2000 LAKSHMANAN1986 (HDRS) TAN1994 (GDS and BASDEC)	*DSM-IV* WISE2007	*DSM-II-R / DSM-IV* VANHERRINGEN1996 *Clinical Diagnosis (not clearly stated as DSM/ICD):* COSTA1985	*DSM-III-R* RAFFAELE 1996	*DSM-III-R/DSM-IV* VAN DEN BRINK2002

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	EVANS1997 *Clinical Diagnosis (not clearly stated as DSM/ICD):* CHEN2002 *Depression scale:* ANDERSEN1994 (HDRS) GOTTLIEB2007 (BDI) FREUHWALD2003 (HDRS) LUSTMAN2000 (BDI) MCFARLANE2001 (Inventory to Diagnose Depression) MORROW2003 (CES-D) YANG2002 (HDRS)					
Physical health condition	Stroke ANDERSEN1994 CHEN2002 FRUEHWALD2003 MURRAY2005A ROBINSON2000 WIART2000 YANG2002 Diabetes LUSTMAN2000 LUSTMAN2006 PAILEHYVARINEN 2003 PAILEHYVARINEN 2007	Stroke KIMURA2000 LIPSEY1984 ROBINSON 2000 Diabetes LUSTMAN1997A Parkinson's Disease ANDERSEN1980 MENZA2008 General medical illness LAKSHMANAN1986 TAN1994	General medical illness WISE2007	Cancer COSTA1985 VANHEERINGEN1996	Stroke RAFFAELE 1996	Cardiovascular disease VAN DEN BRINK2002

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	SCT-MD-24 Cardiovascular disease GLASSMAN2002 GOTTLIEB2007 LESPERANCE2007 MCFARLANE2001 STRIK2000 Cancer FISCH2003 MORROW2003 MUSSELMAN2006 RAZAVI1996 Parkinson's Disease DEVOS2008 LEENTJENS2003 MENZA2008 WERMUTH1998 General medical illness EVANS1997 TOLLEFSON1993 Asthma BROWN2005A COPD EHDE2008 EISER2005 LACASSE2004 Renal disease BLUMENFIELD1997	COPD BORSON1992 HIV RABKIN1994				

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	HIV MAURI1994 RABKIN1999 RABKIN2004					
Baseline severity: mean (SD)	Subthreshold depressive symptoms *Brief Zung rating scale* FISCH2003 ~ 24(6) *CES-D:* MORROW2003: CES-D ~15(11) *BDI:* LUSTMAN2006 ~4(3)** *BDI:* PAILEHYVARINEN 2003 ~ 13(8) Mild depression *HDRS:* EHDE2008~18(4) RABKIN2004 ~17.5(4) WERMUTH1998 ~17(3) *MADRS:* MURRAY2005A ~19(6) *BDI* EISER2005 ~23(8) GOTTLIEB2007 median =21.5 Moderate depression *HDRS:* ANDERSEN1994 ~ 19(3)	Subthreshold depressive symptoms *BDI* LUSTMAN1997A~18.5(7) *MADRS* TAN1994 ~17.5(3.5) Mild depression *HDRS:* KIMURA2000 ~17.5(4) RABKIN1994 ~17(4) Moderate depression *HDRS:* ROBINSON2000~19(5) MENZA2008 ~20(6) Severe depression *HDRS:* LAKSHMANAN1986 ~30(9) BORSON1992 ~29(6.5)	Moderate depression *HDRS* WISE2007 ~22(3)	Moderate depression: *HDRS* COSTA1985 ~20(4) VANHEERINGEN1996~ 21(4)	Moderate depression: *Zung depression rating scale* RAFFAELE1996 ~61(11)	Moderate depression *HDRS* VANDENBRINK2002 ~ 18

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	BROWN2005A ~ 24 CHEN2002:~ 19(3) EVANS1997: Median ~20 GLASSMAN2002 ~19.6 LUSTMAN2000 ~23(8) MENZA2008 ~19(6) MUSSELMAN2006 ~22(5.5) RABKIN1999 ~19(5) ROBINSON2000 ~19(5) STRIK2000 ~21.6 TOLLEFSON1993 ~24(4) *HADS* PAILEHYVARINEN 2007 ~14(5) *MADRS:* DEVOS2008 ~27(4) RAZAVI1996 ~ 25.5(7) SCT-MD-24 ~30(4) Severe depression *HDRS:* FRUEHWALD2003:~ 31(13) LESPERANCE2007 ~ 30 MAURI1994 ~ 30(4) WIART2000 ~28(7)					
Treatment length	Up to 3 months ANDERSEN1994 BLUMENFIELD1997 CHEN2002 DEVOS2008 EISER2005 EVANS1997	Up to 3 months ANDERSEN1980 LAKSHMANAN1986 LIPSEY1984 LUSTMAN1997A MENZA2008 RABKIN1994	Up to 3 months WISE2007	Up to 3months COSTA1985	Up to 3 months RAFFAELE 1996	Up to 6 months VANDENBRINK2002

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	LEENTJENS2003 LUSTMAN2000 MAURI1994 MENZA2008 MUSSELMAN2006 PAILEHYVARINEN2003 RABKIN1999 RABKIN2004 RAZAVI1996 STRIK2000 TOLLEFSON1993 WIART2000 3 to 6 months BROWN2005A EHDE2008 FISCH2003 FRUEHWALD2003 GOTTLIEB2007 LACASSE2004 LESPERANCE2007 ROBINSON2000 SCT-MD-24 YANG2002 6 to 12 months GLASSMAN2002 LUSTMAN2006 MCFARLANE2001 MURRAY2005A PAILEHYVARINEN2007 Unclear MORROW2003***	TAN1994 3 to 6 months BORSON1992 KIMURA2000 ROBINSON2000				
Length of follow-up / continuation phase	Up to 6 months follow up	No follow-up data reported	No follow-up data reported	No follow-up data reported	No follow-up data reported	No follow up data reported

Table 50. Study information table for trials of antidepressants versus placebo

	SSRIs vs placebo	TCAs vs placebo*	Duloxetine vs placebo	Mianserin vs Placebo	Trazadone vs Placebo	Mirtazapine vs placebo
	MUSSELMAN2006 Continuation phase up to 4 months STRIK2000 Continuation phase up to 12 months WERMUTH1998					
Dose	Range:: Citalopram: 10mg/d to 40mg/d Fluvoxamine: 100 mg/d to 150mg/d Fluoxetine: 10 mg/day to 60mg/d Paroxetine: 10mg/d to 40mg/d Setraline: 50mg/d to 200 mg/d	Range: Doxepin: 10mg/d to 20 mg/d Imipramine: max 200mg/d Lofepramine: 70mg/d Nortriptyline: 48mg/d to max 100mg/d	Mean dose = 60mg/d	Range in mean dose = 45mg/d to 60mg/d	Mean dose = 300mg/d	Range = 15mg/d to 45mg/d
Age	Range of Mean age in years: 35 to 81.5	Mean age in years: 38 to 80	Mean age in years: 58	Range of Mean age in years: 52	Mean age in years = 70	Mean age in years: 58

Notes:
*Trials comparing desipramine to placebo were not included in the analysis.
**Study (LUSTMAN2006) looks at relapse prevention. Baseline figures reported are for the start of maintenance phase.
*** Treatment length up to four cycles of chemotherapy

SSRIs

The majority of research in this area has investigated the use of SSRIs. A total of 36 RCTs compared SSRIs with placebo for people with depression and chronic physical health problems (see Table 51 and Table 52).

Table 51 Evidence summary for SSRIs versus placebo

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Risk Ratios (95% CIs)
Leaving the Study early: Any reason	3137 (25)	⊕⊕⊕O moderate[1]	RR 1.11 (0.96 to 1.27)
Leaving the Study early: Lack of efficacy	358 (5)	⊕⊕⊕O moderate[2]	RR 0.43 (0.16 to 1.16)
Leaving the Study early: Due to adverse events	1661 (13)	⊕⊕⊕O moderate[1]	RR 1.89 (1.23 to 2.89)
Depression: 1. Not achieving success/ remission - patient rated	60 (1)	⊕⊕⊕O moderate[3]	RR 0.74 (0.46 to 1.18)
Depression: 1. Not achieving success/ remission - observer rated	1197 (14)	⊕⊕⊕O moderate[1]	RR 0.81 (0.74 to 0.88)
Depression: 2. Non-response - patient rated	279 (3)	⊕⊕OO low[2,4]	RR 0.73 (0.44 to 1.22)
Depression: 2. Non-response –observer rated	1267 (19)	⊕⊕OO low[1,4]	RR 0.83 (0.71 to 0.97)

[1] some studies did not clearly report whether double blinded
[2] CIs compatible with benefit and no benefit
[3] Sparse data - only one study
[4] I-squared >50%

There were mixed data concerning tolerability of SSRIs. No differences were found with placebo for leaving the study for any reason (RR = 1.11; CIs 0.96, 1.27). However participants receiving SSRIs were more likely to leave the study due to adverse events (RR = 1.89; CIs 1.23, 2.89).

There was consistent evidence that SSRIs had a small-to-medium benefit on depression outcomes in comparison with placebo. SSRIs were associated with lower levels of non-remission (all studies: RR = 0.81, CIs 0.74, 0.88; double blind only: RR=0.86, CIs 0.78, 0.94) and non-response (all studies: RR = 0.83, CIs 0.71, 0.97; double blind only: 0.85, CIs 0.76, 0.94) compared with placebo.

Table 52 Evidence summary of SSRIs versus Placebo for continuous data

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect size (95% CIs)
Depression: 3. Patient-rated Continuous measures	992 (13)	⊕⊕⊕O moderate[1]	SMD -0.17 (-0.30 to -0.04)
Depression: 4. Observer-rated Continuous measures	2116 (25)	⊕⊕OO low[1,3]	SMD -0.33 (-0.47 to -0.19)
QoL: 1. continuous measures e.g. SQOLI, FACT-G	524 (7)	⊕⊕⊕O moderate[1]	SMD -0.27 (-0.44 to -0.1)
Physical outcome / QoL - General physical functioning/ wellbeing (SF-36 physical component)	338 (5)	⊕⊕⊕O moderate[2]	SMD 0.02 (-0.19 to 0.23)

[1] some studies did not clearly report whether double blinded
[2] CIs compatible with benefit and no benefit
[3] I-squared >50%

A robust positive effect was also found for mean change in depression rating scale score (see Table 52) although there were differences in the size of the effect depending on whether patient-rated (all studies: SMD = -0.17, CIs -0.30, -0.04 double blind only: SMD = -0.17, CIs -0.30, -0.04) or observer-rated (all studies SMD = -0.33, CIs -0.47, -0.19; double blind only: SMD = -0.29, CIs -0.41, -0.29) scales were used.

There were many fewer data on both quality of life and physical health outcomes. In addition, where these are reported, measures differ substantially between studies. In total there were seven studies that provided data on quality of life indicating a small benefit in favour of SSRIs (SMD = -0.27; CIs -0.44, -0.10). However, there were a further five studies reporting the physical sub-scale of the SF-36 which showed no difference between groups (SMD = 0.02; CIs -0.19, 0.23).

It was problematic to pool data on physical health outcomes because of differences between physical health conditions in which outcomes were examined but also because of varied reporting of outcomes. Few conclusions can be drawn on the impact of SSRIs on such outcomes.

TCAs

Table 53 Evidence summary of TCAs versus placebo

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect sizes
Leaving the study early: Any reason	302 (6)	⊕⊕⊕O moderate[1]	RR 1.33 (0.88 to 2.01)
Leaving due to adverse events	239 (5)	⊕⊕⊕⊕ high	RR 2.00 (1.06 to 3.78)
Depression: 1. Non-response (<50% improvement) - observer rated	224 (5)	⊕⊕⊕O moderate[3]	RR 0.53 (0.41 to 0.68)
Depression: 2. Not achieving success/ remission (reaching a specified cut off) Patient-rated	75 (2)	⊕⊕OO low[1,2]	RR 0.71 (0.40 to 1.29)
Depression: 4. Observer-rated Continuous measures	324 (8)	⊕⊕⊕O moderate[3]	SMD -0.69 (-0.92 to -0.47)

[1] CIs compatible with benefit and no benefit
[2] two small studies
3 some studies not clear if they were double blinded

There were only nine RCTs that compared TCAs with placebo mostly conducted in the 1980s and 1990s. There was consistent evidence that TCAs were less well tolerated compared with placebo (see Table 53). People on TCAs were more likely to leave the study for any reason (RR = 1.33; CIs 0.88, 2.01) and because of adverse events (RR = 2.00; CIs 1.06, 3.78).

There appeared to be evidence of medium-to-large benefits on most depression outcomes. Participants receiving TCAs were more likely to respond to treatment (RR = 0.53; CIs 0.41, 0.68). However, including only double-blinded studies reduced the size of the effect, resulted in very high heterogeneity (I^2 = 85.4%) and the difference was no longer statistically significant (RR = 0.64; CIs 0.34, 1.21).

There was no statistically significant effect on non-remission (RR =0.71; CIs 0.40, 1.29), but this may be due to a lack of power as only two small studies reported this outcome. Mean differences on observer-rated depression scales were also of a medium-to-large magnitude (all studies: SMD = -0.69, CIs -0.92, -0.47; just double blinded: SMD = -0.55, CIs -0.95, -0.15). Similar effects were found on patient rated scales (all studies double blinded: SMD = -0.58, CIs -1.14, -0.02), but only two studies reported such data.

There were very limited data on quality of life and physical health outcomes therefore a meta-analysis of these outcomes was not prudent.

Other Drugs

There was only one study on trazodone (RAFFAELE1996) which indicated large benefits in comparison with placebo for mean depression rating scale score (SMD = -1.03; CIs -1.93, -0.13). However this study was not double blinded therefore it is difficult to draw conclusions from this.

There was also one study on mirtazapine (VAN DEN BRINK2002). Participants in the mirtazapine group were less likely to leave the study for any reason compared to placebo (RR = 0.57; CIs 0.35, 0.94). There were small benefits in favour of mirtazapine in terms of non-remission (0.87; CIs 0.63, 1.21), non-response (0.83; CIs 0.58, 1.20), and mean difference (SMD = -0.21; CIs -0.62, 0.20) in depression scale data. None of these effects was statistically significant.

WISE2007 conducted a trial on duloxetine which was found to be associated with a small-to-medium benefit in terms of mean difference on depression scale score (patient rated: SMD = -0.37; CIs -0.67, -0.14; observer rated: SMD = -0.43; CIs -0.71, -0.16).

There were two studies examining mianserin versus placebo (COSTA1985, VANHEERINGEN1996), which found strong benefits favouring mianserin on leaving the study for any reason (RR=0.43; CIs 0.25, 0.75) non-response (RR = -0.47; CIs 0.30, 0.74) and mean difference for depression score as measured on the HDRS (WMD = -5.97; CIs -9.14. -2.80, SMD = -0.64; CIs -1.00, -0.29). There was one trial on psychostimulants (WAGNER2000) for people with HIV which lasted two weeks. There was a small, but not statistically significant, effect on depression (SMD = -0.36; CIs -1.20, 0.49). There was a large effect on fatigue (SMD = -1.64; CIs -2.64, -0.65).

8.2.5 Examining possible confounding effects on antidepressants versus placebo analyses

While there was reasonable consistency in the findings comparing antidepressants and placebo the impact of differences in physical health problems, diagnosis of depression, baseline severity of depression, and funding of the trial were considered important potential confounding factors. The impact of the type of physical health problems was assessed by subgroup analysis. All other outcomes were assessed with meta-regression using double blinded trials on clinician rated mean depression (as this outcome had the largest number of trials). Given the lack of data for all other drug classes sensitivity analyses were limited to SSRIs and TCAs.

SSRIs

Assessing the impact of differences in the type of chronic physical health problems targeted by studies on depression outcome was limited by the dearth of studies for each physical illness. There was considerable overlap in confidence intervals for most disorders including stroke (SMD = -0.28; -0.70, 0.13), cardiovascular disease (SMD = -0.22; -0.39, -0.05) and diabetes (SMD = -0.24; -0.51, 0.03) which had the largest number of studies. This suggests that the type of physical health problem had little impact on antidepressant effect.

Whether or not a trial was sponsored by a drug company was not associated with treatment effect (β = -0.03; -0.34, 0.27, p=0.82). Furthermore, mean

baseline depression scores were not associated with effect size (β=-0.01; -0.05, 0.01, p=0.27). The effect of studies recruiting for people with a DSM/ICD diagnosis of depression had a slightly greater impact but this was also not statistically significant (β=-0.21; -0.63, 0.20, p=0.30).

TCAs

For TCAs only the impact of mean baseline depression and DSM/ICD diagnosis of depression could be assessed due to lack of data. Mean baseline depression score did not appear to predict mean change in depression (β = -0.02; -0.12, 0.08, p=0.63). But having a DSM/ICD diagnosis was associated with an increase in effect (β = -0.41; -1.18, 0.37, p=0.23) although this was not statistically significant.

8.2.6 Clinical evidence for head-to-head trials of antidepressants

Evidence from the important outcomes and overall quality of evidence are presented in Table 54. The full evidence profiles and associated forest plots can be found in Appendix 21 and Appendix 19, respectively.

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
Total no. of trials (total no. of participants)	14 RCTs (N = 2,487)	1 RCT (N=23)	1 RCT (N=82)	1 RCT (N=42)	1 RCT (N=48)
Study ID	ANTONINI2006 BARONE2006 BIRD2000 CHEN2002 DEVOS2008 HOLLAND1998 HUANG2005 LI2005 MENZA2008 MUSSELMAN2006 NELSON1999 PEZELLA2001 POLLOCK2000 ROBINSON2000 SCHWARTZ1999	GULSEREN2005	ZHAO2005	ROBERTSON1985	SCHIFANO1990
Diagnostic tool	*DSM-III-R/DSM-IV:* ANTONINI2006 BARONE2006 DEVOS2008 HOLLAND1998 MUSSELMAN2006 NELSON1999 POLLOCK2000 ROBINSON2000 SCHWARTZ1999 *ICD-10:* BIRD2000 PEZELLA2001 *Clinical Diagnosis (not DSM/ICD):* CHEN2002 HUANG2005	*DSM-IV* GULSEREN2005	*Clinical Diagnosis (not DSM/ICD)* ZHAO2005	*DSM-III* ROBERTSON1985	*DSM-III* SCHIFANO1990

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
	LI2005				
Physical health condition	Stroke CHEN2002 ROBINSON2000 Heart disease HUANG2005 NELSON1999 POLLOCK2000 Cancer MUSSELMAN2006 PEZELLA2001 HOLLAND1998 Parkinson's Disease ANTONINI2006 BARONE2006 DEVOS2008 Arthritis BIRD2000 Epilepsy LI2005 HIV SCHWARTZ1999	Diabetes GULSEREN2005	Stroke ZHAO2005	Epilepsy ROBERTSON1985	General medical SCHIFANO1990
Baseline severity: mean (SD)	Mild depression *MADRS* BIRD2000 ~24(5) Moderate depression *HDRS*	Mild depression *HDRS* GULSEREN2005 ~18(3)	Not reported	Moderate depression *HDRS* ROBERTSON1985 ~23(5)	*GDS* SCHIFANO1990 ~19(5)

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
	ANTONINI2006 ~ 20(3) BARONE2006 ~ 20(4) HOLLAND1998 ~23 HUANG ~21(3) MENZA2008 ~20(6) MUSSELMAN2006 ~22(6) NELSON1999 ~23 POLLOCK2000 ~20 ROBINSON2000 ~19(5) SCHWARTZ1999 ~21(8) *MADRS* DEVOS2008 ~27(4)				
Treatment length	Up to 3 months BIRD2000 CHEN2002 DEVOS2008 HOLLAND1998 HUANG2005 LI2005 MENZA2008 MUSSELMAN2006 NELSON1999 PEZELLA2001 POLLOCK2000 SCHWARTZ1999 3 to 6 months ANTONINI2006	3 to 6 months GULSEREN2005	Up to 3 months ZHAO2005	Up to 3 months ROBERTSON1985	Up to 3 months SCHIFANO1990

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
	BARONE2006 ROBINSON2000				
Length of follow-up / continuation phase	Up to 6 months follow up MUSSELMAN2006	No follow-up data reported	No follow-up data reported	No follow-up data reported	No follow-up data reported
Dose:	ANTONINI2006 Sertraline – Mean 50mg/d Amitriptyline - Mean 25mg/d BARONE2006 Sertraline – Mean 48.1mg/d Pramipexole – Mean 3.24mg/d BIRD2000 Paroxetine – Range 20-40mg/d Amitriptyline – Range 74 - 150mg/d CHEN2002 Paroxetine - 200mg/d Doxepin - 25mg/d DEVOS2008 Citalopram – 20mg/d Despiramine – 75mg/d HOLLAND1998	GULSEREN2005 Fluoxetine – Mean 20mg/d Paroxetine – Mean 20mg/d	ZHAO2005 Citalopram – Range 20-40mg/d Venlafaxine – up to max 200mg/d	ROBERTSON1985 Nomifensine – Range 25-50mg tid Amitriptyline – Range 25-50mg tid	SCHIFANO1990 Mianserin – up to max 90mg/d Maprotiline – up to max 150mg/d

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
	Fluoxetine – Range 20-60mg/d Desipramine – Range 100-150mg/d HUANG2005 Fluoxetine 20mg/day Clomipramine-Range 50-250mg/tid LI2005 Paroxetine – Range 20-40mg Doxepin – Range 25-100mg/d MENZA2008 Paroxetine – Range 12.5-37.5mg/d Nortriptyline - blood level 25 – 75 ng/ml MUSSELMAN2006 Paroxetine – Mean 31mg/d Desipramine – Mean 113mg/d NELSON1999 Paroxetine – Range 20-40mg/d Nortriptyline – blood level 50 –				

Table 54. Study information table for trials of head-to-head trials of antidepressants

	SSRIs vs TCAs	Paroxetine vs Fluoxetine	Citalopram vs Venlafaxine	TCA vs Nomifesene	Tetracyclic vs Mianserin
	150 ng/ml PEZELLA2001 Paroxetine – Range 20-40mg/d Amitriptyline – Range 75-150mg/d POLLOCK2000 Paroxetine – Range 10-20mg/d Nortriptyline - blood level 50 – 120 ng/ml ROBINSON2000 Fluoxetine – dose escalation up to max 40mg/d Nortriptyline – dose escalation up to max 100mg/d SCHWARTZ1999 Fluoxetine – Range 20-40mg Desipramine – Range 75-100mg/d				
Age	Range of Mean age in years: 34 to 70	Mean age in years: 57	Mean age in years: 59	Mean age in years: 36	Mean age in years: 75

SSRIs versus TCAs

Table 55 and Table 56 below summarises the main outcomes of the analysis comparing SSRIs and TCAs. There is consistent evidence that SSRIs were associated with better tolerability. For example, people who received SSRIs were less likely (although not statistically significant) to leave the study early for any reason (RR = 0.77; CIs 0.58, 1.01), less likely (although not statistically significant) to leave the study due to adverse events (RR =0.81; CIs 0.52, 1.27).

