The epidemiology of major depressive disorder: consequences for society and for the individual

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Abstract

Depression is a common and debilitating disorder that affects people from adolescence to old age. Its sub-groups are described and defined. The prevalence of depression is universally high: the cumulative prevalence in those aged 18 - 32 may be over 40%, although the retrospective figures, which depend on reliability of memory, are much lower, around 17% in one major study. The impact of depression extends beyond the individual with depressive symptoms. Depression adversely affects not only mental and physical health but also the social and financial welfare of individuals and society. Major depressive disorder has a widespread prevalence. Symptom onset can be relatively early. There are genetic vulnerabilities and precipitation or accentuation can occur because of relatively unavoidable stressors. There is a longitudinal pattern of frequent recurrences with increasing frequency, severity, and consequences unless it is treated with effective maintenance strategies. However, the management of depression is characterised by severe underdiagnosis and undertreatment as well as inadequate prioritisation of recurrence prevention by clinicians. Factors including sex, age, ethnicity, societal changes and common co-morbid conditions can all affect the prevalence of depression. These factors contribute to the morbidity and severity of the disease burden of depression. Early treatment for adequate duration can help to improve health, reduce morbidity and reduce the burden of depression. Treatment includes antidepressant medication of adequate dose and duration, with due regard to the mode of action of the medication, in combination with appropriate psychotherapy. There are potential benefits in treating depression in ongoing illnesses such as stroke and coronary heart disease.

Keywords: depression, epidemiology, sex, age, ethnicity, treatment, cost

Introduction

The prevalence of depression depends on a number of factors, including the operational definition of depression and on the type of prevalence: point prevalence, retrospective period prevalence, prospective period prevalence or lifetime prevalence. For example, Moffitt et al. (1) in a major analysis, found that the retrospective lifetime prevalence of depression at 32 years, which depended on recall, was 16.9% but the prospective figure was 40.1%. What is not subject to debate is that depression is a very common and important condition.

Prevalence of depression

Major depression is a commonly occurring disorder in all countries where epidemiological surveys have been carried out as indicated for example in the paper by Kessler et al. (2). However, lifetime prevalence estimates of major depression do vary markedly across countries, and the lifetime prevalence figures are generally greater in high-income versus low-to-middle-income countries. The lifetime prevalence estimates of major depressive disorder (MDD) episodes were between 1.5% (Taiwan) and 19.0% (Beirut), with the midpoints at 9.2% (West Germany) and 9.6% (Edmonton, Canada) (2, 3). Lifetime prevalence estimates of MDD episodes for other locations were: 5.2% (USA), 4.3% (Puerto Rico),16.4% (Paris, France), 12.4% (Florence, Italy), 2.9 % (Korea) and 11.6% (Christchurch, New Zealand) (4, 5). The 12-month prevalence

estimates of MDD episodes were between 0.8% (Taiwan) and 5.8% (Christchurch, New Zealand), with the midpoints at 3.0% (US) and 4.5% (Paris). The other 12-month prevalence estimates of MDD episodes were 5.2% (Edmonton, Canada), 3.0% (Puerto Rico), 5.0% (West Germany), and 2.3% (Korea) (2, 3). It is worth noting the higher prevalence in major older European cities such as Paris and Florence, where housing and income problems may be a factor, and lower rates in developing countries such as Puerto Rico. Beirut is also a large conurbation with threats of war, while affluent areas such as USA and West Germany have low prevalence.

12-month prevalence rates for males and females (2, 3)

Country/region	*Male (%)*	*Female (%)*
USA	2.8	7.4
Edmonton, Alberta, Canada	6.6	12.3
Puerto Rico	3.1	5.5
West Germany	4.4	13.5
Florence, Italy	6.1	18.1
Beirut, Lebanon	14.7	23.1
Taiwan	1.1	1.8
Korea	1.9	3.8
Christchurch, New Zealand	7.5	15.5
Paris, France	10.5	21.9

It is clear that there is a greater prevalence of depression in women than in men (2, 3). The lifetime prevalence estimates of MDD were 1.0% (Czech Republic) to 16.9% (US), with midpoints at 8.3% (Canada) and 9.0% (Chile) (3, 6), while the 12-month prevalence estimates of MDD were 0.3% (Czech Republic) to 10% (US), with midpoints at 4.5% (Mexico) and 5.2% (West Germany) (2, 7).

