

SAMPLE CHAPTER FROM:

## **Depression**

### **The NICE Guideline on the Treatment and Management of Depression in Adults**

(Updated edition)

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## 2 DEPRESSION

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

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

### 2.1 THE DISORDER

#### 2.1.1 Symptoms, presentation and pattern of illness

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

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

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

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

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

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

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

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

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

### **2.1.2 Course and prognosis**

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

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

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

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

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

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

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

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

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

### **2.1.3 Disability and mortality**

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

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

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

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

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

### **2.1.4 Incidence and prevalence**

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

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

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

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

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

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

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

### **2.1.5 Diagnosis**

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

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

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

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

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

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

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

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

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

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

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

## 2.2 AETIOLOGY

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

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

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

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

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

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

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

### **2.3 ECONOMIC COSTS OF DEPRESSION**

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

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

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

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

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

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

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

### **2.4 TREATMENT AND MANAGEMENT IN THE NATIONAL HEALTH SERVICE**

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

#### **2.4.1 Detection, recognition and referral in primary care**

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

Of the 80 depressed people per 1000 who do consult their GP, 49 are not recognised as depressed, mainly because most of such patients are consulting for a somatic symptom and do not consider themselves mentally unwell, despite the presence of symptoms of depression (Kisely *et al.*, 1995). This group also has milder illnesses (Goldberg *et al.*, 1998; Thompson *et al.*, 2001). Of those that are recognised as depressed, most are treated in primary care and about one in four or five are referred to secondary mental health services. There is considerable variation among individual GPs in their referral rates to mental health services, but those seen by specialist services are a highly selected group – they are skewed towards those who do not respond to antidepressants, people with more severe illnesses, single women and those below 35 years of age (Goldberg & Huxley, 1980).

GPs are immensely variable in their ability to recognise depressive illnesses, with some recognising virtually all the patients found to be depressed at independent research interview, and others recognising very few (Goldberg & Huxley, 1992; Üstün & Sartorius, 1995). GPs’ communication skills make a vital contribution to determining

their ability to detect emotional distress and those with superior skills allow their patients to show more evidence of distress during their interviews, thus making detection easy. Those GPs with poor communication skills are more likely to collude with their patients, who may not themselves wish to complain of their distress unless they are asked directly about it (Goldberg & Bridges, 1988; Goldberg *et al.*, 1993).

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

This view has gained confirmation from a Dutch study in which providing skills training for GPs did not improve detection, but did improve outcomes. Moreover, about half of the observed improvement in patient outcomes was mediated by the combined improvements in process of care. In combination with the strong mediating effect of empathy and psychoeducation they suggest that other, probably also non-specific, aspects of the process of care must be responsible for the training effect on symptoms and disability (Van Os *et al.*, 2004). In addition, the communication skills needed by GPs can be learned and incorporated into routine practice with evident improvement in patient outcomes (Gask *et al.*, 1988; Roter *et al.*, 1995).

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

#### **2.4.2 Assessment and co-ordination of care**

Given the low detection and recognition rates, it is essential that primary care and mental health practitioners have the required skills to assess people with depression, their social circumstances and relationships, and the risk they may pose to themselves and others. This is especially important in view of the fact that depression is associated with an increased suicide rate, a strong tendency for recurrence, and high personal and social costs. The effective assessment of a patient, including risk assessment and

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the subsequent co-ordination of their care (through the use of the Care Programme Approach [CPA] in secondary care services), is highly likely to improve outcomes and should, therefore, be comprehensive.

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

The aim of intervention is to restore health through the relief of symptoms and restoration of function and, in the longer term, to prevent relapse. Where possible, the key goal of an intervention should be complete relief of symptoms (remission), which is associated with better functioning and a lower likelihood of relapse (Kennedy & Foy, 2005). It may not always be possible to achieve remission, but it is usually possible to improve symptoms and functioning to an important degree. For this reason the GDG examined a range of outcomes (where available), including response, remission, change in symptoms and relapse. The relative importance of these depends on many factors, including the severity of depression, the degree of impairment to everyday functioning experienced and the patient's psychiatric history. Among those seeking treatment for depression, those put on waiting lists do improve steadily with time. Posternak and Miller (2001) studied 221 patients assigned to waiting lists in 19 treatment trials of specific interventions and found that 20% improved within 4 to 8 weeks, and 50% improved within 6 months. They estimated that 60% of responders to placebo and 30% of responders to antidepressants may experience spontaneous resolution of symptoms (if untreated). An earlier study by Coryell and colleagues (1994) followed up 114 patients with untreated depression for 6 months: the mean duration of an episode was 6 months, with 50% remission in 25 weeks. It should be noted that there is a high relapse rate associated with depression (see Section 2.1.2, above).