Efficacy did not differ between these two drugs with no statistically significant differences on non-remission (RR = 1.22; CIs 0.88, 1.67), non-response (RR =0.97; CIs 0.83, 1.14) or mean differences (SMD = 0.04; CIs -0.14, 0.22).

Table 55 Evidence summary of SSRIs versus TCAs

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect size
Leaving the study early - any reason	699 (10)	⊕⊕⊕⊕ high	RR 0.77 (0.58 to 1.01)
Leaving study early due to adverse events	441 (8)	⊕⊕⊕O moderate[1]	RR 0.81 (0.52 to 1.27)
Leaving study early due to adverse cardiac events	81 (1)	⊕⊕⊕O moderate[2]	RR 0.14 (0.02 to 1.08)
Leaving the study early: Due to lack of efficacy - At end of treatment	24 (1)	⊕⊕⊕O moderate[2]	RR 0.85 (0.14 to 5.06)
Depression: 1. Remission (below cut-off)	170 (5)	⊕⊕⊕O moderate[1]	RR 1.22 (0.88 to 1.67)
Depression: 2. Non-response (<50% reduction)	625 (8)	⊕⊕⊕O moderate[1]	RR 0.97 (0.83 to 1.14)

[1] CIs compatible with benefit and no benefit
[2] Just one study
[3] visual inspection suggests important heterogeneity

Table 56 Evidence summary of SSRIs versus TCAs continuous data

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Effect Size
Depression: 3. Continuous measures - observer rated scales	471 (9)	⊕⊕⊕O moderate[1,2]	SMD 0.04 (-0.14 to 0.22)

[1] CIs compatible with benefit and no benefit

[2] visual inspection suggests important heterogeneity

Other comparisons

There was a paucity of data comparing other drug classes. Only five head-to-head trials included comparisons besides SSRI s vs. TCAs, all trials indicated little benefit of one drug class over another. The trials covered a range of medical conditions including diabetes (GULSEREN2005), epilepsy (ROBERTSON1985), stroke (ZHAO2005) and general medical illness (SCHIFANO1990) and included participants with both mild and moderate depression.

One study comparing two different SSRIs (GULSEREN2005), did not indicate any benefit for either drug (fluoxetine and paroxetine) in terms of efficacy and tolerability with no statistically significant differences on leaving the study early (RR = 0.46; CIs 0.05, 4.38) non-remission (RR = 0.76; CIs0.32, 1.80), non-response (RR =1.15; CIs 0.41, 3.21) or mean differences (SMD = 0.00; CIs -0.88, 0.88). One study comparing citalopram and venlafaxine (ZHAO2005) did not indicate any benefit for either drug class. The results for leaving the study early (RR = 0.69; CIs 0.31, 1.55), non-remission (RR = 0.90; CIs 0.71, 1.13) and non-response (RR = 0.81; CIs 0.50, 1.13) were not statistically significant. Based on one small study (ROBERTSON1985), there was no benefit in terms of efficacy for TCAs when compared with Nomifesene, with non-response data indicating no statistically significant differences (RR = 3.50 (0.89, 13.78). SCHIFANO1990 compared maprotiline and mianserin but failed to indicate any statistically significantly differences between the two. For example, results for leaving the study early (RR = 0.58; CIs 0.22, 1.51), non-response (RR = 0.75 (0.47, 1.19) and mean differences (SMD = -0.47, CIs -1.15, 0.21) did not indicate that one drug was more efficacious than the other.

8.2.7 Effectiveness studies on antidepressants

There were two studies that met the eligibility criteria of the review on the use of antidepressants in effectiveness trials. These studies used a slightly different methodological approach to the efficacy studies reviewed above and therefore were not included in the meta-analysis but are discussed in this section.

The advantages of these effectiveness studies are, firstly, that sample sizes tend to be larger and provide longer follow up than efficacy studies in this area. Secondly, effectiveness trials seek to minimize differences between study

conditions and routine clinical practice and so such findings are more readily applicable to clinical practice. Therefore it is important to compare the results found in these trials with the efficacy trials reviewed above to assess whether they confirm conclusions of the efficacy studies and/or provide additional data not usually reported in other trials. However, it should also be noted there are clear disadvantages in that given the complexity, and the reduced level of control usually associated with these studies, it is difficult to draw firm conclusions on causality.

MIND-IT

MIND-IT is the largest European trial of interventions for people with depression and chronic physical health problems. This study focused on the safety of antidepressants in people who had a myocardial infarction, within this study a nested RCT was conducted comparing mirtazapine and placebo which is included in the meta-analysis above (VAN DEN BRINK2002).
In total, 209 participants were randomised to receive an intervention and 122 care as usual. Of those assigned to treatment, however 115 were subsequently excluded (87 broke with the protocol, and 28 did not have depressive disorder). Of the remaining 94 in the treatment group, three dropped out, 47 received double blind mirtazapine (and 15 of these did not respond and then received open label citalopram after 8 weeks), 23 received double blind placebo followed by citalopram after 8 weeks, and 21 only received placebo. In addition, of those who received care as usual 20 also received antidepressants. Given the large drop out after randomisation and the many differences within groups in their treatment it is difficult to draw firm conclusions. However, this is a large study with relatively long follow up data (18 months) and given the general paucity of data it is still of some importance in assessing the effectiveness of antidepressants.

It was observed (Van Melle *et al.*, 2007) that non-remission (according to ICD-10 depression diagnosis) of 30.5% in the intervention group and 32.1% in the control group occurred, which was not statistically significant (OR = 0.93; 0.53, 1.63). For intention-to-treat analyses a similar lack of difference was found (OR=1.09; 0.70, 1.70). This lack of effect may partly be explained by the often short-lived nature of depression after an MI.

There were also no differences in the incidence of cardiac events (14% in the intervention group and 13% in the control group). Specifically comparing those receiving pharmacological treatment with those who did not in the usual care arm, similarly found little difference (OR=0.84 CIs 0.38, 1.84). This effect is reduced further when using an ITT analysis (OR = 0.95; 0.41, 2.19). This suggests the use of mirtazapine is safe in people who have had an MI but does not indicate a protective effect on further cardiac events.

ENRICHD

ENRICHD was a US study conducted on people who had experienced an MI. This mainly consisted of participants who had a relatively recent MI (median 6 days) compared to a minimum period of 3 months post-MI for MIND-IT. This section will focus on the antidepressant treatment aspect of the trial for further details on the results of this trial see chapter 7.

ENRICHD (2003) reported the main findings of this trial. The sample size was very large with a total of 1238 patients randomized to receive an intervention and 1243 to receive usual care. There was high usage of antidepressants (mainly SSRIs) in both treatment (baseline 9.1%, 6 months 20.5%, end of follow up 28%) and usual care (baseline 3.8%, 6 months 9.4%, end of follow up 20.6%) groups. Although this study does not provide randomized data on antidepressant use versus control it is still a large data set that maybe informative on evaluating their effectiveness.

For the primary outcome of the study, death or non-fatal MI, there was a reduced risk for those taking antidepressants (adjusted HR = 0.63; 0.46, 0.87). Specifically for SSRI use there was a further reduction in risk (adjusted HR = 0.57; 0.36, 0.85).

8.2.8 Clinical evidence summary

Antidepressants were associated with a reduction in depression outcomes of a small-to-medium magnitude. Most of the studies compared SSRIs with placebo and these reductions in depression were consistent across a range of physical health disorders including cancer, diabetes, stroke and heart disease. There was also some evidence for benefit for TCAs compared with placebo. There was limited evidence for all other drugs. A number of trials compared SSRIs with TCAs and there appeared to be little difference in efficacy but SSRIs appeared to be better tolerated and safer than TCAs.

Data on physical health outcomes and quality of life were limited and this was further hampered by inconsistent reporting in the efficacy trials. There was better reporting of cardiac outcomes in the two effectiveness trials. MIND-IT found no difference between people using antidepressants and those who did not on cardiac events. However, ENRICHD found a relatively large reduction in hazard ratio for fatal or non-fatal MI particularly for participants receiving SSRIs. Therefore there is some evidence that SSRIs and mirtazapine are safe for people who have had an MI, and that SSRIs may actually be protective of further cardiovascular events.

8.3 Adverse effects of pharmacological interventions

8.3.1 Introduction

At present there are few reviews that seek comprehensively to evaluate antidepressants for people with depression and chronic physical health problems in terms of effectiveness, adverse effects and interactions with other medications.

This is particularly important given that treating depression in people with physical health problems is potentially more challenging in terms of the adverse effects of medication (as the physical illness may make people more vulnerable to effects such as gastrointestinal bleeding and cognitive deficits). In addition, people in this population are likely to be taking a number of different medications related to their physical condition therefore there is a greater likelihood of potential interactions with antidepressants. This issue of interactions is dealt with in detail in section 8.4.

Definition and aim of review

The purpose of this review was to assess the adverse effects and adverse effect burden of antidepressants for the treatment of depression in people with chronic physical health problems. Following discussion with the GDG the search was limited to systematic reviews assessing adverse effects related to weight (gain/loss), sexual functioning, cognition, gastro-intestinal symptoms, cardio-toxicity and mortality. In addition, antidepressants were limited to those most commonly used in clinical practice including SSRIs, third generation antidepressants, TCAs, MAOIs.

8.3.2 Databases searched and inclusion/exclusion criteria

Information about the databases searched and the inclusion/ exclusion criteria used for this section of the guideline can be found in Table 57 (further information about the search for health economic evidence can be found in section 8.4).

Table 57. Databases searched and inclusion/exclusion criteria for clinical evidence.

Electronic databases	MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Library
Date searched	Database inception to January 2009
Study design	Systematic reviews
Patient population	People with depression and chronic physical health problems
Interventions	SSRIs, Third generation antidepressants, TCAs, MAOIs, Trazadone, Psychostimulants
Outcomes	Adverse effects of pharmacological interventions: weight, sexual functioning, cognition, gastro-intestinal symptoms, cardio-toxicity, and mortality

8.3.3 Studies considered[22]

The review team conducted a new systematic search for RCTs that assessed the efficacy and safety of antidepressants and related health economic evidence (see section 8.4).

Nineteen systematic reviews relating to clinical evidence met the eligibility criteria set by the GDG. All were published in peer-reviewed journals between 1999 and 2008. In addition, 58 studies were excluded from the analysis. The most common reason for exclusion was that no relevant outcomes were reported in the review (further information about both included and excluded studies can be found in Appendix 18).

8.3.4 Clinical evidence on adverse effects of antidepressants

The key characteristics of the included systematic reviews are summarized in Table 58.

[22] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).

Table 58 Summary characteristics of included systematic reviews on adverse effects

Study ID	Focus of review	Method of synthesis	Inclusion criteria	Results
Taylor (2008)	Cardiovascular	Narrative	Design: no restriction (focus on meta-analyses) Population: people with cardiovascular diseases Intervention: Most antidepressants	Tricyclics: highly cardiotoxic in overdose and may induce CVD Reboxetine, Duloxetine, Venlafaxine increase blood pressure Other antidepressants: neutral or beneficial in various CVDs
Swenson (2006)	Cardiovascular	Meta-analysis	Design: RCT Population: people with chronic physical health problems, substance misuse, and older adults Interventions: SSRIs and TCAs	SSRIs vs placebo: reduced risk of serious adverse events (not statistically significant) SSRIs vs TCAs: reduced risk of non-serious adverse events
Ramasubbu (2004)	Cerebrovascular	Narrative	Design: RCTs, controlled studies, WHO data monitoring programme, case studies Interventions: SSRIs	Controlled studies: no association between SSRIs and increased adverse cerebrovascular effects WHO data on SSRI induced cardiovascular effects: fluoxetine (122 cases), paroxetine (51), sertraline (47), citalopram (13), fluvoxamine (7) Case studies: 4 cases of vasoconstricitve stroked related to SSRIs
Weinreib (2003)	Bleeding	Narrative	Design: controlled studies, national prescribing databases, case studies Intervention: SSRIs	Increased risk of bleeding associated with SSRIs and SSRI/NSAID use
Yuan (2006)	Bleeding	Narrative	Design: controlled studies, national prescribing databases, case studies Intervention: SSRIs	Increased risk of bleeding associated with SSRIs and SSRI/NSAID use
Werneke *et al.* (2006)	Sexual dysfunction	Narrative	Design: primarily RCTs, meta-analyses, supplemented with controlled studies, case studies where data limited	SSRIs: paroxetine highest prevalence Third generation: venlafaxine highest prevalence; reboxetine,

Study ID	Focus of review	Method of synthesis	Inclusion criteria	Results
			Intervention: SSRIs, Third generation, TCAs, MAOIs	buproprion less risk TCAs: clomipramine highest prevalence; amitryptyline, doxepin lowest prevalence MAOIs: high prevalence but less in moclobemide
Gregorian *et al.* (2002)	Sexual dysfunction	Narrative	Design: no limitations Interventions: SSRIs, Third generation	SSRIs: consistent evidence of high prevalence of sexual adverse effects compared with placebo; buproprion less adverse effects, nefazadone also compared with SSRIs
Beasley (2000)	Fluoxetine	Meta-analysis	Design: RCTs Intervention: Fluoxetine	Increased risk of GI symptoms, sexual dysfunction compared with placebo Increased risk of GI symptoms (exception constipation) but less risk of postural hypotension compared with TCAs
Wernicke *et al.* (2004)	Fluoxetine	Narrative	Design: no limitations Intervention: Fluoxetine	Acceptable tolerability in a range of populations (diabetes, stroke, cancer, cardiovascular disease) Increased risk of GI symptoms One case report of loss of hypoglaecemic awareness in diabetes
Brambilla *et al.* (2005)	Fluoxetine	Meta-analysis	Design: RCT Intervention: Fluoxetine	GI symptoms (nausea, vomiting, diarrhoea) higher prevalence in fluoxetine Weight: loss greater in fluoxetine compared with TCAs and other SSRIs
Dhillon (2008)	Buproprion	Narrative	Design: no limitation Intervention: Buproprion	Risk of seizures with an incidence ~0.4% but increases 10-fold with higher doses (450-600mg) Less risk of sexual dysfunction compared with SSRIs Risk of weight loss compared with placebo Risk of increase in blood pressure
Demyttenaere & Jaspers (2008)	Buproprion and SSRIs	Narrative	Design: no limitation	Reduced risk of risk of adverse sexual effects in buproprion compared with SSRIs

Study ID	Focus of review	Method of synthesis	Inclusion criteria	Results
				Risk of weight loss for buproprion Risk of weight loss for some SSRIs early on treatment but risk of weight gain later on in treatment
Duggan & Fuller (2004)	Duloxetine	Narrative	Design: no limitation Intervention: Duloxetine	Increase in blood pressure Possible risk of weight loss Higher risk of sexual dysfunction compared with placebo
Wernicke *et al.* (2007)	Duloxetine	Narrative	Design: no limitation Intervention: Duloxetine	Increase in palpitations, tachycardia, orthostatic hypotension, cholesterol compared with placebo Sexual dysfunction higher than placebo
Hansen *et al.* (2005)	Second and Third Generation Antidepressants	Narrative	Design: no limitation Intervention: Duloxetine	Venlafaxine higher risk of nausea and vomiting than SSRIs Mirtazapine associated with weight gain
Machado *et al.* (2006)	Antidepressants	Meta-analysis	Design: RCTs Intervention: most antidepressants	TCAs the highest overall adverse event profile, followed by SNRIs
Wade & Rosenberg (2000)	Citalopram	Narrative	Design: no limitations Intervention: citalopram	Less adverse events than TCAs (constipation, tachycardia) No differences found between citalopram and other SSRIs
Keller (2000)	Citalopram	Narrative	Design: no limitations	Greater risk of nausea than placebo but less than fluvoxamine Risk of small increase in heart beat
Edwards & Anderson (1999)	SSRIs	Meta-analysis and Narrative	Design: Minor limitation – a number of included studies also included a percentage of patients with psychosis.	CSM and Prescription-event monitoring data: Greater risk of adverse events, including discontinuation reaction to Paroxetine and greater risk of gastrointestinal adverse events to Fluvoxamine and Paroxetine compared with other SSRIs. Controlled studies: More patients discontinued Fluvoxamine because of adverse events. Less patients discontinued Sertraline.

Cardiovascular

Cardiovascular symptoms have received the most extensive attention in the literature in comparison with other adverse effects.

There is broad consensus that SSRIs are well tolerated in people with cardiovascular and cerebrovascular diseases (for example, Swenson *et al.*, 2006; Taylor, 2008). In addition, SSRIs do not appear to be associated with an increase in risk of cardiovascular adverse effects (Ramasubbu, 2004; Swenson *et al.*, 2006; Taylor, 2008). For example, in a meta-analysis assessing cardiovascular adverse effects in a variety of physical health problems, Swenson and colleagues (2006) found that the SSRI group had reduced risk of cardiovascular adverse events compared with placebo (OR = 0.69; 95% CI 0.39, 1.21) and TCAs (OR = 0.46; 95% CI 0.24, 0.86).This is also supported by a relatively low Fatal Toxicity Index (FTI; number of poisoning deaths per million prescriptions) for SSRIs of two (Taylor, 2008) suggesting a low risk of arrhythmia.

TCAs have found to be associated with greater risk of cardiovascular related adverse effects in comparison with SSRIs as discussed above. As a consequence of their Na^+channel blocking properties (Class I anti-arrhythmic effect), TCAs are likely to be pro-arrhythmic in patients with recent myocardial infarction and their use is contraindicated (BNF issue 56). Following the CAST I study (Echt *et al.,* 1991) all Class I anti-arrhythmics are used extremely cautiously in all patients with significant structural heart disease hence the same should apply to TCAs. In addition, they have found to be highly cardiotoxic in overdose and may induce CVD (Taylor, 2008). The FTIs for TCAs range from 12 to 43. However, lofepramine is an exception with a low FTI of between 1.3 and 2.7. In tricyclic overdose, cardiac arrhythmia and seizures probably account for the majority of deaths (Taylor, 2008).

Other antidepressants were associated with possible risk of cardiovascular problems although further data is required to confirm this. Duloxetine appears to be associated with small increases in diastolic blood pressure, tachycardia, and cholesterol compared with placebo (Duggan & Fuller, 2004; Wernicke *et al*., 2007). In addition, buproprion was found to increase blood pressure in two case reports (Dhillon *et al*., 2008). The FTI for venlafaxine is estimated between 13 and 18, which indicates moderate acute toxicity. However, it appears not to effect changes in ECG in standard doses or be associated with arrhythmia in overdose (Taylor, 2008). In contrast, for mirtazapine, reboxetine and mianserin their FTIs are of a similar magnitude to the SSRIs (Taylor, 2008) suggesting they are relatively safe in respect to proarrhythmic effects.

Bleeding

Two systematic reviews were identified concerning the association between SSRIs and bleeding (Weinrieb *et al.,* 2003; Yuan *et al.,* 2006). Evidence on this association is provided from several observational studies often using data from national prescribing databases. A study (De Abajo *et al*., 1999) utilizing data from the GPRD in the UK found an increased risk of bleeding for people on SSRIs (adjusted rate ratio = 3.0, 95% CI 2.1, 4.4), this risk was magnified with concurrent SSRI and NSAID use (rate ratio of 15.6). Similar findings were also identified when using a Danish prescribing database (Dalton *et al*., 2003), SSRI use (RR = 3.6; 95% CI 2.7, 4.7) and particularly concurrent NSAID and SSRI use (RR = 12; 95% CI 7.1, 19.5) were associated with gastro-intestinal (GI) bleeding. Both systematic reviews concluded that extreme caution was required when prescribing SSRIs in populations at risk of bleeding disorders.

Gastro-intestinal symptoms

There was some evidence that SSRIs were associated with a greater risk of GI symptoms such as nausea, vomiting and diarrhoea. This was slightly higher in fluoxetine than other SSRIs, TCAs and placebo (Brambilla *et al.,* 2005; Beasley *et al.,* 2000). Citalopram was associated with a lower risk of nausea compared with fluvoxamine (Keller, 2000).TCAs were associated with higher risk of constipation when compared with fluoxetine (Beasley *et al.,* 2000)

Sexual dysfunction

The association between antidepressants and sexual dysfunction was considered specifically in two of the included systematic reviews (Werneke *et al*., 2006; Gregorian *et al*., 2002) but also as an outcome in a number of other included reviews.

There was consistent evidence of sexual adverse effects in association with SSRI use (Werneke *et al.,* 2006; Gregorian *et al.,* 2002; Beasley *et al.,* 2000; Keller, 2000). The prevalence of sexual adverse effects appeared to be particularly high in paroxetine (Werneke *et al.,* 2006). There was also evidence of increased risk of sexual adverse effects in citalopram (Werneke *et al*., 2006), fluoxetine (Beasley *et al.,* 2000) and most other SSRIs in comparison with placebo. Comparisons between SSRIs and other antidepressants show lower risk of sexual adverse effects in buproprion compared with both sertraline and fluoxetine. There was more sparse evidence showing amitryptiline and nefazadone were also associated with lower risk of sexual dysfunction compared with SSRIs.

TCAs as a class had the highest risk with up to 90% of participants reporting adverse effects. Although there were marked differences between TCAs with clomipramine associated with the highest risk and amitriptyline and doxepin the lowest.

Venlafaxine (Werneke *et al.,* 2006) and duloxetine (Duggan & Fuller, 2004) also appeared to increase risk of sexual adverse effects compared with placebo. Although Duloxetine (50.2%) was associated with a slightly lower prevalence of sexual dysfunction than Paroxetine (61.5%) the risk was much higher than with placebo. As discussed above buproprion seems to have a low risk of sexual adverse effects this was also found for reboxetine (Werneke *et al.,* 2006).