Prevalence of MDD episodes per 100

	Brazil	*Canada*	*Chile*	*Czech Republic*	*Germany*	*Japan*	*Mexico*	*Netherlands*	*Turkey*	*USA*
Lifetime	12.6	8.3	9.0	7.8	11.5	3.0	8.1	15.7	6.3	16.9
12-month	5.8	4.3	5.6	2.0	5.2	1.2	4.5	5.9	3.5	10.0
30-day	3.9	1.9	3.3	1.0	1.3	0.9	2.2	2.7	3.1	4.6

There is a difference between the prevalence of MDD episodes and MDD, because MDD episodes include bipolar depression as well as unipolar depression from various causes.

Defining depression

Depression is described as consisting of 'depressive episodes' (DEs) in the official WHO classification of disease (4). DEs, according to the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), include both those episodes caused by genetic or other endogenous factors and those caused by a reaction to life events. Therefore, the distinction between endogenous and

reactive depression has been abolished. Depressive symptoms must be present for at least 14 days to fulfil the criteria for a depressive episode. A depressive episode may last for weeks or months. However, if a patient has low mood for less than two weeks following an untoward life event, this can be classified as an adjustment reaction.

The core depressive symptoms are low mood, most of the day every day, and diminished interest or pleasure in activities most of the day, nearly every day, as well as fatigue or loss of energy nearly every day.

Other depressive symptoms include:

- decrease or increase in appetite nearly every day which may be reflected in weight loss when not dieting, or weight gain
- insomnia or hypersomnia
- psychomotor agitation or retardation
- feeling of worthlessness, excessive or inappropriate guilt
- diminished ability to think or concentrate, or indecisiveness
- recurrent thoughts about death, suicidal ideation without a specific plan, or a suicide attempt with a specific plan for committing suicide (5)

In a mild depressive episode (F32.0), two or three of the above symptoms are usually present. The depressed patient will usually be distressed by the symptoms but he/she should be able to continue with most activities.

In a moderate depressive episode (F32.1), four or more of the above symptoms will usually be present and the patient is likely to have great difficulty in continuing with ordinary activities.

In a severe depressive episode without psychotic symptoms (F32.2), all of the above symptoms are present. Several of these symptoms will be marked and distressing; they typically include loss of self-esteem as well as ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of "somatic" symptoms will usually also be present.

If psychotic symptoms are present, then the patient is said to have F32.3: 'severe depressive episode with psychotic symptoms' (4).

Many patients have recurrent episodes of depression. These patients are said to have recurrent depressive disorder (F33). This is a disorder which is characterized by repeated episodes of depression as described for depressive episode (F32.x), without any history of independent episodes interspersed between the depressive episodes of mood elevation and increased energy (hypomania or mania). The first episode might occur at any age from childhood to old age. The onset may be either acute or insidious and the duration may vary between a few weeks and many months. The risk that a patient with recurrent depressive disorder will have an episode of mania never disappears completely; however many depressive episodes may have occurred before the first manic episode. This means that ongoing surveillance needs to be carried out on patients with recurrent depressive disorder so as to identify a manic or hypomanic episode should it occur. If such an episode does occur, the diagnosis should be changed to bipolar affective disorder (F31) (4). This is important because the treatment of bipolar affective disorder is different from that of unipolar depression.

The classification of recurrent depressive disorder is as follows:

- F33.0: recurrent depressive disorder, current episode mild
- F33.1: recurrent depressive disorder, current episode moderate
- F33.2: recurrent depressive disorder, current episode severe without psychotic symptoms
- F33.3: recurrent depressive disorder, current episode severe with psychotic symptoms
- F33.4: recurrent depressive disorder, currently in remission (4)

It is necessary to define when a patient has responded to treatment, when the episode has remitted, and when a relapse, (which is in fact a new episode), has occurred.