Despite their greater severity and other differences, Furukawa and colleagues (2000) showed that patients treated by psychiatrists with antidepressants showed greater improvements than untreated patients: the median time to recovery was 3 months, with 26% recovering in 1 month, 63% in 6 months; 85% in 1 year, and 88% in 2 years.

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

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

#### **2.4.4 Pharmacological treatments**

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

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

In response to the side-effect profile and the toxicity of TCAs in overdose, new classes of antidepressants have been developed, including: selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine; drugs chemically related to but different from the TCAs, such as trazodone; and a range of other chemically unrelated antidepressants, including mirtazapine (BNF 57, 2009). Their effects and side effects vary considerably, although their mood-elevating effects are again thought to be mediated through increasing intra-synaptic levels of monoamines, some primarily affecting NA, some 5HT and others affecting both to varying degrees and in different ways.

Other drugs used either alone or in combination with antidepressants include lithium salts (BNF 57, 2009) and antipsychotics (BNF 57, 2009), although the use of these drugs is usually reserved for people with severe, psychotic or chronic depressions, or as prophylactics. A full review of the evidence base for the use of the different types of antidepressants is presented in Chapter 10.

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

#### **2.4.5 Psychological treatments**

In 1917, Freud published 'Mourning and melancholia', which is probably the first modern psychological theory on the causes, meaning and psychological treatment of

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

Psychological treatments for depression currently claiming efficacy in the treatment of people with depressive illnesses and reviewed for this guideline in Chapter 8 include: cognitive behavioural therapies; behavioural activation; interpersonal therapy (IPT); problem-solving therapy; counselling; short-term psychodynamic psychotherapy; and couples therapy. Psychological treatments have expanded rapidly in recent years and generally have more widespread acceptance from patients (Priest *et al.*, 1996). In the last 15 years in the UK there has been a very significant expansion of psychological treatments in primary care for depression, in particular primary care counselling.

### **2.4.6 Service-level and other interventions**

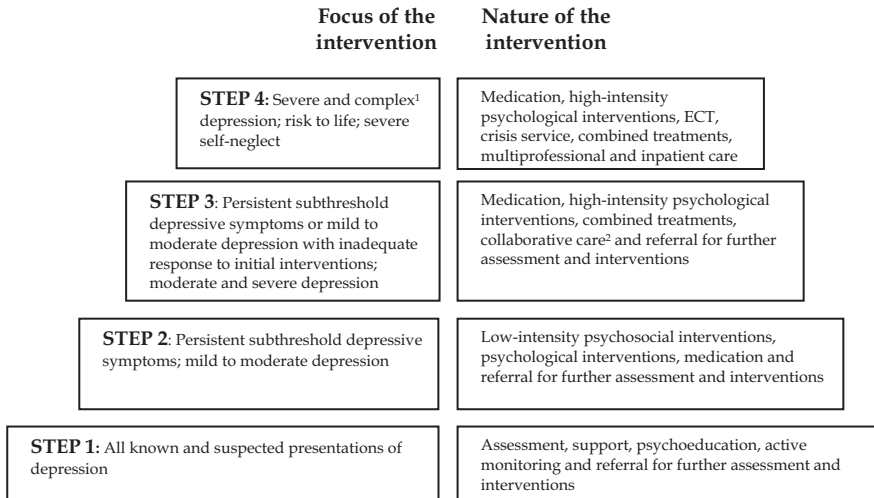
Given the complexity of healthcare organisations, and the variation in the way care is delivered (inpatient, outpatient, day hospital, community teams, and so on), choosing the right service configuration for the delivery of care to specific groups of people has gained increasing interest with regard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

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

### **2.4.7 Stepped care**

In Figure 1, a ‘stepped-care’ model is developed that draws attention to the different needs that depressed individuals have – depending on the characteristics of their depression and their personal and social circumstances – and the responses that are required from services. Stepped care provides a framework in which to organise the

**Figure 1: The stepped-care model**



<sup>1</sup> Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.

<sup>2</sup> Only for depression where the person also has a chronic physical health problem and associated functional impairment (see NICE, 2009c).

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

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

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

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