Weight

There was consistent evidence that fluoxetine was associated with greater loss in weight compared with placebo (Beasley *et al.,* 2000), TCAs and other SSRIs (Brambilla *et al.,* 2005). However, as noted by Demyttenaere and Jaspers (2008), these effects are reported early on in treatment. When assessing continuation studies there is a possibility that paroxetine and fluoxetine may actually be associated with weight gain but this needs further research to establish this finding.

There was evidence that some other antidepressants have an impact on weight. People receiving buproprion were twice as likely to experience greater than 2kgs reduction in weight than people on placebo (Dhillon *et al.,* 2008). Duloxetine was also associated with weight loss with a mean reduction of 2.2kg compared with 1kg for placebo (Duggan & Fuller, 2004). In contrast, mirtazapine was associated with weight gain of approximately 2kgs over 8-13 weeks (Hansen *et al.,* 2005). There is also some evidence from early studies that TCAs were also associated with weight gain (Berken *et al.,* 1984; Fava, 2000).

8.4 Interactions between medications for treating physical health conditions and antidepressants

8.4.1 Introduction

Drug interactions are classified as pharmacokinetic or pharmacodynamic in nature. In pharmacokinetic interactions, one drug affects the absorption, distribution, metabolism or elimination of other co-administered drugs. In pharmacodynamic interactions, one drug opposes or enhances the pharmacological action of another through, for example, competition for receptor sites or by affecting the same physiological process in different ways. Antidepressant drugs are associated with both pharmacokinetic and pharmacodynamic interactions; the former being more clinically relevant with selective serotonin re-uptake inhibitors (SSRIs) and lithium, and the latter with tricyclic antidepressants (TCAs).

The British National Formulary (BNF) includes a summary appendix dedicated to drug interactions. More detailed information can be found in Stockley's Drug Interactions (Stockley, 2008). These sources should be

checked before adding new drugs to a prescription, particularly if; (1) any of the drugs prescribed have a narrow therapeutic index, that is are ineffective at low doses/plasma levels and potentially toxic at higher doses/plasma levels, or; (2) are known to affect cardiac or renal function. The narrative summary below is illustrative only; it is not a comprehensive account of all drug interactions with antidepressants. For further details see Appendix 16.

8.4.2 Pharmacokinetic interactions

The most significant pharmacokinetic interactions involving antidepressants are mediated through inhibition of hepatic cytochrome P450 (CYP) metabolising enzymes. Some SSRIs are potent inhibitors of individual or multiple CYP pathways. It should be noted that the clinical consequences of pharmacokinetic interactions in an individual patient can be difficult to predict; the degree of enzyme inhibition, the relationship between plasma level and pharmacodynamic effect for each affected drug, and patient specific factors such as variability in the role of primary and secondary metabolic pathways and the presence of co-morbid physical illness will all influence outcome.

In general, inhibition of a specific CYP enzyme will lead to increased plasma levels and enhanced effect (possibly frank toxicity) from other co-administered drugs that are metabolised by the same CYP enzyme. Examples of antidepressant mediated interactions can be seen in Table 59.

Inducers of CYP have the potential to reduce plasma levels of co-prescribed drugs leading to treatment failure. Known inducers include cigarette smoke (CYP1A2), carbamazepine (CYP1A2 , 2D6 and 3A4) and rifampicin (CYP3A4). A patient, for example, who is prescribed a TCA and who stops smoking may experience increased side-effects, or even toxicity from the TCA. While no licensed antidepressants are known inducers of CYP, the herbal preparation St John's Wort, can precipitate a number of significant interactions in this way.

Table 59 Pharmacokinetic interactions (Mitchell 1997; Lin & Lu, 1998; Richelson, 1998; Greenblatt *et al*, 1998; Taylor 1997; HIVInSite, 2008)

CYP4501A2	CYP4502C9/19	CYP4502D6	CYP4503A4
Inhibited by:	***Inhibited by:***	***Inhibited by:***	***Inhibited by:***
cimetidine	cimetidine	chlorpromazine	amprenavir
ciprofloxacin	delavirdine	**duloxetine**	delavirdine
erythromycin	**fluoxetine**	**fluoxetine**	erythromycin
fluvoxamine	**fluvoxamine**	fluphenazine	**fluoxetine**
paroxetine	**sertraline**	haloperidol	**fluvoxamine**
		paroxetine	ketoconazole
		ritonavir	nelfinavir
		sertraline	**paroxetine**
		tricyclics	saquinavir
			sertraline
			tricyclics
Metabolises:	***Metabolises:***	***Metabolises:***	***Metabolises:***
caffeine	diazepam	clozapine	benzodiazepines
clozapine	omeprazole	codeine	calcium blockers
duloxetine	phenytoin	donepezil	carbamazepine
tolbutamide	flecainide	cimetidine	haloperidol
mirtazapine	tricyclics	haloperidol	clozapine
warfarin	metoprolol	codeine	olanzapine
propranolol		mirtazapine	donepezil
theophylline		phenothiazines	erythromycin
tricyclics		pimozide	galantamine
warfarin		propafenone	methadone
		risperidone	mirtazapine
		tricyclics	reboxetine
		tramadol	risperidone
		trazodone	steroids
		venlafaxine	terfenadine
			trazodone
			tricyclics
			valproate
			venlafaxine
			Z-hypnotics

Most SSRIs are CYP inhibitors and the magnitude of the effect is dose related. Notable examples are; (1) f**luvoxamine** is a potent inhibitor of CYP1A2 which results in a significant interaction potential with a variety of other drugs; for example increased bleeding risk with warfarin, and increased seizure risk

with clozapine; (2) f**luoxetine** and **paroxetine** are potent inhibitors of CYP2D6 and CYP3A4 (3) c**italopram, escitalopram, sertraline** and **duloxetine** are moderate inhibitors of CYP2D6.

Tricyclic antidepressants are thought to have minimal effects on CYP enzymes but there are few clinical studies to support this assumption. The metabolism of TCAs is inhibited (TCA levels increased with an associated increased risk of side-effects) by drugs which inhibit CYP1A2, CYP2C9/19, CYP2D6 and CYP3A4. For example, the addition of fluoxetine to imipramine or nortriptyline can result in an up to four-fold increase in serum levels of the TCA. Other commonly prescribed drugs that can raise TCA levels include ciprofloxacin, erythromycin and cimetidine.

St John's Wort (SJW) is a herbal preparation that can be bought without a prescription. It is a known potent inducer of several CYP enzymes; an effect that can lead to increased metabolism of co-prescribed drugs and consequent treatment failure. Clinically significant interactions with SJW include anticonvulsant drugs, digoxin, protease inhibitors, theophylline, ciclosporin, oral contraceptives and warfarin (Committee on Safety of Medicines, 2000). In addition, being a serotonergic drug, SJW can precipitate serotonin syndrome when used in combination with SSRIs or other serotonergic drugs.

Pharmacokinetic interactions involving lithium

Unlike antidepressants, lithium is not metabolised by the liver. It is primarily excreted unchanged in urine; to the kidney, lithium is indistinguishable from sodium. Lithium has a narrow therapeutic index; the differences between a sub-therapeutic, therapeutic and toxic plasma level are small. It therefore follows that other drugs that alter the way in which the kidney handles sodium, or reduce the glomerular filtration rate, can precipitate clinically significant interactions with lithium. In addition, lithium is often prescribed for elderly patients, many of whom also require treatment with drugs that have the potential to decrease renal elimination of lithium (Juurlink *et al.*, 2004). These drugs include ACE inhibitors and diuretics (used to treat cardiovascular disease), and NSAIDs (used to treat pain and inflammation). Such drugs can be co-prescribed safely with lithium if the interacting drug is taken regularly and lithium levels are checked (and the dose altered as necessary) after the interacting drug is initiated or the dose is changed.

ACE inhibitors, can increase lithium serum levels. The magnitude of this effect is unpredictable and ranges from no increase to four-fold. The full effect can take several weeks to develop. ACE inhibitors can also precipitate renal failure, so extra care is needed in monitoring both serum creatinine and lithium, if these drugs are prescribed together. Care is also required with angiotensin-2 antagonists.

Diuretics can increase serum lithium levels, any effect usually being apparent within 10 days of a thiazide diuretic being prescribed; again, the magnitude of the rise is unpredictable and can vary from 25% to 400%. Loop diuretics are somewhat safer. Patients taking diuretics may have been advised to restrict their salt intake and this may contribute to the risk of lithium toxicity in these individuals. The addition of diuretic therapy to ongoing lithium treatment can cause severe lithium toxicity.

Non-steroidal anti-inflammatory drugs (**NSAIDs**) can increase serum lithium levels. Both the onset (from a few days to several months) and magnitude of the rise (10% to over 400%) are unpredictable for any given patient. Ibuprofen can be obtained without a prescription and so patients should be aware of the potential interaction. Lithium toxicity has also been reported with COX 2 inhibitors.

8.4.3 Pharmacodynamic interactions

Tricyclic antidepressants are involved in a number of pharmacodynamic interactions (Watsky & Salzman, 1991). They are antagonists at histamine, H1, receptors and show additive effects with other sedative drugs and alcohol. Tricyclics also possess anticholinergic properties which exacerbate dry mouth, constipation, blurred vision and problems with cognition associated with other anticholinergic drugs. They cause postural hypotension by antagonising adrenergic alpha-1, receptors and may show additive effects with other alpha blockers and hypotensive drugs in general; this may, for example increase the risk of falls. All TCAs are cardiac sodium channel antagonists and are associated with arrhythmogenic activity and QRS prolongation. Their use should be avoided in patients taking drugs which affect cardiac conduction (e.g. antiarrhythmics, moxifloxacin) and caution is required with drugs likely to lead to electrolyte disturbance (e.g. diuretics). Tricyclics also lower seizure threshold; caution is required when prescribing other proconvulsive drugs and in epilepsy. Some TCAs (amitriptyline, clomipramine) are serotonergic and may have additive effects (risk of serotonin syndrome) with other serotonergic drugs (e.g. SSRIs, selegiline, tramadol, Triptans, St John's Wort).

SSRIs (Mitchell, 1997; Edwards & Anderson, 1999) increase serotonergic transmission and show additive effects with other serotonergic drugs (e.g. tramadol, selegiline, Triptans, St John's Wort), increasing the risk of serotonin syndrome. SSRIs also inhibit platelet aggregation and are associated with an increased risk of bleeding. Upper gastrointestinal bleeding is a particular concern in elderly patients receiving SSRIs in combination with aspirin or NSAIDs (Loke *et al.*, 2008). SSRIs may also lower seizure threshold which can complicate the management of epilepsy and may cause osteopenia (which complicates the management of osteoporosis). They seem to be more likely than other antidepressants to cause hyponatraemia, particularly in the

elderly; the risk may be increased by other drugs that increase sodium loss, such as diuretics. **Duloxetine** and **venlafaxine** have a similar profile.

Monoamine oxidase inhibitors (**MAOIs;** Livingston & Livingston, 1996) are involved in potentially serious pharmacodynamic interactions with sympathomimetic drugs, pressor agents, and serotonergic or noradrenergic drugs. Hypertensive crisis and serotonin syndrome can result.

Mirtazapine causes additional drowsiness and cognitive impairment when given with other sedatives. It should not be used at the same time as MAOIs and used with caution with other serotonergic or noradrenergic drugs.

Reboxetine should not be given at the same time as MAOIs or ergot derivatives.

8.4.4 Health economic evidence

The guideline systematic literature search identified one economic study on pharmacological interventions in this population. The study by O'Connor and colleagues (2005) compared the costs and benefits of Sertraline versus placebo.

The study conducted in the US evaluated the potential economic and clinical implications associated with sertraline in the treatment of patients with major depressive disorder (DSM-IV) hospitalised for acute coronary syndrome (ACS). The effectiveness evidence was derived from SADHART (Sertraline Antidepressant Heart Attack Randomised Trial), a randomized, double blind, 24-week trial. Patients were given a 50mg/day dosage of Sertraline for the first 6 weeks and depending on response and tolerability it was increased to a maximum of 200mg/day at week 12. A minimum daily dose of 50 mg was maintained.

Direct costs relating strictly to inpatient services were estimated from the perspective of the 3rd party payer using Medicare fee schedules and average wholesale prices. Resource use data was collected prospectively on the same sample of patients as that used in the clinical trial.

The clinical study highlighted that fewer adverse events i.e. psychiatric and/or cardiovascular hospitalizations, were observed in the intervention group than in the placebo group, although the difference was not statistically significant. The mean cost per patient in the intervention group was $2,733 (+/- 6,764) and $3,326 (+/- 7,195) in the placebo group, (p=0.32), these costs excluded the cost of medication. The costs for the intervention group increased to $3093 after inclusion of the cost of medication compared to $3326 for the placebo group.

The authors concluded that sertraline appeared to be a cost-effective strategy in the treatment of major depressive disorder following hospitalization for a recent myocardial infarction or unstable angina. They also noted that their results were likely to have underestimated real cost-differences, as some potential cost-savings associated with sertraline, such as reduced outpatient use, were not considered. This trial was conducted in multiple sites including Europe thereby suggesting that, the results are generalisable to many patient populations.

Summary

The pharmaco-economic evidence identified was limited to one study. The evidence is on patients with acute coronary syndrome and may not be truly representative of all patients with depression and chronic physical health problems. This limits the use of the economic evidence in making any solid conclusions about a pharmacological intervention in this population.

When making treatment decisions regarding the use of an antidepressant many factors should be taken into consideration i.e. patient choice, clinical history, current medication, side effect profiles and the cost of the drug (Table 60. In this population, a special emphasis is placed on the side effect profile and potential drug interactions, since many service users may already be on other treatments for their physical condition and this increases the potential for such events to occur. People with co-morbidities tend to be high utilisers of services and incur many costs over the course of their treatment. Therefore, when selecting an antidepressant, explore the potential of any adverse events as it may reduce further costs being incurred. It may result in cost savings, as the potential costs of treating such events are preventable.

Table 60: Drug acquisition costs

Drug	ADQ Unit	Unit cost (BNF 56, September 2008)	Weekly cost
Sertraline	50 mg	50 mg, net price 28-tab pack = £1.31	£0.33
Citalopram	20 mg	20 mg, 28-tab pack = £1.24	£0.31
Mianserin	30mg	30 mg, 28-tab pack = £11.23	£2.81
Mirtazapine	30mg	30 mg, 28-tab pack = £3.14	£0.79
Reboxetine	8mg	4 mg, net price 60-tab pack = £18.91	£4.41
Trazodone	150mg	trazodone hydrochloride 150 mg, net price 28-tab pack = £7.07	£1.77

Moclobemide	300mg	300 mg, 30-tab pack = £3.96	£0.92
Escitalopram	10mg	Cipralex®(Lundbeck) 10 mg (scored), 28-tab pack = £14.91	£3.73
Venlafaxine XR	100mg	Efexor® XL(Wyeth) 75 mg 28-cap pack = £23.41; Non-proprietary 75mg, 56-tab = £31.61*	£7.80 £5.26

*based on the Electronic Drug Tariff as of 23 May 2009 (NHS, Business Services Authority, 2009).

8.4.5 Network meta-analysis of newer antidepressants

A network meta-analysis conducted by Cipriani and colleagues (2009) was published at the end of the guideline development process and was briefly considered by the GDG in view of its methodology and importance. A full discussion of the study and a preliminary *de novo* economic analysis based on its findings are presented in the updated depression guideline (NICE, 2009).

In summary, a multiple-treatments meta-analysis, using both direct and indirect comparisons, assessed the effects of 12 new-generation antidepressants on major depression in terms of efficacy (response) and tolerability (dropouts). The results showed that mirtazapine, escitalopram, venlafaxine and sertraline were ranked as the four most efficacious treatments whilst escitalopram, sertraline, bupropion and citalopram were ranked as the four most tolerated antidepressants. The results of the economic analysis ranked mirtazapine, sertraline, escitalopram and citalopram as the four most cost-effective treatments. Mirtazapine dominated (cheaper and more effective) all other antidepressants considered in the analysis. Overall, given the considerable uncertainty surrounding both the results of the original meta-analysis and the *de novo* economic analysis, it was decided that any recommendations on specific pharmacological treatments in the updated depression guideline (NICE, 2009) would not be influenced by the findings of Cipriani and colleagues (2009). In addition, as the study was not based on participants with chronic health problems, the findings may be of limited relevance to this guideline.

8.5 Overall summary on Efficacy, Safety, Side Effects and Interactions, and Economic Evidence

Antidepressants are effective in the treatment of depression associated with chronic physical illnesses. Effect sizes are small to moderate; similar to those seen in depression not associated with physical illness. There is a clear distinction between the acute effects of antidepressants and placebo but there is very little information on the longer term therapeutic effects of antidepressants in chronic physical illness.

In respect to therapeutic effects there appears to be little to choose between individual antidepressants or antidepressant groups. SSRIs tend to be better tolerated than tricyclic drugs. Newer non-SSRI antidepressants are also effective and appear to be reasonably well-tolerated.

Interaction potential differs somewhat between individual antidepressants, but generally speaking, no particular drug can be recommended for all clinical conditions. Tricyclics are involved in a wide range of interactions and are contra-indicated in some physical illnesses particularly those involving in cardiac disease. SSRIs, particularly fluoxetine and paroxetine, are potent enzyme inhibitors involved in a wide range of interactions. SSRIs in general are linked to anti-platelet effects which preclude their use in a number of cardiovascular and other conditions. In some cases, the use of alternatives to SSRIs and tricyclics may be necessary. These alternatives may include widely used drugs such as mirtazapine and trazodone, but may also include rarely used drugs such as mianserin and moclobemide.

8.5.1 From evidence to recommendations

As has been noted in this chapter the clinical and economic evidence base for pharmacological interventions for people with depression and chronic physical health problems is more limited than that identified for depression in the absence of chronic physical health problems. However, the broad pattern of evidence is similar. Given that the GDG's view was that the nature of depression in chronic physical health problems is not fundamentally different from depression in the absence of such problems the group considered it appropriate to draw on the evidence base for depression more generally in drawing up its recommendations. In doing so the group drew on a number of principles when extrapolating from the general depression evidence base.

Firstly, when there was data on people with chronic physical health problems that was largely consistent with the general depression guideline (for example, the use of sertraline due to lower propensity for interactions) evidence from the latter guideline was taken into account when forming recommendations. Secondly, when there was uncertainty whether evidence concerning people with chronic physical health problems was consistent with that found in the general depression guideline then extrapolation was not attempted. Thirdly, when there was no evidence available concerning the population for the present guideline, and the GDG considered the recommendation to be of importance (for example, switching antidepressants), extrapolation was made from evidence in the general depression guideline.

Generally, SSRIs should be first-line treatment for depression associated with physical illness. Of the SSRIs, sertraline and citalopram probably have the lowest interaction potential, appear to be safe and possibly protective of further cardiac events so generally should be the drugs of first choice. These

are generic drugs and are available relatively cheaply. Their low interaction potential and protective properties make it potentially worthwhile from a cost-effectiveness perspective, as it may result in cost savings due to potential adverse events that are prevented and offer a potential for additional QALY gains. The economic study conducted by O'Connor and colleagues (2005) evaluated sertraline versus placebo in hospitalised population with acute coronary syndrome and found it to be cost-effective. This evidence, although limited to one study, supports recommending sertraline in this population. Tricyclics, despite evidence supporting their therapeutic activity, should generally be avoided as there is evidence of cardio-toxicity and poor tolerability. Where SSRIs are contra-indicated, suitable alternatives include mirtazapine, trazodone, reboxetine, mianserin and moclobemide. The choice of drug can be expected to be largely dependent upon relevant contra-indications related to the physical illness and potential for interaction with co-administered drugs. It is on these latter issues that many of the recommendations focus.

For the pharmacological treatment of patients who have responded poorly to initial pharmacological interventions and more complex depression the NICE Depression Guideline (Update) (NICE, 2009) should be consulted.

8.5.2 Recommendations

Drug treatment

8.5.2.1 Do not use antidepressants routinely to treat subthreshold depressive symptoms or mild depression in patients with a chronic physical health problem (because the risk–benefit ratio is poor), but consider them for patients with:

- a past history of moderate or severe depression **or**
- initial presentation of persistent subthreshold depressive symptoms (that have been present for a long period—typically at least 2 years) or mild depression that complicate(s) the care of the physical health problem **or**
- subthreshold depressive symptoms or mild depression that persist(s) after other interventions. [KP]

8.5.2.2 Although there is evidence that St John's wort may be of benefit in mild or moderate depression, practitioners should:

- not prescribe or advise its use by patients with depression and a chronic physical health problem because of uncertainty about appropriate doses, persistence of effect, variation in the nature of preparations and potential serious interactions with

other drugs (including oral contraceptives, anticoagulants and anticonvulsants)

- advise patients with depression of the different potencies of the preparations available and of the potential serious interactions of St John's wort with other drugs.

The choice of antidepressants

8.5.2.3 When an antidepressant is to be prescribed, tailor it to the patient with depression and a chronic physical health problem, and take into account the following:

- the presence of additional physical health disorders
- the side effects of antidepressants, which may impact on the underlying physical disease (in particular, SSRIs may result in or exacerbate hyponatraemia, especially in older people)
- that there is no evidence as yet supporting the use of specific antidepressants for people with particular chronic physical health problems
- interactions with other medications. [KP]

8.5.2.4 When an antidepressant is to be prescribed, be aware of drug interactions and:

- refer to appendix 1 of the BNF[23] and the table of interactions in appendix 16 for information
- seek specialist advice if there is uncertainty
- if necessary, refer the patient to specialist mental health services for continued prescribing. [KP]

8.5.2.5 First prescribe an SSRI in generic form unless there are interactions with other drugs; consider using citalopram or sertraline as they have less propensity for interactions.

8.5.2.6 When prescribing antidepressants, be aware that:

- dosulepin should not be prescribed
- non-reversible monoamine oxidase inhibitors (MAOIs; for example, phenelzine), combined antidepressants and lithium augmentation of antidepressants should normally be prescribed only by specialist mental health professionals.

[23] Available from: www.bnf.org

8.5.2.7 Take into account toxicity in overdose when choosing an antidepressant for patients at significant risk of suicide. Be aware that:

- compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose
- tricyclic antidepressants (TCAs), except for lofepramine, are associated with the greatest risk in overdose.