Response to treatment is the initial improvement in symptoms with treatment. The end of a MDE (major depressive episode), otherwise known as remission, is described as "four consecutive weeks of asymptomatic recovery and the beginning of a stable well state with improved psychosocial function".

It is important to be aware that apparent symptom resolution with residual symptoms is in fact a continuation of an active state of the episode, not the end of a major depressive episode (6).

A relapse is said to have occurred if the depressive symptoms recur after four weeks have passed from the beginning of a remission.

Why is it important that we examine the epidemiology of major depressive disorder?

- **Depression is a common and debilitating disease**

  In 2012 the World Health Organization Global Burden of Disease Survey ranked depression as the 4th leading cause of disability worldwide and predicted that by the year 2020, MDD will be second only to ischaemic heart disease in terms of disability experienced by sufferers (8). Depressive symptoms may often start at a young age (9) and often are recurring (10-12).

- **MDD and other mood disorders cause an important and increasing burden on society**

  Depression has a destructive impact on the individual patient and also, because of the patient's altered functionality, on society in general. The extent of this burden can be demonstrated by the amount of disability attributed to MDD, as well as its economic and social impact. In 2001, neuropsychiatric conditions accounted for almost 30% of the world's total years lived with disability, and of this, 11% was attributed to unipolar MDD (13). There is evidence that the size of this burden is increasing. Depression accounted for 3.7% of all disability adjusted life years (DALYs) in 1990 and for 4.4% of total DALYs in 2000. In the year 2000, it was responsible for the largest non-fatal disease burden (14). Treatment-resistant depression causes the greatest disability and consequently has a high economic and social impact (13). It is of concern that these data are likely to be an underestimate of the extent of the strain MDD causes to society (15).

- **The economic burden of depression appears to be rising**

  The economic burden of depression in the US rose by 7% from 1990 to 2000, despite an over 50% increase in the proportion of those with depression receiving treatment (16). Untreated depression appears to be a greater economic threat than treating depression. The cost engendered by depression in Sweden increased from €1.7 billion in 1997 to €3.5 billion in 2005. The cost to society nearly doubled during this time period because of a significant increase in indirect costs due to sick leave and early retirement, while direct costs remained relatively stable (17).

- **The disease burden due to MDD has a significant financial impact on both healthcare systems and employers**

  The cost of mood disorders in Europe in 2010 was estimated as €113.4 billion. This estimate includes the direct healthcare costs, the non-medical costs (approx. 60%) and the costs associated with patients' production losses (approx. 40%) (18). A study on the total annual cost of depression in Catalonia showed that a large percentage of the costs were outside direct healthcare expenses. Only 21.2% of the total cost (€735.4 million) was due to direct costs, including primary care (5.6%), mental health specialised care (1.1%), hospitalisation (0.8%) and pharmacological care (13.7%), while 78.8% of the total figure represented indirect costs which were due to losses in productivity. 3.7 million work days were lost due to temporary disability caused by depression, costing €199.6 million. Permanent disability and mortality attributed to suicide also accounted for significant losses (19).

  Employees with depression cost US employers an excess of $31 billion per year when compared with employees without depression. Of interest is that most of this lost productive time was not attributed

to absence from work but to reduced performance while at work (which has been called presenteeism) (20). It has been reported that the presence of somatic symptoms, including pain or fibromyalgia, with significant psychiatric symptoms increases the disease burden (21). It is therefore suggested that earlier intervention in patients with 'depression with somatic symptoms' may be warranted in order to reduce its significantly greater economic impact.

As well as the economic stress caused by unmanaged MDD, there are significant functional impairments in home life, work, relationships and social functioning (22).

- **MDD has a major impact on children**

The adverse impact of poorly managed depression on society extends beyond the individual person with psychiatric symptoms. Children of low income depressed women in a general practice have been reported as having a three-times greater risk of serious emotional problems compared to children of non-depressed mothers. Many of the mothers in the study were not treated for their depression (23). In a study including 72% of mothers with severe depression, 45% of their children were found to have a lifetime psychiatric disorder, including disruptive behaviour (29%), anxiety (20%) and depressive disorders (19%).