Alternatives to SSRIs where interactions preclude their use

8.5.2.8 Do not normally offer SSRIs to patients taking non-steroidal anti-inflammatory drugs (NSAIDs) because of the increased risk of gastrointestinal bleeding. Consider offering an antidepressant with a lower propensity for, or a different range of, interactions, such as mianserin, mirtazapine, moclobemide, reboxetine or trazodone.

8.5.2.9 If no suitable alternative antidepressant can be identified, SSRIs may be prescribed at the same time as NSAIDs if gastroprotective medicines (for example, proton-pump inhibitors) are also offered.

8.5.2.10 Do not normally offer SSRIs to patients taking warfarin or heparin because of their anti-platelet effect.

8.5.2.11 Use SSRIs with caution in patients taking aspirin. When aspirin is used as a single agent, consider alternatives that may be safer, such as trazodone, mianserin or reboxetine.

8.5.2.12 Consider offering mirtazapine to patients taking heparin, aspirin or warfarin (but note that when taken with warfarin, the international normalised ratio [INR] may increase slightly).

8.5.2.13 Do not offer SSRIs to patients receiving 'triptan' drugs for migraine. Offer a safer alternative such as mirtazapine, trazodone, mianserin or reboxetine.

8.5.2.14 Do not normally offer SSRIs at the same time as monoamine-oxidase B (MAO-B) inhibitors such as selegiline and rasagiline. Offer a safer alternative such as mirtazapine, trazodone, mianserin or reboxetine.

8.5.2.15 Do not normally offer fluvoxamine to patients taking theophylline, clozapine, methadone or tizamidine. Offer a safer alternative such as sertraline or citalopram.

8.5.2.16 Offer sertraline as the preferred antidepressant for patients taking flecainide or propafenone, although mirtazapine and moclobemide may also be used.

8.5.2.17 Do not offer fluoxetine or paroxetine to patients taking atomoxetine. Offer a different SSRI.

Starting treatment

8.5.2.18 When prescribing antidepressants, explore any concerns the patient with depression and a chronic physical health problem has about taking medication, explain fully the reasons for prescribing, and provide information about taking antidepressants, including:

- the gradual development of the full antidepressant effect
- the importance of taking medication as prescribed and the need to continue treatment after remission
- potential side effects
- the potential for interactions with other medications
- the risk and nature of discontinuation symptoms with all antidepressants, particularly with drugs with a shorter half-life (such as paroxetine and venlafaxine), and how these symptoms can be minimised
- the fact that physical dependence does not occur with antidepressants.

Offer written information appropriate to the patient's needs.

8.5.2.19 Prescribe antidepressant medication at a recognised therapeutic dose for patients with depression and a chronic physical health problem (that is, avoid the tendency to prescribe at subtherapeutic doses in these patients).

8.5.2.20 For patients started on antidepressants who are not considered to be at increased risk of suicide, normally see them after 2 weeks. See them regularly thereafter, for example at intervals of 2 to 4 weeks in the first 3 months, and then at longer intervals if response is good.

8.5.2.21 A patient with depression started on antidepressants who is considered to present an increased suicide risk or is younger than 30 years (because of the potential increased prevalence of suicidal thoughts in the early stages of antidepressant treatment for this group) should normally be

seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered clinically significant.

8.5.2.22 If a patient with depression and a chronic physical health problem develops side effects early in antidepressant treatment, provide appropriate information and consider one of the following strategies:

- monitor symptoms closely where side effects are mild and acceptable to the person **or**
- stop the antidepressant or change to a different antidepressant if the patient prefers **or**
- in discussion with the patient, consider short-term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic, but:
  - do not offer benzodiazepines to patients with chronic symptoms of anxiety
  - use benzodiazepines with caution in patients at risk of falls
  - in order to prevent the development of dependence, do not use benzodiazepines for longer than 2 weeks.

Continuing treatment

8.5.2.23 Support and encourage patients with a chronic physical health problem who are taking antidepressants to continue medication for at least 6 months after remission of an episode of depression. Discuss with the patient that:

- this greatly reduces the risk of relapse
- antidepressants are not associated with physical dependence.

8.5.2.24 Review with the patient with depression and a chronic physical health problem the need for continued antidepressant treatment beyond 6 months after remission, taking into account:

- the number of previous episodes of depression
- the presence of residual symptoms
- concurrent physical health problems and psychosocial difficulties.

Failure of treatment to provide benefit

8.5.2.25 If the patient's depression shows no improvement after 2 to 4 weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose.

8.5.2.26 If response is absent or minimal after 3 to 4 weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support (for example, by weekly face-to-face or telephone contact) and consider:

- increasing the dose in line with the summary of product characteristics if there are no significant side effects **or**
- switching to another antidepressant as described in section 1.8 of the Depression update guideline[24] if there are side effects or if the patient prefers.

8.5.2.27 If the patient's depression shows some improvement by 4 weeks, continue treatment for another 2 to 4 weeks. Consider switching to another antidepressant as described in section 1.8 of the Depression update guideline[22] if:

- response is still not adequate **or**
- there are side effects **or**
- the patient prefers to change treatment.

8.5.2.28 When switching from one antidepressant to another, be aware of:

- the need for gradual and modest incremental increases in dose
- interactions between antidepressants
- the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed[25].

8.5.2.29 If an antidepressant has not been effective or is poorly tolerated:

- consider offering other treatment options, including high-intensity psychological treatments
- prescribe another single antidepressant (which can be from the same class) if the decision is made to offer a further course of antidepressants.

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[24] 'Depression: the treatment and management of depression in adults (update) (NICE clinical guideline XX)

[25] Features of serotonin syndrome include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus.

Stopping and reducing antidepressants

8.5.2.30 Advise patients with depression and a chronic physical health problem who are taking antidepressants that discontinuation symptoms[26] may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. Explain that symptoms are usually mild and self-limiting over about 1 week, but can be severe, particularly if the drug is stopped abruptly.

8.5.2.31 When stopping an antidepressant, gradually reduce the dose, normally over a 4-week period, although some patients may require longer periods. This is not required with fluoxetine because of its long half-life.

8.5.2.32 Inform the patient that they should seek advice from their practitioner if they experience significant discontinuation symptoms. If discontinuation symptoms occur:

- monitor symptoms and reassure the patient if symptoms are mild
- consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) if symptoms are severe, and reduce the dose gradually while monitoring symptoms.

Treatment options

8.5.2.33 For patients with persistent subthreshold depressive symptoms or mild to moderate depression and a chronic physical health problem who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the patient and provide:

- an antidepressant (normally a selective serotonin reuptake inhibitor [SSRI]) or
- one of the following high-intensity psychological interventions:
  - group-based CBT **or**
  - individual CBT for patients who decline group-based CBT or for whom it is not appropriate, or where a group is not available **or**
  - couples therapy for people who have a regular partner and where the relationship may contribute to the development

[26] Discontinuation symptoms include increased mood change, restlessness, difficulty sleeping, unsteadiness, sweating, abdominal symptoms and altered sensations.

or maintenance of depression, or where involving the partner is considered to be of potential therapeutic benefit.[27]

8.5.2.34 For patients with initial presentation of severe depression and a chronic physical health problem, consider offering a combination of individual CBT and an antidepressant.[28]

8.5.2.35 The choice of intervention should be influenced by the:

- duration of the episode of depression and the trajectory of symptoms
- previous course of depression and response to treatment
- likelihood of adherence to treatment and any potential adverse effects
- course and treatment of the chronic physical health problem
- patient's treatment preference and priorities.[29]

8.6 Research Recommendations

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

8.6.1 Antidepressant medication compared with placebo in patients with depression and COPD

What is the clinical and cost effectiveness of antidepressant medication compared with placebo in patients with depression and chronic obstructive pulmonary disease (COPD)?

Why this is important

There is limited evidence for the effectiveness of antidepressant treatment in patients with depression and a chronic physical health problem. Of particular concern to the Guideline Development Group was the high incidence of depression in patients with COPD (which is also known to be associated with a high incidence of anxiety disorders). The Guideline Development Group considered it important to measure the effectiveness of antidepressant medication in the treatment of COPD. The answer to this question has

[27] This recommendation also appears in section 7.4.1 where the psychosocial data is presented.
[28] This recommendation also appears in section 7.4.1 where the psychosocial data is presented.
[29] This recommendation also appears in section 7.4.1 where the psychosocial data is presented.

important practical implications for service delivery, particularly for a patient group with mental health needs that are traditionally under-treated within the NHS.

The question should be answered using a randomised controlled trial in which patients with moderate depression and COPD receive either placebo or antidepressant medication. The outcomes chosen should reflect both observer-rated and patient-rated assessments for acute and medium-term outcomes for at least 6 months and an assessment of the acceptability and burden of treatment. In addition to the assessment of symptoms of depression, the study should also assess the impact of antidepressant medication on symptoms of anxiety. The study should be large enough to determine the presence or absence of clinically important effects using a non-inferiority design together with robust health economic measures.

9 Appendices

Appendix 1: Scope for the development of the clinical guideline

Final version

26th October 2007

Guideline title

The treatment and management of depression in adults with chronic physical health problems

Short title

Depression – chronic health problems

Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Mental Health to develop a clinical guideline on the treatment of depression in people with chronic physical health problems for use in the NHS in England and Wales. This is a partial update of the existing guideline 'Depression (amended): management of depression in primary and secondary care' (NICE clinical guideline 23, 2007). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will 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, where 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 large demands on the healthcare system. Among all diseases, depression is currently the fourth leading cause of burden to society. World Health Organization projections indicate that it will be the highest ranking cause of disease burden in developed countries by the year 2020.

There is a greater prevalence of depression in patients with chronic physical health problems than in the general population. Approximately 15–25% of people with chronic physical health problems such as coronary heart disease, diabetes, cancer, stroke, rheumatoid arthritis and multiple sclerosis also meet diagnostic criteria for depression.

Depression is also associated with worse physical health outcomes for people with chronic health problems. For example, people with depression are more likely to die within 4 months of a myocardial infarction than those without depression, and have an increased risk for future cardiac events. Similarly, people with diabetes mellitus and depression often have more severe symptoms, increased functional impairment and more diabetes complications than those without depression.

People with depression are less likely to adhere to physical health treatment as well as adapt to and self manage their condition effectively. For example, people with both depression and diabetes are less likely to adhere to diet, exercise and medication treatment than people who have diabetes without depression.

Identification and recognition of depression in people with chronic physical health problems can be challenging. For example, physical symptoms, such as weight loss, sleep disturbances and low energy are part of the diagnostic criteria for depression. However, medical disorders may also cause these symptoms. Therefore it can be difficult to determine whether such physical symptoms or low mood are due to a depressive disorder or a reaction to the physical illness.

The NICE clinical guideline 'Depression: management of depression in primary and secondary care' (NICE clinical guideline 23) was published in December 2004, and was amended in 2007 to take into account new prescribing advice for venlafaxine. The guideline did not specifically address the management of depression for patients with chronic physical health problems. For that reason it was decided by NICE that this should be included in the update of the original clinical guideline.

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' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' 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 (18 years and older) with a clinical working diagnosis of a depressive disorder and a chronic physical health problem with associated impact on function. This could include, for example, people with cancer, heart disease, neurological disorders or diabetes, and depression.
- The guideline will cover the necessary variations to the assessment of depression, and the systems for accessing and delivering treatment required to take account of the needs of individuals with learning difficulties, acquired cognitive impairments, or language difficulties.

Groups that will not be covered:

- People with other psychiatric disorders, such as, schizophrenia, dementia or substance misuse.
- People with co morbid physical health problems unexplained by physical pathology.
- People with depressive disorders that primarily occur as a side effect of the treatment of a physical disorder.

Healthcare setting

Settings that will be covered:

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

Settings that will not be covered:

- Palliative care
- Clinical management

Topics that will be covered:

- Identification, recognition and assessment of depression in patients with chronic physical health problems.
- The 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, electroconvulsive therapy (ECT)).

- The use of interventions to reduce the risk of relapse after an acute depressive episode.
- The assessment and management of the known side effects and other disbenefits of psychotropic medication, physical interventions and psychosocial interventions, including long-term side effects and risks concerning suicide.
- The use of combined psychosocial and pharmacological treatments, the use of combined pharmacological treatments and the sequencing of both pharmacological and psychosocial interventions.
- The safe discontinuation of psychotropic medication.
- Interactions between psychotropic medication and prescription and over-the-counter drugs commonly used for the relevant co morbid physical disorder.
- The varying approaches of different races and cultures and issues of internal and external social exclusion.
- Ensuring that people with depression and chronic physical health problems have the information they need and the opportunities to discuss with their clinicians the advantages, disadvantages and potential side effects of treatment so that they can make informed choices about the options for their care.
- The role of families and carers in the treatment and support of people with depression and chronic physical health problems.

How 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.

Advice on treatment options will be based on the best evidence available to the guideline development group. The recommendations will be based on effectiveness, safety and cost effectiveness. Note that guideline recommendations for pharmacological interventions will normally fall within licensed indications; exceptionally, and only where 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 support joint clinical decision making between service users and prescribers.

The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or

changing the 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.
Topics that will not be covered:

- Diagnosis of depression or co morbid disorders.
- Primary prevention of depression or co morbid disorders.

Status

Scope

This is the final version of the scope for NICE sign off.
The guideline will update, in part, the following guidance.
Depression (amended): management of depression in primary and secondary care. NICE clinical guideline 23 (amended) (2007). Available from: www.nice.org.uk/CG023
The guideline will incorporate/update the following NICE guidance.
Computerised cognitive behaviour therapy for depression and anxiety. NICE technology appraisal guidance 97. (2006). Available from: www.nice.org.uk/TA097
Guidance on the use of electroconvulsive therapy. NICE technology appraisal guidance 59 (2003). Available from: www.nice.org.uk/TA059

Guideline

The development of the guideline recommendations will begin in January 2008. Its development will be closely coordinated with the update of the Depression (amended): management of depression in primary and secondary care. NICE clinical guideline 23 (amended) (2007) and where appropriate will draw on the evidence base and recommendations from that guideline.

Further information

Information on the guideline development process is provided in:
'The guideline development process: an overview for stakeholders, the public and the NHS'
'The guidelines manual'.
These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health

Depression: the treatment and management of depression in adults with chronic physical health problems is a partial update of the existing guideline 'Depression (amended): management of depression in primary and secondary care' (NICE clinical guideline 23, 2007). The guideline will be developed in

conjunction with 'Depression: the treatment and management of depression in adults (update)'
The original remit from the Department of Health for NICE CG23 is enclosed below:

'We would like the guideline to cover adult patients with moderate to severe depression who have failed to respond to two adequate treatment trials. We would like there to be clear guidance on the role of ECT and other treatment choices'.

Appendix 2: Declarations of interests by GDG members

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

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

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

Categories of interest

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 in adults with chronic physical health problems, holding office in a professional organisation or advocacy group with a direct interest in adults with depression and chronic physical health problems, other reputational risks relevant to depression and chronic physical health problems.

Guideline Development Group - Declarations of interest	
Prof. Sir David Goldberg - Chair, Guideline Development Group	
Employment	Professor Emeritus, Institute of Psychiatry, King's College London
Personal pecuniary interest	Consultant to Ultrasys, providing advice on computerised CBT.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr. Neil Andrews	
Employment	Consultant Cardiologist and Electrophysiologist, Portsmouth NHS Hospital Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Prof. Francis Creed	
Employment	Professor of Psychological Medicine, University of Manchester
Personal pecuniary interest	Given talks sponsored by an educational grant from Eli Lilly.
Personal family interest	None
Non-personal pecuniary interest	A member of research group has received a grant fund.
Personal non-pecuniary interest	Results of research projects in this area have all been published and publicised in talks etc.
Prof. Christopher Dowrick	

Employment	Professor of Primary Medical Care, University of Liverpool
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	My opinions on the complex inter-relationships between physical and psychological problems have been expressed in a variety of publications, and are best summarised in a) Disputed Diagnoses, Chapter 3 of my book Beyond Depression (OUP, 2005), and b) my editorial 'Chickens and Eggs' in International Journal of Psychiatric Medicine 2006; 36:263-267
Dr. Gwyneth Grout	
Employment	Consultant Nurse, Mental Health Liaison (Older People), Hampshire Partnership NHS Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr. Mark Haddad	
Employment	Clinical Research Fellow, Health Service and Population Research Department, Institute of Psychiatry
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Committee member - Royal College of Nursing Mental Health Forum. Board member – American Psychiatric Nurses Association (president elect). Collaborating with mental health charity Rethink on 3-year study of mental health problems in secondary school pupils funded by Health Foundation Improving Quality in Primary Care.

Dr. John Hindle	
Employment	Consultant Physician Care of the Elderly, Clinical Director of Medicine, North West Wales NHS Trust
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Research project on the use of inhaled apomorphine for Parkinson's disease – A clinic-based, phase 11a, randomised, double-blind, placebo-controlled, ascending-dose, multicentre study investigating the safety, tolerability, efficacy and pharmacokinetics of VR040 in patients with established idiopathic Parkinson's disease. Sponsored by Vectura group PLC. Fees received and paid into North West Wales NHS Trust drug trials account to cover the costs of the study and staff time. This company makes no treatments for depression. Study on depression in Parkinson's disease using Pramipexole-248.596. A randomised double-blind, placebo-controlled, parallel group efficacy study of pramipexole and placebo administered over a 12 week treatment phase in Parkinson's disease patients with stable motor function and depressive symptoms. No patients recruited (in fact no UK centre managed to recruit a patient and the study was withdrawn). Sponsored by Boehringer. £500 set up payment paid into the North West Wales NHS Trust drug trials account – used for screened patient travel expenses.
Personal non-pecuniary interest	None
Dr. David Kessler	
Employment	Walport Clinical Lecturer - Primary Care, Bristol University
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Principal investigator in RCT of Cognitive Behavioural Therapy delivered over the internet. This is funded by a grant from the BUPA Foundation.

Personal non-pecuniary interest	None
Prof. James Lindesay	
Employment	Professor of Psychiatry for the Elderly, University of Leicester
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Provided witness Statement for the recent Judicial Review of NICE guidelines for cholinesterase inhibitors. Member of the Alzheimer's Society.
Ms. Margaret Ogden	
Employment	Service user and carer representative
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	
Personal non-pecuniary interest	None
Dr. Jonathan Packham	
Employment	Consultant Rheumatologist, Haywood Hospital. Senior Lecturer, Primary Care Musculoskeletal Research Centre, Arthritis Research Campaign National Primary Care Centre, Keele University
Personal pecuniary interest	Wife runs a consultancy business predominantly training pharmaceutical companies and doing medical writing. She is not closely linked to any one pharmaceutical company and would normally train professionals from all the top 20 pharmaceutical companies during the course of a year.
Personal family interest	None
Non-personal pecuniary interest	Grants received by Rheumatology Department, Haywoods Hospital for: Independent investigators grants from Wyeth and Roche UK Sponsoring a research fellow post from Wyeth Commissioned research as part of multi-centred drug trials – Roche, Wyeth, Celgene,

	Bristol Myers Squibb, Amgen, Genmab.
Personal non-pecuniary interest	None
Prof. David Taylor	
Employment	Chief Pharmacist, South London and Maudsley NHS Trust Professor of Psychopharmacology, King's College, London
Personal pecuniary interest	Consultancy (occasional) for Lundbeck, Eli Lilly, Servier, Wyeth. Fee-paid work for Lundbeck, Wyeth, Eli Lilly.
Personal family interest	Wife is an employee of Novartis; shareholder of Novartis and GlaxoSmithKline stock (non-specific).
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Veronica (Nicky) Thomas	
Employment	Consultant Health Psychologist, Guy's and St. Thomas' NHS Foundation Trust, Honorary Lecturer Department of Psychology, Institute of Psychiatry, Kings College London
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr. Steve Wilcox	
Employment	Head of Occupational Therapy, Specialist Services Directorate, Leeds Partnership NHS Foundation Trust for Mental Health and Learning Disabilities. Honorary Senior Lecturer, Academic Unit of Primary Care, University of Leeds.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

National Collaborating Centre for Mental Health – Declarations of Interest	
Dr. Steve Pilling– Facilitator, Guideline Development Group	
Employment	Joint Director, National Collaborating Centre for Mental Health Director, Centre for Outcomes Research and Effectiveness, University College London.
Personal pecuniary interest	In receipt of funding from NICE to develop clinical guidelines
Personal family interest	None
Non-personal pecuniary interest	Randomised controlled trial to evaluate multi-systemic therapy. Principal investigator is Professor Peter Fonagy. Department of Health funding of £1,000,000. (2008-2012)
Personal non-pecuniary interest	None
Ms. Victoria Bird	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr. Matthew Dyer (2008-2009)	
Employment	Health Economist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms. Katherine Leggett (2008-2009)	
Employment	Project Manager, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Ms. Angela Lewis	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr. Ryan Li (2008)	
Employment	Project Manager, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr. Nicholas Meader	
Employment	Systematic Reviewer, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr. Suffiya Omarjee (2008-2009)	
Employment	Health Economist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms. Catherine Pettinari (2008)	
Employment	Project Manager, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Ms. Maria Rizzo	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr. Rob Saunders (2008-2009)	
Employment	Research Assistant, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms. Sarah Stockton	
Employment	Information Scientist, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr. Clare Taylor	
Employment	Editor, National Collaborating Centre for Mental Health
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Appendix 3: Special advisors to the Guideline Development Group

Name	Position
Cliff Bucknall	Cardiologist
Dr Dominic Bray	Consultant Clinical Health Psychologist

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

Stakeholders

Association for Family Therapy and Systemic Practice in the UK (AFT)
British Association for Counselling and Psychotherapy
British Association for Psychopharmacology
British Association of Art Therapists, British Association of Drama Therapists and the Association of Professional Music Therapists
British Thoracic Society
UK Psychiatric Pharmacy Group (UKPPG)
Department of Health
Diabetes UK
Eli Lilly and Company Limited
Boehringer Ingelheim Ltd
GlaxoSmithKline UK
Guide Dogs for the Blind Association
Headway – The Brain Injury Association
Herpes Viruses Association
Lundbeck Ltd
Mental Health Nurses Association
Mental Health Providers Forum
Mind
NHS Direct
Oxfordshire and Buckinghamshire Mental Health Partnership NHS Foundation Trust
Royal College of Nursing
Royal College of Physicians
Social Care Institute for Excellence (SCIE)
South West London & St George's NHS Trust
St Mungos
Tees Esk & Wear Valleys NHS Foundation Trust
The British Pain Society
The British Psychological Society
The Pernicious Anaemia Society
The Royal College of Psychiatrists

Experts

Professor Elspeth Guthrie
Professor of Psychological Medine & Medical Psychotherapy, Manchester Royal Infirmary

Dr Peter Trigwell, MBChB,MRCPsych
Consultant in Liaison Psychiatry, Leeds Teaching Hospitals NHS. Trust.

Professor Linda Gask MB ChB MSc PhD FRCPsych
Professor of Primary Care Psychiatry

Professor Robert Peveler
Professor of Psychiatry, University of Southampton, Royal South Hants Hospital

Professor Debbie Sharp
Head of Academic Unit and Professor of Primary Health care, University of Bristol

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

Stakeholders

To be completed post-consultation

Experts

To be completed post-consultation

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

Professor Kathleen Ell

Appendix 7: Clinical questions

Note: 'depression' is used in the clinical questions to refer to major depressive disorder, dysthymia, minor depression and subthreshold depression. These are terms used in the literature which forms the evidence base for the guideline but they are not necessarily the terms that will be used in the guideline nor are they assumed to form one homogenous population. Similarly, terms relating to phases of depressive illness, such as treatment-resistant, are intended to help with identifying relevant literature, rather than necessarily reflecting the terms that will be used in the guideline.

Service configuration

1) What methods are effective in identifying people with depression who have physical health problems in primary care, hospital (including general medical), and residential settings?

In which populations should identification methods be used?

2) In the treatment of depression for people with chronic physical health problems, which models of care produce the best outcomes?

- collaborative care
- stepped care
- case management
- stratified (matched) care
- attached professional model
- chronic disease (disease management) model

Are different models appropriate to the care of people in different phases of the illness, such as treatment resistant depression and relapse prevention?

3) In the treatment of depression for people with chronic physical health problems, what systems promote more effective access to care, for example for black and minority ethnic (BME) groups, people with learning difficulties, people in care homes and people experiencing social deprivation?

Psychological/Psychosocial interventions

4) In the treatment of depression for people with chronic physical health problems, do any of the following (either alone or in combination with

pharmacotherapy) improve outcomes compared with other interventions (including treatment as usual):

- Cognitive and behavioural interventions (including problem solving therapy, acceptance and commitment therapy, self-help/guided self-help, computerised CBT)
- counselling/person-centred therapy
- IPT
- psychodynamic psychotherapy
- family, couples and systemic interventions
- psychoeducation
- solution-focused therapy
- occupational therapy
- support (including groups, befriending, and non-statutory provision)
- programmes to facilitate employment
- exercise

Does mode of delivery (group-based or individual) impact on outcomes?
Does setting impact on outcomes?
Are brief interventions (eg 6-8 weeks) effective?
Are psychological interventions harmful?

5) In people with chronic physical health problems whose depression has responded to treatment, what psychological, psychosocial and pharmacological strategies are effective in preventing relapse (including maintenance treatment, continued support)?

Pharmacological interventions

6) In the treatment of depression for people with chronic physical health problems, which drugs improve outcomes compared with placebo:

- SSRIs (e.g. escitalopram)
- 'Third generation' antidepressants (e.g. venlafaxine, desvenlafaxine, agomelatine, duloxetine, mirtazapine, reboxetine)
- MAOIs
- TCAs
- antipsychotics (eg quetiapine)
- trazodone
- maprotiline

7) In the treatment of depression for people with chronic physical health problems, to what extent do the following factors affect the choice of drug:

- interactions with physical health medications
- adverse events (in particular, cardiotoxicity), including long-term adverse events
- discontinuation problems

physical health medications that have depressive effects (for example tetrabenazine, reserpine, beta blockers (such as propranolol), calcium antagonists (verapamil), interferon, retinoids (such as isotretinoin))

8) In the pharmacological treatment of depression for people with chronic physical health problems, what are the most effective strategies for treating patients experiencing treatment side-effects, for example sexual dysfunction and weight gain?

9) In people with chronic physical health problems whose depression does not respond, or responds inadequately, to treatment

which strategies for switching antidepressants are effective?
which strategies for sequencing antidepressants are effective?
which strategies for switching between pharmacological treatment and psychological treatment are most effective and minimize adverse reactions?
which augmentation strategies are safe and effective?

10) What are appropriate ways to promote adherence for depression and physical health medication? (Link to forthcoming NICE guideline)

General

11) Does the treatment of depression for people with chronic physical health problems have an impact on physical health outcomes?

Appendix 8: Clinical review protocol template

Case Identification protocol

Clinical question(s)	Q1 What methods are effective in identifying people with depression who have physical health problems in primary care, hospital (including general medical), and residential settings and/or nursing homes?
Sub-question(s)	?
Chapter	?
Sub-section	?
Topic Group	Service identification
Sub-section lead	?
Objectives	To test the diagnostic accuracy of identification tools in detecting depression
Criteria for considering studies for the review	
• Intervention	**Geriatric Depression Scale (GDS)** (Yesavage & Brink, 1983): a 30-item self-report tool to assess depression in the elderly. A telephone version tested by Burke and colleagues (1995) showed good agreement with self-report questionnaire. A short form containing 15-item also exists. For the 30-item tool a score of 10-19 indicates mild depression and 20-30 severe depression. A cut-off score of 5 is generally used for the 15-item GDS. **Beck Depression Inventory (BDI):** a 21-item questionnaire administrated by an interviewer or by self that measured the severity of depression in adults and adolescents. The BDI was first published in 1961 by Beck and colleagues. Two revisions have been published: the BDI-IA (Beck *et al.,* 1979) and the BDI-II (Beck *et al.,* 1996). There is also a 13-item version (Guy, 1976). Interpretation of severity scores for the BDI-21 is: 0-9 minimal, 10-16 mild, 17-29 moderate and 30-63 severe. For the BDI-13 a cut-off score of 4 is used to indicate depression. **Patient Health Questionnaire (PHQ):** a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument which was designed to diagnose specific disorders in primary care settings using DSM criteria (Spitzer *et al.,* 1994). The depression module comprises 9 questions (PHQ-9). Interpretation of the PHQ-9 is as follows: 0-4 none, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression. The first 2 questions (known as the PHQ-2), can be administered separately as a screening tool and exists in two variations: as a likert-scale where a cut-off of 3 is commonly used, and as a yes or no response item scale, where answering yes to at least one item is used as a cut-off score for depression. **Hospital Anxiety Depression Scale (HADS)** (Zigmond & Snaith, 1983): a 14-item, self-administrated tool to assess anxiety and

	depression on a 4-point Likert-type scale. Two subscales assess depression and anxiety. The seven-item Depression subscale yields a score of 0-21 that has the following cut off pints: 0-7 normal, 8-10 mild mood disturbance, 11-14 moderate mood disturbance and 12-21 severe mood disturbance. **General Health Questionnaire (GHQ)** (Goldberg & Williams, 1991): a self-administered questionnaire designed to assess for the presence of psychiatric distress related to general medical illness. Four variations exist: a 60-, 30-, 28- and 12-item. A cut-off score of 12 for the GHQ-60, 5 for the GHQ-30, 5 for GHQ-28 and 3 for the GHQ-12 are advised in the manual. **Centre for Epidemiological Studies-Depression Scale (CES-D):** a 20 item self-administered tool that assess the frequency and severity with which symptoms of depression are experienced in the general population. A score of 16 or higher was identified in early studies as identifying subjects with depressive illness (American Psychiatric Association, 2000b). **Hamilton Depression Rating Scale (HDRS)**: a 21-item clinician-completed scale, although usually only the first 17 items are scored. There is also a 24-item version. For the 17-item report, the following cut-offs have been reported: > 23 very severe, 19-22 severe, 14-18 moderate, 8-13 mild and ≤7normal. **Single item screen for depression**. **Zung Self-Rating Depression Scale:** a 20-item self-report questionnaire. Each item is scored on a Likert scale ranging from 1 to 4. A total score ranges from 20 to 80. A cut off score of 50 is widely used to indicate mild depression, while a score of 70 and above indicates severe depression.
• Comparator	Gold standard: Diagnostic Statistical Manual (DSM) or International Classification of Diseases (ICD) diagnosis of depression
• Population (including age, gender etc)	General adult population ≥ 18 years of age and also includes those with chronic physical health problems and/or the elderly.
• Outcomes (see Outcomes document for definitions)	**Sensitivity**: the proportion of true positives of all diseased cases in the population **Specificity**: the proportion of true negatives of all non-diseased cases in the population. **Positive Predictive Value (PPV)**: the proportion of patients with positive test results who are correctly diagnosed. **Negative Predictive Value (NPV)**: the proportion of patients with negative test results who are correctly diagnosed. **Area under the Curve (AUC):** are constructed by plotting the true positive rate as a function of the false positive rate for each threshold.
• Study design	No limitations
• Publication	Published studies

status	
• Year of study	No limitations
• Dosage	N/A
• Minimum sample size	No limitations
• Study setting	Primary care, hospital (including general medical), and residential settings and/or nursing homes
Search strategy	**Databases** [searched 13.04.08]**:** MEDLINE, EMBASE, CINAHL, PsycINFO **New search: ?**
Existing reviews	Gilbody *et al.* (2008b) Screening and case-finding instruments for depression: a meta-analysis. Canadian Medical Association Journal, 178, 997-1003.
Updated	
Not updated	
General search filter used	?
Question specific search filter	?
Amendments to filter/ search strategy	?
The review strategy	Meta-analysis will be used
Additional assessments	?

Service review protocol

Clinical question	In the treatment of depression for people with chronic physical health problems, which service level intervention improve outcomes compared to standard care?
Sub-questions	**Which service level interventions improve outcomes when compared to alternative service interventions, psychological and pharmacological management strategies?**
Chapter	?
Sub-section	?
Topic Group	Service
Sub-section lead	David Kessler
Search strategy	**Databases:** CINAHL, CENTRAL, EMBASE, MEDLINE, PSYCINFO **Additional sources:** Reference lists of included studies, Systematic reviews
Existing reviews	
Updated	
Not updated	
Search filters used	Dep update [RCT, mainstream]; Dep update - dysthymia, mild dep, subthreshold dep [mainstream, SR]; Dep update [SR, mainstream]; DCHP [RCT, CENTRAL] Mar08; DCHP [RCT, mainstream] Mar08; DCHP [SR, mainstream] Mar08
Question specific search filter	N/A
Amendments to filter/ search strategy	
Eligibility criteria	
• Intervention	**Graduated access** - one way of changing access is to modify service provision at the point at which people want to access services (Rogers *et al.*, 1999). This may involve 'graduated access' to services, including the use of 'direct health services' which people can access without having face to face contact with professionals and which maximise the use of new technologies such as the internet. **The consultation-liaison model** - This model (e.g. Gask *et al.*, 1997; Darling & Tyler, 1990; Creed & Marks, 1989) is a variant of the training and education model (which is outside of the scope of the guideline), in that it seeks to improve the skills of primary care professionals and improve quality of care through improvements in their skills. However, rather than the provision of training interventions which teach skills in dealing with depressed patients in general, in this model specialists enter into an ongoing educational relationship with the primary care team, in order to support them in caring for specific patients who are currently undergoing care. Referral to specialist care is again only expected to be required in a small proportion of cases. A common implementation of this model involves a psychiatrist visiting practices regularly and discussing patients with primary care professionals. **The attached professional mode**l - In this model (e.g. Bower & Sibbald, 2000) a mental health professional takes on direct

	responsibility for the care of a person (usually in primary care) focusing on the primary treatment of the problem/disorder, be it pharmacological or psychological. The co-ordination of care remains with the general practitioner/primary care team. Contact is usually limited to treatment and involves little or no follow up beyond that determined by the specific intervention offered (for example, booster sessions in CBT). **Stepped care** - Stepped care (e.g. Bower & Gilbody, 2005) is a system for delivering and monitoring treatment with the explicit aim of providing the most effective yet least burdensome treatment first to the patient. Typically stepped care starts by providing low intensive, minimal interventions. In some stepped care systems low intensity care is received by all individuals, although in some systems, patients are stepped up to a higher intensity intervention on immediate contact with the service, for example if they are acutely suicidal. **Stratified (or matched care)**– is a hierarchical model of care (e.g. van Straten *et al.,* 2006), moving from low to high intensity interventions, where at the patient's point of first contact, services are matched to the level of need and the consequent treatment is determined by the assessing professional in consultation with the patient. **Case management** – describes a system where an individual health practitioner takes responsibility for the co-ordination of the care of an individual patient (e.g. Gensichen *et al.,* 2006)) but is not necessarily directly involved in the provision of any intervention; this may also involve the co-ordination of follow-up **Collaborative care** - the collaborative care model (e.g. Katon *et al.,* 2001) emerged from the chronic disease model and has four essential elements: the collaborative definition of problems, in which patient defined problems are identified alongside medical problems diagnosed by health care professionals • a focus on specific problems where targets, goals and plans are jointly developed by the patient and professional to achieve a reasonable set of objectives, in the context of patient preference and readiness • the creation of a range of self-management training and support services in which patients have access to services that teach the necessary skill to carry out treatment plans, guided behaviour change and promote emotional support • the provision of active and sustained follow-up in which patients are contacted at specific intervals to monitor health status, identify possible complications and check and reinforce progress in implementing the care plan. In addition, most collaborative care models include a 'case manager' who often has particular responsibility for delivering the care plan. In mental health services collaborative care also typically includes a consultation liaison role with a specialist mental health professional and generic primary care staff. It may also include elements of many of the other interventions described above.

• Comparator	Standard care Sub-question: Alternative service level interventions, pharmacological or psychological interventions
• Population (including age, gender etc)	Adults >18yr with a chronic physical health problem and a diagnosis of depression (including those scoring above cut-off on recognised depression identification tools) Populations excluded: End-stage diseases and palliative care Chronic pain and fibromyalgia Alcoholism APMH Dementia All psychiatric diagnoses Obesity Headache and Migraine
• Outcomes	Mortality (suicide & natural causes) Depression dichotomous outcomes including response, remission and relapse Depression continuous outcomes (HAM-D; BDI; MADRS etc.) Physical health outcomes Psychosocial functioning QoL Satisfaction with treatment / subjective well-being Adherence to medication Process of care including access to treatment
• Study design	RCT
• Publication status	[Published and unpublished (if criteria met)]
• Year of study	Inception to date [09.03.08]
• Minimum sample size	All sample sizes considered at present Sensitivity analysis to remove studies with > 50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary Care, Hospital, Residential and Nursing, Tertiary care etc.
Additional assessments	Studies were categorised based on the collaborative care component score which assessed the complexity of the intervention delivered.

Psychology review protocol

Clinical question	In the treatment of depression for people with chronic physical health problems, which psychosocial interventions improve outcomes compared with treatment as usual?
Sub-questions	***Which psychosocial improve outcomes when compared to alternative psychosocial/pharmacological management strategies?***
Chapter	?
Sub-section	?
Topic Group	Psychosocial
Sub-section lead	Francis Creed
Search strategy	***Databases:*** CINAHL, CENTRAL, EMBASE, MEDLINE, PSYCINFO ***Additional sources:*** Reference lists of included studies, Systematic reviews
Existing reviews	
Updated	
Not updated	
Search filters used	Dep update [RCT, mainstream]; Dep update - dysthymia, mild dep, subthreshold dep [mainstream, SR]; Dep update [SR, mainstream]; DCHP [RCT, CENTRAL] Mar08; DCHP [RCT, mainstream] Mar08; DCHP [SR, mainstream] Mar08
Question specific search filter	N/A
Amendments to filter/ search strategy	
Eligibility criteria	
• Intervention	Cognitive behavioural interventions CBT Discrete, time limited, structured psychological interventions, derived from the cognitive behavioural model of affective disorders and where the patient: Works collaboratively with the therapist to identify the types and effects of thoughts, beliefs and interpretations on current symptoms, feelings states and/or problem areas

	Develops skills to identify, monitor and then counteract problematic thoughts, beliefs and interpretations related to the target symptoms/problems Learns a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas. ***Problem solving*** Problem solving was defined as a psychological intervention, that focuses on learning to cope with specific problems areas and where: Therapist and patient work collaboratively to identify and prioritise key problem areas, to break problems down into specific, manageable tasks, problems solve, and develop appropriate coping behaviours for problems. ***Guided self help*** Guided self-help was defined as a self-administered intervention designed to treat depression, which makes use of a range of books or a self-help manual that is based on an evidence-based intervention and designed specifically for the purpose. A healthcare professional (or para-professional) would facilitate the use of this material by introducing, monitoring and reviewing the outcome of such treatment. This intervention would have no other therapeutic goal, and would be limited in nature, usually no more than three contacts. ***CCBT*** Computerised cognitive behaviour therapy (CCBT) is a form of CBT, which is delivered using a computer (including CD-ROM and the internet). It can be used as the primary treatment intervention, with minimal therapist involvement or as augmentation to a therapist-delivered programme where the introduction of CCBT supplements the work of the therapist. ***Acceptance and Commitment therapy – definition to follow*** ***Intepersonal therapy (IPT)*** Interpersonal therapy was defined as a discrete, time limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and where therapist and patient:

	• Work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feelings states and/or problems. • Seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas. ***Counselling*** Counselling was defined as a discrete, usually time limited, psychological intervention where: • The intervention may have a facilitative approach often with a strong focus on the therapeutic relationship but may also be structured and at times directive • An intervention was classified as counselling if the intervention(s) offered in the study did not fulfil all the criteria for any other psychological intervention. If a study using counsellors identified a single approach, such as cognitive behavioural or interpersonal, it has been analysed in that category. ***Psychodynamic psychotherapy*** Psychological interventions, derived from a

	psychodynamic/ psychoanalytic model, and where: • Therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapy relationship (e.g. transference and counter-transference). • This leads to patients being given an opportunity to explore feelings, and conscious and unconscious conflicts, originating in the past, with a technical focus on interpreting and working though conflicts. • Therapy is non-directive and recipients are not taught specific skills (e.g. thought monitoring, re-evaluating, or problem-solving). ***Couple focused intervention*** Couple-focused therapies were defined as time limited, psychological interventions derived from a model of the interactional processes in relationships where: • Interventions are aimed to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems. • The aim is to change the nature of the interactions so that they may develop

	more supportive and less conflictual relationships. The style of the therapy can vary and reflect different approaches, e.g. cognitive behavioural or psychodynamic. Family intervention Family sessions with a specific supportive or treatment function based on systemic, cognitive behavioural or psychoanalytic principles, which must contain at least one of the following: a) Psycho-educational intervention, and/or b) Problem solving/crisis management work, and/or c) Intervention with the identified service user [patient] Studies included were also required to use an intervention that was at least six weeks in duration. ***Psychoeducation*** Psychoeducation (or 'patient teaching,' 'patient instruction' and 'patient education') was defined as: • any group or individual programme involving an explicitly described educational interaction between the information provider and the service user/carer as the prime focus of the study • programmes had to address the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives • studies in which service users/carers are provided with information, support

	and different management strategies (characteristic of most programmes) were included • programmes of 10 or fewer sessions were classified as 'brief', and 11 or more as 'standard' for this review • interventions including elements of behavioural training, such as social skills or life skills training were excluded • educational programmes performed by service user peers, and staff education studies were excluded. ***Exercise*** For the purposes of the guideline, exercise was defined as a structured, achievable physical activity characterised by frequency, intensity and duration and used as a treatment for depression. It can be undertaken individually or in a group. Exercise may be divided into aerobic forms (training of cardio-respiratory capacity) and anaerobic forms (training of muscular strength/endurance and flexibility/co-ordination/relaxation) (American College of Sports Medicine, 1980). The aerobic forms of exercise, especially jogging or running, have been most frequently investigated. In addition to the type of exercise, the frequency, duration and intensity should be described. ***Occupational Therapy*** Occupational Therapy enables people to achieve health, wellbeing and life satisfaction through participation in occupation, i.e., daily activities that reflect cultural values, provide structure to

	living and meaning to individuals. These activities meet human needs for self care, enjoyment and participation in society. ***Non statutory support*** A range of community-based interventions often not provided by healthcare professionals, which provide support, activities and social contact in order to improve the outcome of depression. ***Programmes to facilitate employment*** ***Pre-vocational Training:*** any approach to VR in which participants were expected to undergo a period of preparation before being encouraged to seek competitive employment. This preparation phase could involve either work in a sheltered environment (such as a workshop or work unit), or some form of pre-employment training or transitional employment. This included both traditional (sheltered workshop) and Clubhouse approaches. ***Supported Employment:*** any approach to VR that attempted to place clients immediately in competitive employment. It was acceptable for Supported Employment to begin with a short period of preparation, but this had to be of less than one month duration and not involve work placement in a sheltered setting, or training, or transitional employment. ***Modifications of vocational rehabilitation programs:*** defined as either Pre-vocational Training or Supported Employment that had been enhanced by some technique to increase participants' motivation. Typically, such techniques consisted of payment for participation in the programme, or some form of psychological intervention.
• Comparator	Treatment as usual Sub-question: Alternative psychosocial/pharmacological management strategies
• Population (including age, gender etc)	Adults >18yr with a chronic physical health problem and a diagnosis of depression (including those scoring above cut-off on recognised depression identification tools)

	Populations excluded: End-stage diseases and palliative care Chronic pain and fibromyalgia Alcoholism APMH Dementia Obesity Headache and Migraine
• Outcomes	Mortality (suicide & natural causes) Global state (including remission and relapse) Depression (HAM-D; BDI; MADRS etc.) Physical health outcomes Psychosocial functioning QoL Satisfaction with treatment / subjective well-being
• Study design	RCT
• Publication status	[Published and unpublished (if criteria met)]
• Year of study	Inception to date [09.03.08]
• Duration	All durations considered at present
• Minimum sample size	All sample sizes considered at present Exclude studies with > 50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary Care, Hospital, Residential and Nursing, Tertiary care etc.
Additional assessments	Studies were categorised as short-term (<12 weeks), medium-term (12-51 weeks) and long-term (>52 wks)