A history of maternal suicide attempts with co-morbid panic disorder in the mothers was associated with a threefold increase in the odds of depressive disorders in the offspring. Previous maternal suicide attempts and co-morbid agoraphobia in the mothers was associated with an eightfold increase in the odds of depressive disorders in the offspring. Therefore particular consideration needs to be given to the mental health of children with depressed mothers (24).

A family history of depression could indicate either a genetic (25) or an environmental basis for an increased susceptibility to psychiatric conditions including depression. Maternal depression could be an environmental trigger for psychiatric illness. It has been suggested that poor parenting, marital discord, modelling, and other environmental factors can all contribute to the development of psychiatric symptoms in children with affected mothers. Furthermore, this study also noted a significant effect on the male partners of mothers with postnatal depression (26).

Both psychiatric effects and physical disturbances have been observed in children who have depressed mothers. In a community sample of infants, maternal depression in both the prenatal and postnatal periods predicted restricted growth and diarrhoea (27). Treating maternal depression can improve the physical and mental health of offspring, as well as improving the health of the mother.

- **Depression is under-detected by both patients and doctors**

Although clinically significant depressive symptoms have been shown to be prevalent among primary care patients in the U.S., it appears that many patients do not interpret depression as the cause of their illness. Although 20.9% of primary care patients have clinically significant depressive symptoms, only 1.2% of primary care patients cite depression as the reason for their visit to the doctor (28). Patients with MDD may present with only physical complaints. In an international study of 1146 patients with major depression, 69% reported only physical symptoms as the reason for their physician visit (29). In another study, 76% of patients diagnosed with depression or anxiety had "somatic presentations" (physical complaints) (30). Thus, many patients with MDD may deny emotional symptoms and instead present with somatic symptoms alone. One study found that while 50% of MDD patients in primary care settings complain of multiple unexplained somatic symptoms, 11% denied psychological symptoms in primary care settings (29). It is hoped that addressing the stigma surrounding mental health might reduce patient denial of psychological symptoms and could improve the current inadequate rate of diagnosis and delivery of treatment to individuals with depressive symptoms (31).

- **Treatment of depression is reported to often be inadequate**

It has been shown that treatments for depression are often under-used and withdrawn prematurely. Since effective long-term treatment does relieve the disease burden, this practice is detrimental both to patient welfare and to society (32).

In a group of patients (22) who had suffered from depression over the last twelve months, 48.4% received no treatment while 51.6% received treatment. Of those who received treatment, 58.1% received inadequate treatment while 41.9% received adequate treatment according to guidelines, so that in total only 21.6% of the whole group received appropriate treatment. A similar situation has been reported in the UK (33), where as many as 88% of prescriptions for older tricyclic antidepressants prescribed by GPs are at doses which are below those recommended by the consensus guidelines. Newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) were reported as being prescribed at an appropriate dosage, but in both cases treatment was prescribed for a shorter time than that recommended by guidelines. It is reported that maintained drug treatment or cognitive behaviour therapy (CBT) are more effective than episodic treatment in reducing the number of DALYs due to MDD (34).

- **Increasing treatment of depression is reported to reduce the disease burden**

  Fortunately, the rate of diagnosis of cases of MDD is increasing as patients and clinicians become better at recognising depression. Treatment of diagnosed depression is associated with a decrease in disease burden (32). The decrease in disease burden as depression is recognised and treated becomes a strong argument for addressing the problems of under-diagnosis and inadequate treatment of the condition.

  Treating MDD reduces healthcare costs in the elderly. Depressive symptoms are common in older adults and they are associated with a significant increase in the cost of general medical services. Specialty mental-health care and differences in age, sex, and chronic medical illness do not account for the increase in expense (35).

  Understanding the epidemiology of MDD is a step towards planning to improve the current unsatisfactory rates of diagnosis and treatment. Studying MDD in populations may provide insights or explanations into the pathogenesis of depression, reveal the existence of sub-groups of the disorder and help inform treatment strategies to target those most at risk. Improving the understanding of depression in society should help to reduce the stigma surrounding mental health that contributes to the problems faced in successfully treating MDD.