Pharmacology review protocol

Clinical question	In the treatment of depression for people with chronic physical health problems, which drugs improve outcomes compared with placebo?
Sub-questions	***Which drugs improve outcomes when compared to alternative pharmacological management strategies?***
Chapter	?
Sub-section	?
Topic Group	Pharm
Sub-section lead	?
Search strategy	***Databases:*** CINAHL, CENTRAL, EMBASE, MEDLINE, PSYCINFO ***Additional sources:*** Reference lists of included studies, Systematic reviews
Existing reviews	
Updated	
Not updated	
Search filters used	Dep update [RCT, mainstream]; Dep update - dysthymia, mild dep, subthreshold dep [mainstream, SR]; Dep update [SR, mainstream]; DCHP [RCT, CENTRAL] Mar08; DCHP [RCT, mainstream] Mar08; DCHP [SR, mainstream] Mar08
Question specific search filter	N/A
Amendments to filter/ search strategy	
Eligibility criteria	
• Intervention	• SSRIs • 'Third generation' antidepressants (e.g. venlafaxine, desvenlafaxine, agomelatine, duloxetine, mirtazapine, reboxetine • MAOIs • TCAs • Antipsychotics • Trazodone • Maprotiline

• Comparator	Placebo Sub-question: Alternative pharmacological management strategies
• Population (including age, gender etc)	Adults >18yr with a chronic physical health problem and a diagnosis of depression (including those scoring above cut-off on recognised depression identification tools) Populations excluded: End-stage diseases and palliative care Chronic pain and fibromyalgia Alcoholism APMH Dementia All psychiatric diagnoses Obesity Headache and Migraine
• Outcomes	Mortality (suicide & natural causes) Global state (including remission and relapse) Depression (HAM-D; BDI; MADRS etc.) Physical health outcomes Psychosocial functioning QoL Satisfaction with treatment / subjective well-being Adherence to medication / study protocol Adverse events (sexual dysfunction, weight gain, cardiovascular , GI bleeding)
• Study design	RCT
• Publication status	[Published and unpublished (if criteria met)]
• Year of study	Inception to date [09.03.08]
• Dosage	All dosage considered at present
• Minimum sample size	All sample sizes considered at present Exclude studies with > 50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
• Study setting	Primary Care, Hospital, Residential and Nursing, Tertiary care etc.
Additional assessments	Studies were categorised as short-term (<12 weeks), medium-term (12-51 weeks) and long-term (>52 wks)

Appendix 9: Search strategies for the identification of clinical studies

1. General search strategies

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

1 (depression or depressive disorder or depression, postpartum or depressive disorder, major or dysthymic disorder or mood disorders or seasonal affective disorder).sh,id.
2 (affective disorders or depression or depression, postpartum or depression, reactive or dysthymic disorder or seasonal affective disorder).sh,id.
3 (depression or agitated depression or atypical depression or depressive psychosis or dysphoria or dysthymia or endogenous depression or 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

#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)

2. Systematic review search filters

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

(literature searching or (systematic review$ or metaanal$ or meta anal$)).sh,id.
((analy$ 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$).ti,ab.
((electronic database$ 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.)
(metaanal$ or meta anal$ or metasynthes$ or meta synethes$).ti,ab.
(research adj (review$ or integration)).ti,ab.
reference list$.ab.
bibliograph$.ab.
published studies.ab.
relevant journals.ab.
selection criteria.ab.
(data adj (extraction or synthesis)).ab.
(handsearch$ or ((hand or manual) adj search$)).ti,ab.
(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
(fixed effect$ or random effect$).ti,ab.
(systematic$ or meta$).pt. or (literature review or meta analysis or systematic review).md.
((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
or/1-16

3. Randomised controlled trial search filters

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

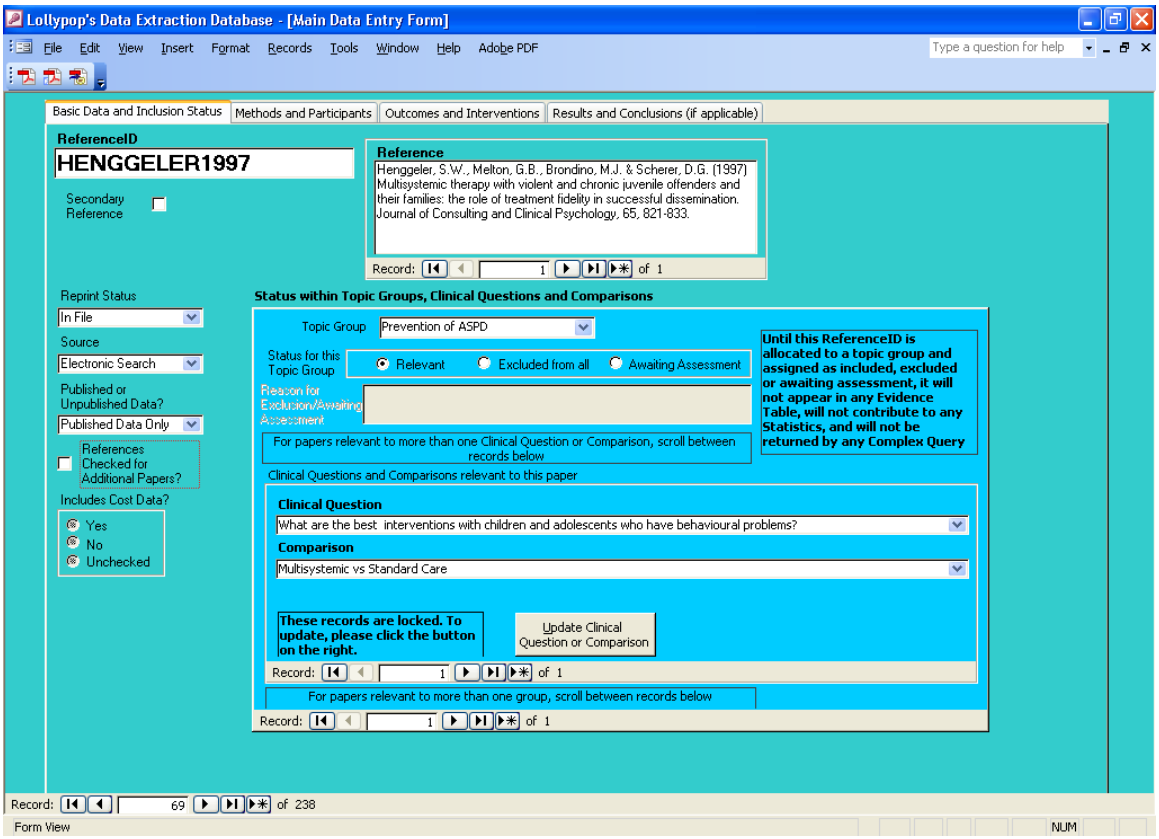
exp clinical trial/ or exp clinical trials/ or exp clinical trials as topic/ or exp controlled clinical trials/
(placebo$1 or random allocation or random assignment or random sample or random sampling or randomization).sh,id.
(double blind$ or single blind$ or triple blind$).sh,id.
(crossover procedure or crossover design or cross over studies).sh,id.
(clinical adj2 trial$).tw.
(crossover or cross over).tw.

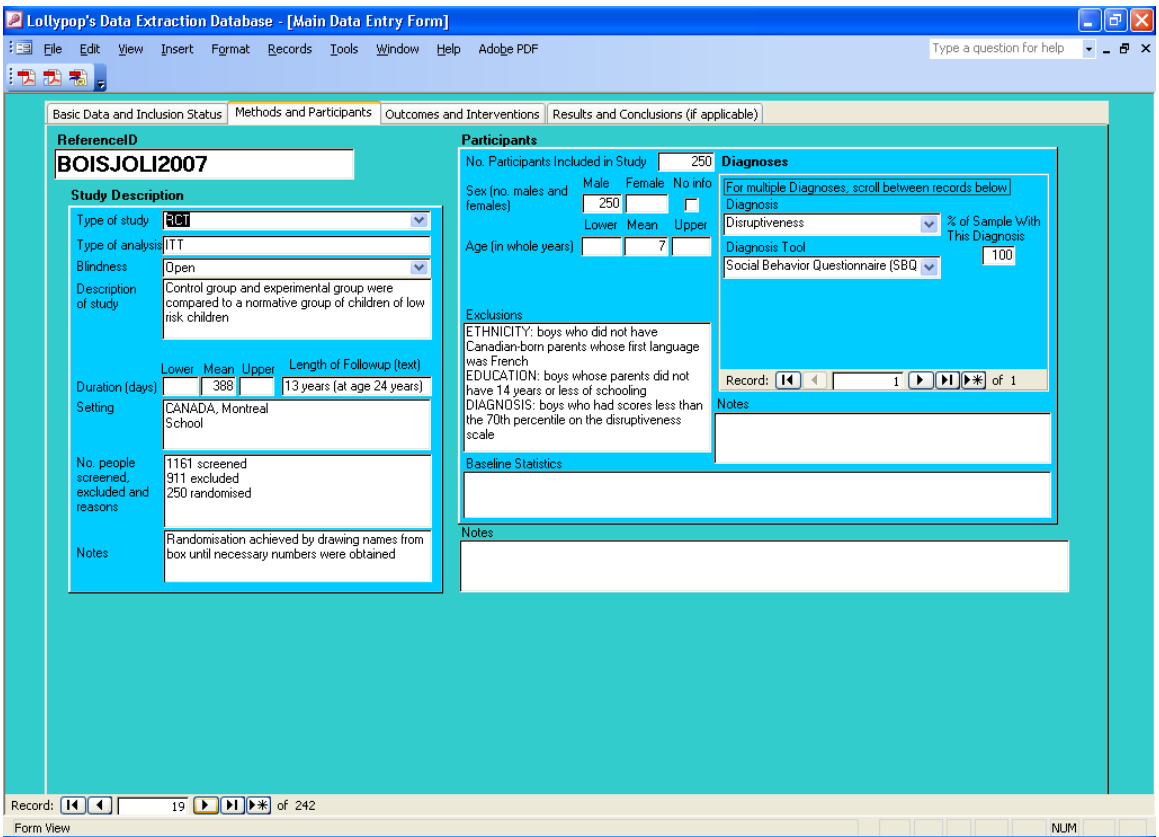
(((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
(placebo$ or random$).mp.
(clinical trial$ or controlled clinical trial$ or random$).pt. or treatment outcome$.md.
animals/ not (animals/ and human$.mp.)
animal$/ not (animal$/ and human$/)
(animal not (animal and human)).po.
(or/1-9) not (or/10-12)

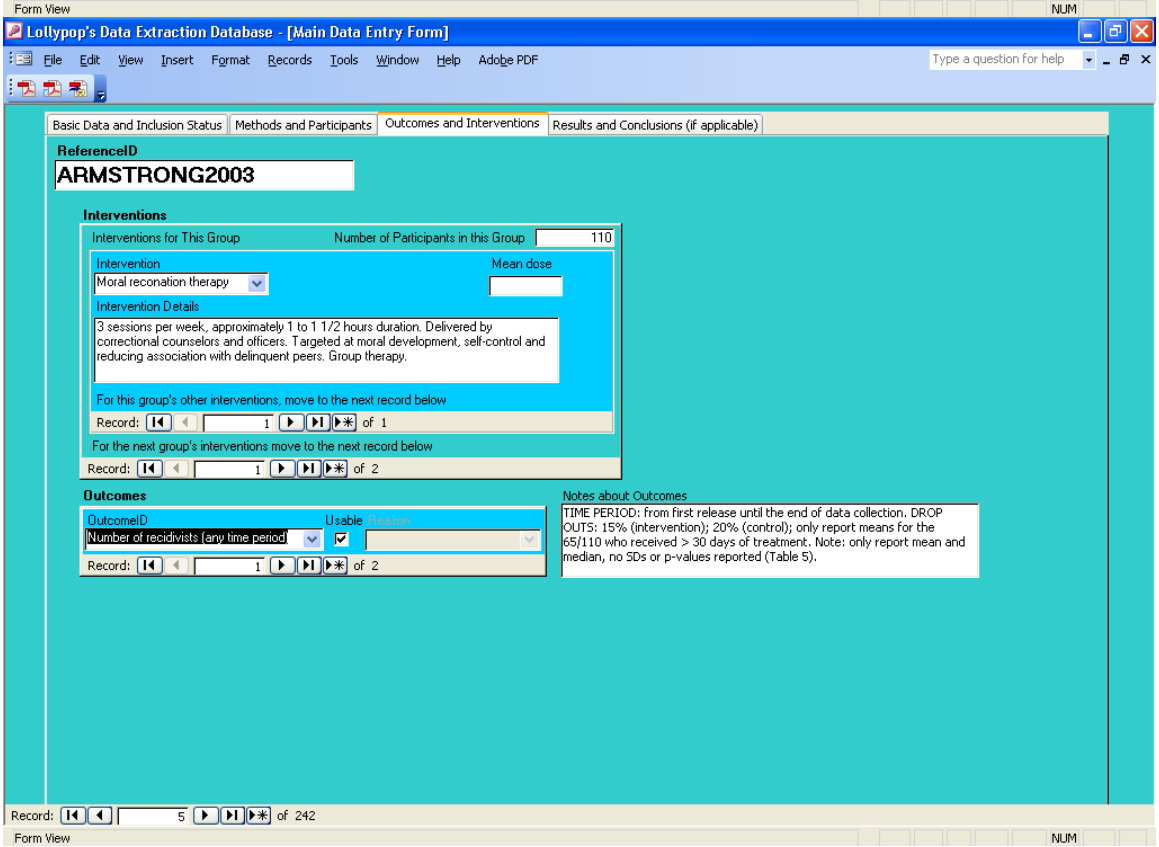
Details of additional searches undertaken to support the development of this guideline are available on request.

Appendix 10: Clinical study data extraction form

Screenshots of bespoke database for extraction of study characteristics.




Lollypop's Data Extraction Database - [Main Data Entry Form]
File Edit View Insert Format Records Tools Window Help Adobe PDF
Type a question for help
Basic Data and Inclusion Status
Methods and Participants
Outcomes and Interventions
Results and Conclusions (if applicable)
ReferenceID
BOISJOLI2007
Study Description
Type of study
RCT
Type of analysis
ITT
Blindness
Open
Description of study
Control group and experimental group were compared to a normative group of children of low risk children
Lower Mean Upper
Length of Followup (text)
Duration (days)
388
13 years (at age 24 years)
Setting
CANADA, Montreal School
No. people screened, excluded and reasons
1161 screened
911 excluded
250 randomised
Notes
Randomisation achieved by drawing names from box until necessary numbers were obtained
Participants
No. Participants Included in Study
250
Sex (no. males and females)
Male Female No info
250
Age (in whole years)
Lower Mean Upper
7
Exclusions
ETHNICITY: boys who did not have Canadian-born parents whose first language was French
EDUCATION: boys whose parents did not have 14 years or less of schooling
DIAGNOSIS: boys who had scores less than the 70th percentile on the disruptiveness scale
Baseline Statistics
Notes
Diagnoses
For multiple Diagnoses, scroll between records below
Diagnosis
Disruptiveness
% of Sample With This Diagnosis
100
Diagnosis Tool
Social Behavior Questionnaire (SBQ
Record: 1 of 1
Notes
Record: 19 of 242
Form View
NUM


Lollypop's Data Extraction Database - [Main Data Entry Form]
File Edit View Insert Format Records Tools Window Help Adobe PDF
Type a question for help
Basic Data and Inclusion Status
Methods and Participants
Outcomes and Interventions
Results and Conclusions (if applicable)
ReferenceID
ARMSTRONG2003
Interventions
Interventions for This Group
Number of Participants in this Group
110
Intervention
Moral reconation therapy
Mean dose
Intervention Details
3 sessions per week, approximately 1 to 1 1/2 hours duration. Delivered by correctional counselors and officers. Targeted at moral development, self-control and reducing association with delinquent peers. Group therapy.
For this group's other interventions, move to the next record below
Record: 1 of 1
For the next group's interventions move to the next record below
Record: 1 of 2
Outcomes
OutcomeID
Usable
Reason
Number of recidivists (any time period
Record: 1 of 2
Notes about Outcomes
TIME PERIOD: from first release until the end of data collection. DROP OUTS: 15% (intervention); 20% (control); only report means for the 65/110 who received > 30 days of treatment. Note: only report mean and median, no SDs or p-values reported (Table 5).
Record: 5 of 242
Form View
NUM

Appendix 11: Quality checklists for clinical studies and reviews

Methodology checklist: diagnostic studies

Criterion	Meaning
(1) Well covered	Clear description of good methodology.
(2) Adequately addressed	Description OK & methodology meets minimum criteria.
(3) Poorly addressed	Description OK, but methodology does not meet minimum criteria.
(4) Not addressed	No description of methodology.
(5) Not reported adequately	Description is insufficient to allow assessment to be made.
(6) Not applicable	

Study ID:			
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted diagnostic study		In this study this criterion is: (Circle one option for each question)	
1.1	The nature of the test being studied is clearly specified.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.2	The test is compared with an appropriate gold standard.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.3	Where no gold standard exists, a validated reference standard is used as a comparator.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.4	Patients for testing are selected either as a consecutive series or randomly, from a clearly defined population	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.5	The test and gold standard are measured independently (blind) of each other.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately

1.6	The test and gold standard are applied as close together in time as possible	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.7	Results are reported for all patients that are entered into the study	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
ASSESSMENT			
1.8	A pre-diagnosis is made and reported.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How reliable are the conclusions of this study? Code ++, + or –	
2.2	Is the spectrum of patients assessed in this study comparable with the patient group targeted by this guideline in terms of the proportion with the disease, or the proportion with severe versus mild disease?	

Methodology checklist: randomised controlled trials

Study ID:			
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted RCT study:		In this study this criterion is: (Circle one option for each question)	
1.1	The study addresses an appropriate and clearly focused question.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.2	The assignment of subjects to treatment groups is randomised. Adequate=computer generated. Poor=alternation; by date.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.3	An adequate concealment method is used. Adequate=sequentially numbered opaque sealed envelopes. Poor=allocation done by person	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately

	who assesses eligibility using non-concealed randomisation sequence.		
1.4	Subjects and investigators are kept 'blind' about treatment allocation. Adequate=single-blind. Poor=no blinding used.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.5	The treatment and control groups are similar at the start of the trial. Adequate=no major differences at baseline (may be OK due to inclusion/exclusion criteria). Poor=major differences not corrected statistically.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.6	The only difference between groups is the treatment under investigation. Poor=confounding factors not explained.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.7	All relevant outcomes are measured in a standard, valid and reliable way. Poor=measures applied inconsistently &/or no information about reliability/validity.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis). Poor=per protocol or observed case analysis.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately
1.10	Where the study is carried out at more than one site, results are comparable for all sites. Poor=one or more site results dropped from analysis.	(1) Well covered (2) Adequately addressed (3) Poorly addressed	(4) Not addressed (5) Not reported adequately (6) Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? Code ++, + or –	

Appendix 12: Classification of Depression

Background

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

DSM-IV was the prefered diagnostic system used to facilitate evaluation of the evidence. However, in practical terms clinicians are not expected to switch to DSM-IV but should be aware that the threshold for mild depression is higher than with ICD-10 (five symptoms not four) and that degree of functional impairment should be routinely assessed before making a diagnosis. Using DSM-IV enables the guideline to better target the use of specific interventions, such as antidepressants, for more severe degrees of depression.

Depression is a heterogeneous disorder in which a number of underlying presentations may share a common phenomenology but have different aetiologies. Despite considerable work on the aetiology of depression including neurobiological, genetic and psychological studies no reliable classificatory system has emerged which links either to the underlying aetiology or which has proven strongly predictive of response to treatment. A number of classification systems/sub-groupings have been used including reactive and endogenous depression, melancholia, atypical depression, seasonal affective disorder and dysthymia. These have been based on varying combinations of the nature, number, severity, pattern and duration of symptoms, and in some cases the assumed aetiology. Over time pragmatic definitions have emerged, enshrined in the current two major classification systems, DSM-IV (American Psychiatric Association, 2000a) and ICD-10 (World Health Organisation, 1992). These have defined a threshold of severity of clinical significance with further classification in terms of severity (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 (Van *et al.,* 2008; Jackson *et al.,* 2007; Barrett *et al.,* 2001; Sullivan *et al.,* 2003; Khan *et al.,* 1991; Holma *et al.,* 2008; Conradi *et al.,* 2008; Blom *et al.,* 2007) although social support, social impairment or personality factors also need to

be taken into account. Lower severity and duration of a depressive episode predicts, to some extent, a greater likelihood of spontaneous or earlier and eventual improvement whereas greater severity, chronicity and number of previous episodes predict a higher chance of subsequent relapse.

The lack of a highly reliable or valid classificatory system has significant and practical clinical consequences, particularly in primary care where the full range of depression presents. A major concern is whether depression should be classified using dimensions or categories. Categories help distinguish cases from non-cases, whilst dimensions help identify severe disorder from mild (Cole *et al.,* 2008). Clinicians are often required to make a categorical decisions – for example to treat with antidepressants or not, to refer for further interventions or not - and consequently there can be pressure to interpret data on a single dimension in a categorical way 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 view on the cause of symptoms and acceptable treatment, and in the guideline update a major challenge has been to provide a useful categorisation which adequately captures the complexity.

Classification of Depression and NICE Guidance

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

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

significant depressive episode and therefore what is considered subthreshold or 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 2 of the remaining 7 symptoms, whilst in DSM-IV the patient must have five or more out of 9 symptoms with at least at least one from the first two (depressed mood and loss of interest). Both diagnostic systems require symptoms to have been present for at least 2 weeks to make a diagnosis (but can be shorter in ICD10 if symptoms are unusually severe or of rapid onset). In both ICD-10 and DSM-IV the symptoms must result in impairment of functioning which increases with the episode severity. Table 61 compares the symptoms required in ICD-10 and DSM-IV.

Table 61 Comparison of depression symptoms in ICD-10 and DSM-IV

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

* core symptoms

Determining severity of a depressive/major depressive episode

Both ICD-10 and DSM-IV classify clinically significant depressive episodes as mild, moderate and severe based on the number, type and severity of symptoms present and degree of functional impairment. Table 62 shows the number of symptoms required by each diagnostic system which are less

specific DSM-IV. The prescriptive symptom counting approach of ICD-10 tends to lend itself to using symptom counting alone to determine severity.

Table 62 Number of symptoms required in ICD-10 and DSM-IV for a diagnosis of depressive episode/major depression (but note they also need assessment of severity and functional impairment to ascertain diagnosis and severity)

	ICD-10 depressive episode	DSM-IV major depression
Mild	4	Minimal above the minimum (5)
Moderate	5-6	Between mild and severe
Severe	7+	Several symptoms in excess of 5

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

Diagnosis of minor depressive disorder

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

There is no accepted classification for this in the current diagnostic systems with the closest being minor depression, a research diagnosis in DSM-IV. At least two but less than 5 symptoms are required of which one must be depressed mood or diminished interest. This includes ICD-10 depressive episode with 4 symptoms and, given the practical difficulty and inherent

uncertainty in deciding thresholds for significant symptom severity and disability, there is no natural discontinuity between minor depression and mild major depression in routine clinical practice.

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

ICD10 has a category of mixed anxiety and depression, which is less clearly defined than minor depression, and is largely a diagnosis of exclusion in those with anxiety and depressive symptoms sub-threshold for specific disorders. Not unexpectedly it appears to be a heterogeneous category with a lack of diagnostic stability over time (Barkow *et al.,* 2004; Wittchen *et al.,* 2001b). For this reason it has not been included in this guideline.

Duration

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

Traditionally the minimum duration of persistent symptoms for major depression is 2 weeks and for chronic depression (or dysthymia) 2 years. These conventional definitions have been adopted in the absence of good evidence as there is only a modest empirical base for the minimum duration (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 2-3 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 consist of a worsening of symptoms in a continuum going from depressive symptoms through to major depression. Phases of improvement with treatment consist of response (significant improvement) to remission (absence of depressive symptoms) which if stable for 4-6 months results in (symptomatic) recovery, meaning that the episode is over (Frank *et al.*, 1991). It is important to distinguish this use of recovery from more recent concepts related to quality and meaning of life in spite of continued symptoms. After recovery a further episode of depression is viewed as a recurrence to distinguish it from a relapse of the same episode. There has been no consensus as to how long a period of remission is needed to declare recovery; different definitions result in different definitions of episode length and time to full or sub-threshold depressive recurrence (Furukawa *et al.,* 2008). In practice it can therefore be difficult to distinguish between relapse and recurrence, particularly when people have mild residual symptoms. Follow-up studies of people with depression have shown that overall more time is spent with sub-threshold depressive symptoms than in major depression and there is a variable individual pattern ranging from persisting chronic major depression, through significant but not full improvement (partial remission), to full remission and recovery (Judd *et al.,* 1998). DSM-IV defines full remission when there has been an absence of symptoms for at least two months. For partial remission, full criteria for a major depressive episode are no longer met, or there are no substantial symptoms but two months have not yet passed. DSM-IV specifies 'With Full Inter-episode Recovery' if full remission is attained between the two most recent depressive episodes and 'Without Full Inter-episode Recovery' if full remission is not attained. In DSM-IV therefore separate episodes are distinguished by at least 2 months of not meeting major depression criteria which is in contrast to the more stringent ICD-10 requirements of 2 months without any significant symptoms. There is therefore some ambiguity as to whether full remission is required to define separate episodes.

Nevertheless the number of episodes and degree of symptom resolution have important implications for considering the course of an individual patient's depressive disorder. The risk of a further episode of major depression within a given time frame is greater with an increasing number of previous episodes (Solomon *et al.,* 2000; Kessing & Andersen, 2005) and also if there has not been full remission/symptomatic recovery (Paykel *et al.,* 1995; Kanai *et al.,* 2003; 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.

Depression subtypes

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

Classification of Depression in the Depression Guideline Update

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

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

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

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

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

Somatic symptoms
3) significant weight loss when not dieting or weight gain (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 abuse, 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 (Krupinski & Tiller, 2001; Rapp & Davis, 1989) which has important implications for the application of these criteria. In addition there is need to be able consistently diagnose depression in patients where physical symptoms may be due to medical illness. Zimmermann 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%-97%) and good sensitivity (93%) and specificity (95-98%) when a cut-down list (excluding the 4 somatic symptoms) is used with a requirement for 3 out of the remaining 5 symptoms.

It is therefore possible to use an abridged list, first asking about the two core symptoms of depression:
1) Persistent depressed mood
2) Markedly diminished interest or pleasure

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

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

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

a) Severity

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

1) **subthreshold** depression typically consisting of 2-4 symptoms with maintained function.

2) **mild** depression where there are few, if any, symptoms in excess of those required to make the diagnosis and symptoms result in only minor functional impairment.

3) **moderate** depression where symptoms or functional impairment are between 'mild' and 'severe'. Some symptoms would be expected to be marked.

4) **severe** depression where there are several symptoms in excess of those required to make the diagnosis and the symptoms markedly interfere with functioning. Some symptoms would be expected to be severe.

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

Symptom severity and degree of functional impairment correlate highly (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 etc.

b) Duration

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

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

2) **Chronic** – meeting one of the severity criteria for longer than 2 years

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

c) Course

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

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

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

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

Classification in relation to depression rating scales and questionnaires.

Depression rating scales and questionnaires give ranges that are proposed to describe different severities of depression. Some of these were described in the previous guideline (Appendix 13). In reconsidering this for the update it quickly became apparent, not only that there is no consensus for the proposed

ranges, but also that the ranges in different rating scales and questionnaires do not correspond with each other. In addition there a variable degree of correlation between different scales which indicates that the they do not measure precisely the same aspects of depression. When these factors are added to the need to consider more than symptoms in determining severity, and more than severity in considering diagnosis, the guideline development group was concerned not to perpetuate a spurious precision in relating scores in depression rating scales and questionnaires to the diagnosis or severity of depression which must in the end be a clinical judgement.

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

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

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

[1] Used in the last guideline

Implications of the proposed classification

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

Diagnosis using the three aspects listed above (severity, duration, course) necessarily only provides a partial description of the individual experience of depression. Depressed people vary in the pattern of symptoms they experience, their family history, personalities, pre-morbid difficulties (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 co-morbidity, or for the depression to occur in the context of bipolar disorder (not considered in this guideline). Gender and socio-economic factors account for large variations in the population rates of depression, and few studies of pharmacological, psychological or indeed other treatments, for depression control for or examine these variations. This emphasises that choice of treatment is a complex process and involves negotiation and discussion with patients, and, given the current limited knowledge about what factors are associated with better antidepressant or psychotherapy response, most decisions will rely upon clinical judgement and patient preference until we have further research evidence. Trials of treatment in unclear cases may be warranted but the uncertainty needs to be discussed with the patient and benefits from treatment carefully monitored.

Appendix 13: Search strategies for the identification of health economics evidence

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

1. General search strategies

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

(depression or depressive disorder or depression, postpartum or depressive disorder, major or dysthymic disorder or mood disorders or seasonal affective disorder).sh,id.
(affective disorders or depression or depression, postpartum or depression, reactive or dysthymic disorder or seasonal affective disorder).sh,id.
(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 "/
(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)"/
(depress$ or dysphori$ or dysthym$ or melancholy or seasonal affective disorder$).tw.
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

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

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

Appendix 14: Quality checklist for economic studies

	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	❑	❑	❑
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 15: Data extraction form for economic studies

Reviewer: Date of Review:

Authors:
Publication Date:
Title:
Country:
Language:

Economic study design:

❑CEA ❑ CCA
❑CBA ❑ CA
❑CUA
❑CMA

Modelling:

❑ No ❑Yes

Source of data for effect size measure(s):

❑RCT
❑Quasi experimental study
❑Cohort study
❑Mirror image (before-after) study study
❑ Expert opinion

❑Meta-analysis
❑RCT
❑ Quasi experimental study
❑ Cohort study
❑ Mirror image (before-after)

Comments

Primary outcome measure(s) (please list):

Interventions compared (please describe):

Treatment:

Comparator:

Setting (please describe):

_____

_____

Patient population characteristics (please describe):

_____

_____

_____

Perspective of analysis:

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

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 health care	❑ 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: _____

Appendix 16: Interactions with drugs used in other conditions

The British National Formulary (BNF) includes a summary appendix dedicated to drug interactions. More detailed information can be found in Stockley's Drug Interactions (Stockley, 2008). These sources should be checked before adding new drugs to a prescription, particularly if; (1) any of the drugs prescribed have a narrow therapeutic index, that is are ineffective at low doses/plasma levels and potentially toxic at higher doses/plasma levels, or;(2) are known to affect cardiac or renal function.

Physical condition	Drug/drug group	Antidepressants to avoid (A) or use with caution (C)	Antidepressants recommended	Comments
1.1.1 **Dyspepsia**	Antacids (e.g. aluminium hydroxide)	None specifically contra-indicated	Any	
1.2 **Antispasmodics**	Antimuscarinics (e.g. hyoscine butylbromide, propantheline bromide)	Tricyclics (C) (slow gut motility) Paroxetine (C) (may slow gut motility) Reboxetine (C) (may slow gut motility)	Any alternative (e.g. SSRIs, SNRIs, trazodone)	Tricyclics, MAOIs and paroxetine may also add to peripheral antimuscarinic effects
1.3 **Peptic ulcer**	H_2 antagonists (e.g. cimetidine, ranitidine, etc)	Citalopram/ escitalopram (C) (cimetidine inhibits metabolism) Sertraline (C) (cimetidine inhibits metabolism) Mirtazapine (C) (cimetidine inhibits metabolism) Lofepramine (C) (cimetidine inhibits metabolism) Moclobemide (C) (cimetidine inhibits metabolism)	Any alternative (e.g. SSRIs, SNRIs, reboxetine) Any antidepressant (with ranitidine, nizatidine, etc)	Cimetidine may inhibit metabolism of many antidepressants Use of SSRIs and SNRIs in active peptic ulcer may increase risk of GI bleed
	Proton pump inhibitors (e.g. omeprazole, lansoprazole, etc)	Citalopram/ escitalopram (C) (omeprazole inhibits metabolism)	Any alternative	
1.4 **Diarrhoea**	Antimotility drugs (e.g. codeine, loperamide)	None specifically contra-indicated	Any	SSRIs may cause or worsen diarrhoea. SSRIs and SNRIs cause nausea
1.5 **Inflammatory bowel disorders**	Aminosalicylates (e.g. mesalazine, olsalazine, balsalazide) Corticosteroids Cytokine modulators (e.g. infliximab, adalimumab)	None specifically contra-indicated	Any	Absorption of antidepressants may be impaired in inflammatory bowel conditions
1.6 **Constipation**	Bulk-forming and stimulant laxatives; faecal softeners	Tricyclics (A) (slow gut motility) Paroxetine (A)	Any alternative (e.g. SSRIs)	Laxatives may be required to treat antidepressant-induced constipation

		(may slow gut motility) Reboxetine (A) (may slow gut motility)	May increase risk of antidepressant-associated hyponatraemia	
2.1/2.2 **Heart failure**	Cardiac glycosides (digoxin; digitoxin)	St Johns Wort (A) (reduces digoxin plasma levels) Tricyclic antidepressants (A) (possibly proarrhythmic in cardiac disease) Venlafaxine (A) (not recommended in those at risk of arrhythmia) Trazodone (A) (increases digoxin plasma levels)	Any alternative (e.g. SSRIs, mirtazapine)	
	Thiazide diuretics (bendroflumethiazide, etc)	Reboxetine (A) (increased risk of hypokalaemia) MAOIs/Tricyclics/Mirtazapine (C) (increased risk of postural hypotension)	Any alternative (e.g. SSRIs)	Avoid lithium – plasma levels increased by thiazides May increase risk of antidepressant-associated hyponatraemia
	Loop diuretics (furosemide, bumetanide)	Reboxetine (A) (increased risk of hypocalcaemia) MAOIs/Tricyclics (C) (increased risk of postural hypotension)	Any alternative (e.g. SSRIs, mirtazapine)	Avoid lithium – plasma levels increased by loop diuretics May increase risk of antidepressant-associated hyponatraemia
	Other diuretics (amiloride, eplerenone, etc)	St John's Wort (A) (reduces eplerenone plasma levels)	Any alternative (e.g. SSRIs)	May increase risk of antidepressant-associated hyponatraemia
2.3.2 **Cardiac arrhythmia**	Antiarrhythmics (e.g. amiodarone, disopyramide, flecainide, lidocaine, propafenone, etc)	Tricyclics (A) (increased risk of arrhythmia) Citalopram/ escitalopram (A) (increases plasma levels of flecainide and propafenone) Fluoxetine (A) (increases plasma levels of flecainide and propafenone) Paroxetine (A) (increases plasma levels of flecainide and	Sertraline Mirtazapine Moclobemide Mianserin	All recommended drugs should be used with caution

		propafenone) Duloxetine (A) (increases plasma levels of flecainide) Venlafaxine (A) (possibly increased risk of arrhythmia) Trazodone (C) (possibly increased risk of arrhythmia) Reboxetine (C) (may cause hypokalaemia)		
2.4/2.5 **Hypertension**	Beta-adrenoceptor blocking drugs (e.g. propranolol, metoprolol, etc)	Tricyclics (A) (increased risk of arrhythmia with sotalol) Tricyclics (C) (increased risk of postural hypotension) Tricyclics (C) (plasma levels increased by labetalol and propranolol) Citalopram/ escitalopram (C) (increases plasma level of metoprolol) Paroxetine (C) (may increase plasma levels of metoprolol) Fluvoxamine (C) (increases plasma levels of propranolol) Mirtazapine (C) (increased risk of postural hypotension) Venlafaxine (A) (may worsen hypertension) Duloxetine (A) (may worsen hypertension) Reboxetine (A) (may worsen hypertension) Trazodone (C) (increased risk of postural hypotension)	Sertraline	Probably best to avoid all MAOIs because of the risk of hypertensive crisis

	Vasodilator drugs (e.g. diazoxide, hydralazine, prazosin, doxazosin	Tricyclics (C) (increased risk of postural hypertension) Mirtazapine (C) (increased risk of postural hypertension) Venlafaxine (A) (may worsen hypertension) Duloxetine (A) (may worsen hypertension) Reboxetine (A) (may worsen hypertension)	Any alternative (e.g. SSRIs)	Probably best to avoid all MAOIs because of the risk of hypertensive crisis Paroxetine and fluoxetine may inhibit metabolism of doxazosin
	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, etc)	Tricyclics (A) (antagonise effects of clonidine) Mirtazapine (C) (increased risk of postural hypertension) Venlafaxine (A) (may worsen hypertension) Duloxetine (A) (may worsen hypertension) Reboxetine (A) (may worsen hypertension) Trazodone (C) (increased risk of postural hypotension)	Any alternative (e.g. SSRIs)	Probably best to avoid all MAOIs because of the risk of hypertensive crisis Mirtazapine and trazodone may antagonise effects of clonidine
	ACE inhibitors; Angiotensin-II antagonists; renin inhibitors (e.g. captopril, enalapril; losartan; aliskiren)	Tricyclics (C) (increased risk of postural hypotension) Mirtazapine (C) (increased risk of postural hypotension) MAOIs (A) (may enhance hypotensive effects of ACE inhibitors and angiotensin antagonists). Venlafaxine (A) (may worsen hypertension) Duloxetine (A) (may worsen hypertension) Reboxetine (A) (may worsen hypertension)	Any alternative (e.g. SSRIs)	Avoid lithium – plasma levels increased by ACE inhibitors

	Calcium channel antagonists (e.g. nifedipine, verapamil)	Tricyclics (C) (increased risk of postural hypotension) Mirtazapine (C) (increased risk of postural hypotension) Venlafaxine (A) (may worsen hypertension) Duloxetine (A) (may worsen hypertension) Reboxetine (A) (may worsen hypertension) Trazodone (C) (increased risk of postural hypotension)	Any alternative (e.g. SSRIs)	Avoid lithium – diltiazem and verapamil may precipitate neurotoxicity
2.6 **Angina**	Nitrates (e.g. GTN, isosorbide nononitrate)	Tricyclics (C) (dry mouth may reduce absorption of sub-lingual tablets) MAOIs (A) (enhanced hypotensive effects)	Any alternative (e.g. SSRIs)	Paroxetine has mild anticholinergic properties
2.8/2.9 **Conditions requiring anti-coagulation**	Parenteral anti-coagulants (e.g. heparin, LMW heparin)	SSRIs (A) (probable increased risk of bleeding) Venlafaxine (A) (probable increased risk of bleeding) Duloxetine (A) (probable increased risk of bleeding)	Any alternative (e.g. trazodone, reboxetine, tricyclics)	
	Oral anti-coagulants (warfarin, phenindione)	SSRIs (A) (enhanced anti-coagulant effect) TCAs (A) (enhanced or reduced anti-coagulant effect) Mirtazapine (A) (enhanced anti-coagulant effect) St John's Wort (A) (reduced warfarin plasma levels) Venlafaxine (C) (possibly enhanced anti-coagulant effect) Duloxetine (C) (possibly enhanced anti-coagulant effect)	Reboxetine (C) Trazodone (C) Mianserin (C)	Fluvoxamine and fluoxetine inhibit warfarin metabolism Anti-coagulant effect may be enhanced without change in INR
2.12 **Dyslipidaemia**	Bile acid sequestrants (e.g. colestipol, colestyramine)	None specifically contra-indicated	Any	
	Ezetimibe	None specifically contra-indicated	Any	

	Fibrates (e.g. bezafibrate)	None specifically contra-indicated	Any	Probably best to avoid MAOIs with bezafibrate – risk of hepatotoxicity
	Statins (e.g. atorvastatin, simvastatin)	St John's Wort (A) (reduces effect of simvastatin)	Any alternative (e.g. SSRIs, TCAs, others)	
	Omega-3 fatty acids (e.g. Maxepa, Omacor)	None specifically contra-indicated	Any	Omega-3 fatty acids may have antidepressant effects
3.1/3.2/3.3 **Asthma/COPD**	Inhaled bronchodilators (e.g. salbutamol, ipratropium)	None specifically contra-indicated	Any	
	Theophylline	Fluvoxamine (A) (inhibits theophylline metabolism) St John's Wort (A) (increases theophylline metabolism)	Any alternative (e.g. other SSRIs)	
	Corticosteroids (e.g. predrisolone, beclomethasone)	None specifically contra-indicated	Any	
	Leukotriene antagonists (e.g. montelukast)	None specifically contra-indicated	Any	
3.4 **Allergy**	Antihistamines – sedating (e.g. chlorphenamine, hydroxyzine, promethazine)	Tricyclics (C) (increased sedation and anticholinergic effects) Trazodone (C) (increased sedation) Mirtazapine (C) (increased sedation) Phenelzine (C) (increased sedation and anticholinergic effects) SSRIs (C) (effect antagonised by cyproheptadine)	Any alternative (SSRIs, reboxetine)	Probably best to avoid use of cyproheptadine with serotonergic antidepressants
	Antihistamines – non-sedating (e.g. cetirizine, loratidine)	Tricyclics (C) (possibility of increased sedative effects) Trazodone (C) (possibility of increased sedative effects) Mirtazapine (C) (possibility of increased sedative effects)	Any alternative (e.g. SSRIs, reboxetine)	Avoid use of mizolastine with tricyclics and venlafaxine.
	Omalizumab	None specifically contra-indicated	Any	

	Adrenaline	Tricyclics (A) (risk of hypertension and arrhythmia)	Any	Where adrenaline is required in a patient on tricyclics, close monitoring is essential.
	Oral nasal decongestants (e.g. pseudoephedrine)	MAOIs (A) (risk of hypertensive crisis) TCAs (C) (manufacturer advises caution)	Any alternative	
4.1.1 **Insomnia**	Hypnotics (e.g. temazepam, z-drugs, chloral, promethazine)	Tricyclics (C) (increased sedation) Mirtazapine (C) (increased sedation) Trazodone (C) (increased sedation)	Any alternative (e.g. SSRIs (C), SNRIs, reboxetine)	Fluvoxamine, paroxetine and fluoxetine may prolong the action of some benzodiazepines Sertraline may increase sedative effects of zolpidem
4.1.2/3 **Anxiety**	Anxiolytics (e.g. benzodiazepines, buspirone, meprobamate, barbiturates)	Tricyclics (C) (increased sedation) Mirtazapine (C) (increased sedation) Trazodone (C) (increased sedation) MAOIs (A) (avoid with buspirone only)	Any alternative (e.g. SSRIs (C), SNRIs, reboxetine)	Fluvoxamine, paroxetine and fluoxetine may prolong the action of some benzodiazepines St John's Wort may reduce the effect of some benzodiazepines
4.2 **Psychosis**	Antipsychotics (e.g. chlorpromazine, haloperidol, clozapine, olanzapine)	Tricyclics (C) (increased risk of hypotension, sedation and arrhythmia) Mirtazapine (C) (increased risk of sedation) Trazodone (C) (increased risk of sedation and hypotension) Paroxetine (C) (increases clozapine plasma levels) Fluoxetine (C) (increased clozapine plasma levels) Fluvoxamine (A) (substantially increased clozapine plasma levels) Venlafaxine (C)	Any alternative (e.g. citalopram, reboxetine)	Complex interactions with individual drugs – consult specialist before initiating a new antidepressant

		(possible increased risk of arrhythmia)		
4.2.3 **Bipolar Disorder**	Mood stabilisers (e.g. lithium, valproate, carbamazepine)	SSRIs (C) (increased risk of CNS effects) Venlafaxine (C) (increased risk of serotonergic effects; possible risk of increased lithium levels) Tricyclics (C) (increased risk of serotonergic effects; possible increased risk of lithium toxicity) St John's Wort (A) (reduced plasma levels of carbamazepine)	Any alternative (e.g. mirtazapine, reboxetine, duloxetine)	SSRIs and tricyclics are widely used alongside lithium – adverse interactions are rare Carbamazepine is a potent enzyme inducer and reduces plasma levels of many tricyclics and other antidepressants
4.4 **ADHD**	Stimulants (e.g. dexamfetamine, methylphenidate, atomoxetine, modafinil)	Tricyclics (A) (increased risk of arrhythmia) MAOIs (A) (risk of hypertensive crisis) Moclobemide (A) (risk of hypertensive crisis) Fluoxetine (A) (increased plasma levels of atomoxetine) Paroxetine (A) (increased plasma levels of atomoxetine) Mirtazapine (C) (manufacturer advises caution with atomoxetine) Reboxetine (C) (manufacturer advises caution with atomoxetine)	Any alternative (e.g. citalopram, sertraline, reboxetine (C), mirtazapine (C))	All antidepressants may increase risk of convulsions when given with atomoxetine SSRIs/SNRIs may increase risk of serotonin syndrome with dexamfetamine
4.5 **Obesity**	Orlistat	None specifically contra-indicated	Any	Decreased gut transit time may affect absorption of some drugs.
	Centrally acting appetite suppressants (e.g. sibutramine)	All antidepressants (A) (increased risk of CNS toxicity with sibutramine)	None	Avoid co-prescription of antidepressants with sibutramine

4.6 **Nausea and Vertigo**	Antihistamines (e.g. cinnarizine, promethazine)	Tricyclics (C) (increased risk of sedation) Trazodone (C) (increased risk of sedation) Mirtazapine (C) (increased risk of sedation) MAOIs (A) (contra-indicated with promethazine)	Any alternative (e.g. SSRIs, venlafaxine, reboxetine)	SSRIs, venlafaxine, duloxetine frequently cause or worsen nausea and vomiting.
	Phenothiazines (e.g. prochlorperazine)	Tricyclics (C) (increased risk of sedation and possibly arrhythmia) Mirtazapine (C) (increased risk of sedation) Trazodone (C) (increased risk of sedation)	Any alternative (e.g. SSRIs, SNRIs, reboxetine)	
	Domperidone and metoclopramide	None specifically contra-indicated	Any	
	$5HT_3$ antagonists (e.g. ondansetron)	None specifically contra-indicated	Any	
	Nabilone	Tricyclics (C) (increased risk of sedation) Mirtazapine (C) (increased risk of sedation) Trazodone (C) (increased risk of sedation)	Any alternative (e.g. SSRIs, SNRIs, reboxetine)	
	Hyoscine	Tricyclics (C) (increased risk of sedation and antimuscarinic effects) Mirtazapine (C) (increased risk of sedation) Trazodone (C) (increased risk of sedation)	Any alternative (e.g. SSRIs, SNRIs, reboxetine)	
4.7.1/2 **Pain**	Aspirin/paracetamol (with or without mild opiates)	SSRIs (C) (increased risk of bleeding with aspirin) Venlafaxine (C) (increased risk of bleeding with aspirin)	Any alternative (e.g. tricyclics, mirtazapine, trazodone)	

	Opioids	Tricyclics (C) (increased risk of sedation and constipation) Trazodone (C) (increased risk of sedation) Mirtazapine (C) (increased risk of sedation) MAOIs (A) (increased risk of CNS excitation and depression) Moclobemide (A) (increased risk of CNS excitation and depression) SSRIs (C) (increased risk of CNS toxicity with tramadol, pethidine and oxycodone) Fluvoxamine (A) (increased plasma levels of methadone) Duloxetine (C) (increased risk of serotonergic effects with tramadol and pethidine)	Any alternative (e.g. SSRIs (C), mirtazapine (C), reboxetine)	
4.7.4 **Migraine**	$5HT_1$ agonists (e.g. sumatriptan, zolmitriptan)	SSRIs (A) (increased risk of CNS toxicity and serotonergic effects) Duloxetine (A) (increased risk of serotonergic effects) Venlafaxine (A) (increased risk of serotonergic effects) MAOIs (A) (increased risk of CNS toxicity) Moclobemide (A) (increased risk of CNS toxicity)	Any alternative (e.g. tricyclics, trazodone, mirtazapine)	Probably best to avoid clomipramine
	Ergot alkaloids (e.g. ergotamine)	Reboxetine (A) (increased risk of hypertension) SSRIs (C) (increased risk of serotonin syndrome)	Any alternative	

	Migraine prophylactic agents (e.g. pizotifen, clonidine)	Reboxetine (A) (increased risk of hypertension with methysergide) Tricyclics/reboxetine/trazodone/mirtazapine (C) (may antagonise effects of clonidine)	Any alternative (e.g. SSRIs)	Some manufacturers suggest avoiding co-administration of MAOIs and tricyclics with some alpha2 agonists (but not clonidine)
4.8 **Epilepsy**	Anticonvulsants (e.g. valproate, carbamazepine)	Complex interactions – seek specialist advice		
4.9.1/2 **Parkinson's Disease**	Dopamine agonists (e.g. bromocriptine, pramipexole)	None specifically contra-indicated	Any	Dopamine agonists have some antidepressant properties. SSRIs, particularly paroxetine, may worsen symptoms of Parkinson's Disease. Selegiline also has antidepressant activity
	Levodopa (e.g. sinemet, madopar)	MAOIs (A) (increased risk of hypertension) Moclobemide (C) (increased risk of adverse effects)	Any alternative (e.g. SSRIs, SNRIs, tricyclics, trazodone, etc)	
	MAO_B inhibitors (e.g. selegiline, rasagiline)	SSRIs (A) (increased risk of CNS excitation and hypertension) Tricyclics (A) (increased risk of CNS excitation) MAOIs (A) (increased risk of hypotension) Moclobemide (A) (increased risk of CNS excitation) Venlafaxine (A) (increased risk of CNS excitation) Duloxetine (A) (increased risk of CNS excitation)	Trazodone, reboxetine, mirtazapine	

	COMT inhibitors (entacapone, tolcapone)	MAOIs (A) (increased risk of hypertension) Tricyclics (C) (manufacturer advises caution) SSRIs (C) (manufacturer advises caution) Moclobemide (C) (manufacturer advises caution) Venlafaxine (C) (manufacturer advises caution) Duloxetine (C) (manufacturer advises caution)	SSRIs, trazodone (with caution)	
	Amantadine	None specifically contra-indicated	Any	
	Antimuscarinic drugs (e.g. procyclidine, benzatropine)	Tricyclics (C) (increased antimuscarinic effects) MAOIs (C) (Increased antimuscarinic effects) Paroxetine (C) (increased plasma levels of procyclidine)	Any alternative (e.g. SSRIs, mirtazapine, trazodone)	
4.9.3 **Tremor, chorea, tics and related disorders**	Haloperidol	Tricyclics (A) (increased risk of arrhythmia)	Any alternative (e.g. SSRIs, mirtazapine)	
	Riluzole	None specifically contra-indicated	Any	May be best to avoid antidepressants associated with nausea (SSRIs, venlafaxine, duloxetine) and neutropenia (mianserin)
	Tetrabenazine	MAOIs (A) (increased risk of CNS excitation and hypertension)	Any alternative	Tetrabenazine is a well known precipitant of depression Paroxetine/fluoxetine may inhibit metabolism of tetrabenazine
4.10 **Alcohol dependence**	Acamprosate	None specifically contra-indicated	Any alternative	
	Disulfiram	Tricyclics (A) (increased plasma concentration and increased reaction to alcohol)	Any alternative	All antidepressants should be used with caution

4.10 **Smoking**	Bupropion	Tricyclics (A) (increased risk of seizures) MAOIs (A) (manufacturer advises avoid concomitant use) Citalopram (C) (possibly increased plasma levels)	Any alternative (e.g. SSRIs)	Bupropion is an antidepressant. Has been safely used at the same time as SSRIs Probably inhibits metabolism of all SSRIs
	Nicotine	None specifically contra-indicated	Any alternative	Note that smoking induces CYP1A2. Plasma levels of fluvoxamine and some other antidepressants may be decreased by smoking. Increases are to be expected on cessation
	Varenicline	None specifically contra-indicated	Any alternative	Note that mood changes, depression and suicidal ideation have been reported
4.10 **Opioid dependence**	Buprenorphine	Tricyclics (C) (increased risk of sedation and constipation) Trazodone (C) (increased risk of sedation) Mirtazapine (C) (increased risk of sedation)	Any alternative (e.g. any SSRIs)	Manufacturer advises caution with MAOIs
	Methadone	Fluvoxamine (A) (increased levels of methadone) MAOIs (A) (contra-indicated by manufacturer)	Any alternative	Sertraline, paroxetine and fluoxetine may increase methadone plasma levels – caution
	Lofexidine	Tricyclics (A) (increased risk of arrhythmia) Mirtazapine (C) (may antagonise effects of lofexidine)	Any alternative	
	Naltrexone	None specifically contra-indicated	Any	

4.11 **Dementia**	Acetylcholinesterase inhibitors (e.g. donepezil)	Tricyclics (A) (antagonises effect of anti-dementia drugs) MAOIs (A) (antagonises effect of anti-dementia drugs) Paroxetine (C) (increased plasma levels of galantamine) Fluoxetine (C) (may increase plasma levels of galantamine)	Any alternative (e.g. SSRIs, trazodone, mirtazapine)	Antimuscarinic effects of some antidepressants directly antagonise effects of cholinesterase inhibitors Probably best to avoid antimuscarinic antidepressants with memantine
	Memantine	None specifically contra-indicated	Any	
5.1 **Infection** **(bacterial)**	Penicillins (e.g. amoxicillin, phenoxymethylpenicillin, flucloxacillin)	None specifically contra-indicated	Any	
	Cephalosporins (e.g. cefadroxil, cefalexin)	None specifically contra-indicated	Any	
	Tetracyclines (e.g. doxycycline, oxytetracycline)	None specifically contra-indicated	Any	
	Macrolides (e.g. erythromycin, clairthromycin)	Tricyclics (A) (increased risk of QT prolongation) Reboxetine (A) (manufacturer suggests avoid concomitant use) Mirtazapine (C) (plasma levels may be increased) Trazodone (C) (plasma levels may be increased by erythromycin) Venlafaxine (C) (plasma levels may be increased0	Any alternative (e.g. SSRIs)	Erythromycin and fluvoxamine may inhibit each other's metabolism - avoid
	Clindamycin	None specifically contra-indicated	Any	
	Sulphonamides (co-trimoxazole)	Mianserin (C) (increased risk of blood dyscrasia)	Any alternative	
	Anti-tuberculosis drugs (e.g. isoniazid, rifampicin, ethambutol)	Tricyclics (C) (increased risk of seizures with cycloserine; plasma levels reduced by rifampicin)	Any alternative (e.g. SSRIs, mirtazapine, trazodone)	Rifamycins potent enzyme inducers. Caution with all antidepressants
	Metronidazole and tinidazole	None specifically contra-indicated	Any	

	Quinolones (e.g. ciprofloxacin, norfloxacin)	Tricyclics (A) (increased risk of arrhythmia) Duloxetine (C) (metabolism inhibited by ciprofloxacin)	Any alternative (e.g. SSRI, mirtazapine)	
	Drugs for urinary tract infection (e.g. nitrofurantoin, methenamine)	None specifically contra-indicated	Any	
5.2 **Infection** **(fungal)**	Antifungal drugs (fluconazole, itraconazole)	Reboxetine (A) (manufacturer advises avoiding concomitant use of imidazoles and triazoles) Mirtazapine (C) (plasma level increased by ketoconazole) St John's Wort (A) (reduces plasma levels of Voriconazole) Tricyclics (C) (plasma levels increased by terbinafine)	Any alternative (e.g. SSRIs)	Ketoconazole is a CYP3A4 inhibitor. May increase levels of mirtazapine, reboxetine, venlafaxine, trazodone and some tricyclics Terbinafine inhibits CYP2D6. May increase levels of SSRIs and tricyclics
5.3 **Infection** **(viral)**	Drugs for HIV (e.g. zidovudine, indinavir, efavirenx)	SSRIs (C) (plasma levels reduced by amprenavir, darunarvir, ritonavir (may also increase levels) and efavirenz) Tricyclics (C) (possibility of increased plasma levels/side effects with amprenavir and ritonavir) Trazodone (C) (increased side effects with ritonavir) Venlafaxine (A) (decreased plasma levels of indinavir)	Any alternative (e.g. mirtazapine, reboxetine)	Complex interactions. Seek specialist advice where possible SSRIs recommended by specialist guidelines
	Drugs for herpes simplex and varicella (e.g. acyclovir)	None specifically contra-indicated	Any	
	Drugs for cytomegalovirus (e.g. ganciclovir)	None specifically contra-indicated	Any	
	Drugs for hepatitis B (e.g. entecavir)	None specifically contra-indicated	Any	
	Drugs for influenza (e.g. oseltamivir, zanamivir)	None specifically contra-indicated	Any	

5.4 Infection (protozoal)	Antimalarials (e.g. chloroquine, mefloquine)	None specifically contra-indicated (except with artemether/lumefantrine (Riamet))	Any – but see notes	Avoid all antidepressants with artemether /lumefantrine (Riamet) Quinine and mefloquine should not be given at the same time as tricyclics (risk of arrhythmias) Quinine inhibits CYP2D6. May increase levels of SSRIs and tricyclics
	Amoebicides (metronidiazole, tinidazole)	None specifically contra-indicated	Any	
5.5 Infection (helmintic)	Antihelmintics (e.g. mebenazdole, piperazine)	None specifically contra-indicated	Any	
6.1 Diabetes	Insulin	SSRIs (C) (changes in blood glucose reported) Tricyclics (C) (tachycardia/hypotension may mimic hyperglycaemia) MAOIs (A) (hypoglycaemic effects enhanced)	Any alternative (e.g. mirtazapine, SNRIs, reboxetine)	Mirtazapine may cause weight gain
	Oral hypoglycaemics Sulphonylureas (e.g. glibenclamide, glipizide) Biguanides (metformin) Others (e.g. exenatide, pioglitazone, rosiglitazone)	SSRIs (C) (changes in blood glucose reported) Tricyclics (C) (tachycardia/hypotension may mimic hypoglycaemia) MAOIs (C) (hypoglycaemic effects enhanced)	Any alternative (e.g. mirtazapine, SNRIs, reboxetine)	Mirtazapine may cause weight gain

6.2 **Thyroid disease**	Thyroxine; liothyronine	None specifically contra-indicated	Any	Thyroid hormones enhance antidepressant effects Theoretical risk of arrhythmia with tricyclics - caution
	Antithyroid drugs (e.g. carbimazole)	Mianserin (possibly increased risk of blood dyscrasia)	Any alternative	
6.3.2 **Glucocorticoid therapy**	Corticosteroids (e.g. prednisolone)	None specifically contra-indicated (but see notes) SSRIs/venlafaxine/duloxetine (C) (possible increased risk of upper GI bleeding)	Any alternative (e.g. reboxetine, mirtazapine, trazodone)	Corticosteroids associated with euphoria, mood changes, depression and suicide.
6.4 **Menopause**	HRT (various preparations)	None specifically contra-indicated	Any	
6.4 **Testosterone-related syndromes**	Testosterone	None specifically contra-indicated	Any	
	Anti-androgens (cyproterone, dutasteride)	None specifically contra-indicated	Any	
	Anabolic steroids (e.g. nandrolone)	None specifically contra-indicated	Any	
6.5.1 **Infertility**	Clomifene	None specifically contra-indicated	Any	
	Gonadotrophins (e.g. follitropin)	None specifically contra-indicated	Any	
6.5.1 **Growth failure**	Human growth hormone (e.g. somatropin)	None specifically contra-indicated	Any	
6.5.1 **Agromegaly**	Growth hormone antagonists (e.g. pegvisomant)	None specifically contra-indicated	Any	
6.5.2 **Diabetes insipidus**	ADH (e.g. vasopressin, desmopressin)	None specifically contra-indicated	Any	All antidepressants linked to SIADH
6.5 **SIADH**	Demeclocycline	None specifically contra-indicated	Any	All antidepressants associated with SIADH
6.6.2 **Osteoporosis**	Bisphosphonates (e.g. disodium, elidronate, sodium clodronate)	None specifically contra-indicated	Any	
6.7.2 **Endometriosis**	Danazol, gestrinone	None specifically contra-indicated	Any	Danazol has enzyme-inhibiting properties

	Gonadorelin amalogues (e.g. goserelin)	None specifically contra-indicated	Any	
6.7.2 **Female infertility**	LHRH antagonists (e.g. cetrorelix, ganirelix)	None specifically contra-indicated	Any	May induce mood changes
6.7.3 **Cushing's Syndrome**	Metyrapone, trilostane	None specifically contra-indicated	Any	Very high prevalence of depression in Cushing's Syndrome
7.3 **Contraception**	Oral contraceptives (e.g. combined oral/progesterone only)	Tricyclics (C) (possible increased plasma levels and antagonism of antidepressant effects) St John's Wort (A) (reduced contraceptive effect)	Any alternative (e.g. SSRIs, mirtazapine, reboxetine, trazodone)	Oestrogens have depressogenic effects
7.4 **Urinary retention**	Alpha-blockers (e.g. doxazosin, indoramin)	See 2.4/2.5	See 2.4/2.5	
7.4.2 **Urinary frequency/incontinence**	Antimuscarinics (e.g. oxybutynin, propiverine)	Tricyclics (C) (increased antimuscarinic effects) Paroxetine (C) (increased antimuscarinic effects)	Any alternative (e.g. SSRIs, mirtazapine, reboxetine, trazodone)	
7.4.5 **Erectile dysfunction**	Phosphodiesterase inhibitors (e.g. sildenafil)	Tricyclics (C) (possible increased hypotensive effects) Trazodone (C) (possible increased hypotensive effects)	Any alternative (e.g. SSRIs, SNRIs, mirtazapine, reboxetine)	Inhibitors of CYP3A4 (paroxetine, fluoxetine) may increase plasma levels of phosphodiesterase inhibitors. Use with caution

8.1/2 **Malignant diseases**	Cytotoxic drugs Alkylating agents (e.g. chlormabucil, cyclophosphamide) Anthracyclines (e.g. daunorubicin, doxorubicin) Antimetabolites (e.g. methotrexate) Vinca alkaloids (e.g. etoposide, vincristine) Platinum compounds (e.g. cisplatin, carboplatin)	Mianserin (A) (possible increased risk of bone marrow suppression)	Any alternative	
	Protein kinase inhibitors (e.g. imatinib)	Mianserin (A) (possible increased risk of bone marrow suppression) Tricyclics (A) (possibly increased risk of QT prolongation)	Any alternative (e.g. SSRIs, mirtazapine, trazodone)	Nilotinib is an inhibitor of CYP3A4 and 2D6. Caution with all antidepressants
	Taxanes (e.g. paclitaxel)	Mianserin (A) (possible increased risk of bone marrow suppression)	Any alternative	
	Topoisomerase inhibitors (e.g. irinotecan)	Mianserin (A) (possible increased risk of bone marrow suppression)	Any alterative	
	Trastuzumab	Mianserin (A) (possible increased risk of bone marrow suppression) Tricyclics (A) (possible increased risk of arrhythmia)	Any alternative	
8.2.1 **Organ transplantation**	Antiproliferative immunosuppressants (e.g. azathioprine, mycophenolate)	Mianserin (A) (possible increased risk of bone marrow suppression)	Any alternative	

	Other immunosuppressants (e.g. ciclosporin, tacrolimus)	Mianserin (A) (possible increased risk of bone marrow suppression) St John's Wort (A) (reduced plasma levels of ciclosporin and tacrolimus)	Any alternative (e.g. SSRIs, mirtazapine, trazodone)	Paroxetine and fluoxetine inhibit CYP3A4 and may increase ciclosporin and tacrolimus levels
8.2.3 **Lymphoma**	Rituximab and alemtuzumab	Mianserin (A) (possible increased risk of bone marrow suppression) Tricyclics (A) (possible increased risk of hypotension and arrhythmia)	Any alternative (e.g. SSRIs, SNRIs, mirtazapine, trazodone)	
8.2.4 **Hepatitis/multiple sclerosis**	Interferon Alfa, Interferon beta, glatiramer, natalizumab	Mianserin (A) (increased risk of bone marrow suppression)	Any alternative	Depression and suicidal ideation well established adverse effects of interferons
8.3.4 **Breast cancer**	Oestrogenantagonists (tamoxifen); Aromatase inhibitors (e.g. anastrozole, letrozole)	None specifically contra-indicated	Any	
8.3.4 **Prostate cancer**	Gonadorelin antagonists (e.g. goserelin) Anti-androgens (e.g. cyproterone)	None specifically contra-indicated	Any	May induce mood changes
9.1 **Iron deficiency**	Ferrous sulphate, Ferrous fumarate	Tricyclics (C) (worsens constipation)	Any alternative	
9.1 **Megaloblastic anaemias**	Hydroxocobalamin, folic acid	None specifically contra-indicated	Any	
9.1 **Renal anaemias**	Epoetin	Venlafaxine (C) (increased risk of hypertension) Duloxetine (C) (increased risk of hypertension) Reboxetine (C) (increased risk of hypertension)	Any alternative (e.g. SSRIs, mirtazapine, tricyclics)	
9.6 **Vitamin deficiency**	Vitamins (e.g. retinol, thiamine, ascorbic acid, ergocalciterol,	None specifically contra-indicated	Any	

	tocopherols)			
10.1.1 **Musculoskeletal and joint disease**	NSAIDs (e.g. ibuprofen, naproxen, coxibs)	SSRIs (A) (increased risk of bleeding) SNRIs (A) (increased risk of bleeding)	Any alternative (e.g. mirtazapine, reboxetine, tricyclics)	
10.1.3 **Rheumatoid arthritis**	Disease-modifying agents (e.g. gold, penicillin, chloroquine)	Mianserin (A) (increased risk of blood toxicity) Tricyclics (A) (increased risk of arrhythmia with chloroquine/hydroxychloroquine)	Any alternative (e.g. SSRIs, SNRIs, mirtazapine)	
10.1.3 **Drugs affecting immune response in RA**	Methotrexate, azathioprine, ciclosporin, cytokine modulators, TNF-α inhibitors	Mianserin (A) (increased risk of blood dyscrasia) St John's Wort (A) (reduces plasma levels of ciclosporin)	Any alternative	
10.1.4 **Gout and hyperuricaemia**	Colchicine, allopurinol, probenecid (for NSAIDs see above)	Mianserin (A) (increased risk of blood dyscrasia with allopurinol and sulfinpyrazone)	Any alternative	
10.2.1 **Myasthenia Gravis**	Anticholinesterases (e.g. neostigmine, pyridostigmine)	None specifically contra-indicated	Any	Tricyclics may ameliorate some parasympathetic adverse effects
10.2.2. **Muscle spasm or spasticity**	Baclofen, dantrolene, etc	Fluvoxamine (A) (increases plasma levels of tizanidine) Tricyclics (A) (effect of baclofen enhanced)	Any alternative	
11.6 **Glaucoma**	Carbonic anhydrase inhibitors (e.g. acetazolamide)	None specifically contra-indicated	Any	Many antimuscarinic antidepressants are contra-indicated in glaucoma
14.4 **Infectious disease prevention**	Vaccines	None specifically contra-indicated	Any	

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