Sex and hormonal changes affect the risk of depression

MDD is approximately twice as common in females as in males (36, 37). Women are 1.7 times more likely than men to report a lifetime history of a major depressive episode (38, 39). It is reported that the lifetime rate of major depression is up to 2.7 times greater in females than males. This difference begins in early adolescence and continues through the mid-50s. The changes in the risk of depression are associated with several hormonal shifts. The onset of puberty marks the beginning of increased risk for depression in women (38).

Pregnancy does not increase the risk for depression. Women who have a history of depression are at risk of recurrent episodes if antidepressant medication is discontinued during pregnancy. Postpartum hormonal changes increase the incidence of depression (38). The postpartum period is listed as a risk factor for MDD in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (5). Women who are transitioning through the peri-menopause, particularly those with psychiatric histories, report depressive symptoms (38).

Women have a higher rate of 12-month depression than men (40). This is attributable to the largely higher risk of first onset in females. Women with a history of depression do not differ from men with a history of depression in the probability of being chronically depressed in the past year or in the probability of having an acute recurrence in the past year (40).

Sex differences in the rate of MDD are consistent across cultures. This supports the idea that sex differences in prevalence of depression are due to biological factors, including hormonal changes. Sex differences in prevalence may be influenced by psychosocial factors that are consistent across countries (39).

Age affects the prevalence of depression

Risk of depression changes with age, notably at adolescence and ages which align with reproductive hormone changes, as has been described earlier (38). Results of research on age-dependent increases in depression in the elderly are conflicting. Some report a slight increase, particularly in males, while others report a decrease, particularly in females, in the prevalence and incidence of depression in the elderly (41). This suggests that age-related changes in the incidence of depression occur because of particular hormonal and social changes that occur during life, rather than because of gradual biological changes that occur over the course of a lifetime. Increasing age is correlated with increased risk of a number of diseases, including cardiovascular diseases. Depression adversely affects the prognosis of patients with co-morbidities.

The prevalence of depression is affected by ethnicity

There is an unequal risk of depression across different ethnic groups in the UK. British South Asian women have higher rates of depression than their white counterparts (42). In a British population sample, depressive symptoms affected 9.7% of white Europeans and almost double the proportion of South Asian (15.5%) and of black Caribbean (17.7%) participants. The increased prevalence in South Asians was mostly accounted for by co-morbidities. The increased prevalence in black Caribbean participants was mainly explained by socioeconomic disadvantage (43). Finding explanations for these ethnic differences could enable inequalities to be addressed.

Perception of illness and classification of bodily sensations varies between individuals. There is conflicting evidence on whether ethnicity affects illness perception and, given that these differences may exist, whether they account for ethnic variation in the prevalence of depression. North Indian and white British women were presented with a vignette and asked to evaluate the character's problems. The study concluded that ethnic differences in illness perceptions contributed to the lower rate of GP treatment sought by Indian women as compared with white British people (44). However, another study found that there was no difference between South Asian and white people in their understanding of their illness and what they understood to be the cause of their symptoms (45). Differences in diagnosis and treatment of depression between South Asian and white populations appear to be due to disparities in the availability of treatment, rather than cultural differences in identification and perception of disease (45). Thus the pathways to care of different ethnic groups who suffer depression may be affected by different factors. There are complex racial and ethnic variations in those somatic symptoms which are associated with depression because of different social and cultural factors which influence how individuals seek medical attention (31).

Physical symptoms linked with depression may include fainting, menstrual problems, headache, chest pain, dizziness, palpitations, sexual problems, GI symptoms (nausea, vomiting, gas, or indigestion, constipation, diarrhoea), abdominal pain, dyspnoea, fatigue, insomnia, joint or limb pain, and back pain. The presence of any physical symptom increases the likelihood of diagnosis of a mood or anxiety disorder by twofold to threefold. A greater number of physical symptoms is associated with a higher likelihood of depressive disorders and greater loss of functionality (46). Unexpectedly, a study found that depression diagnoses were more common in Punjabis with low scores for somatic symptoms compared with their English counterparts (47). Ethnic and gender variation in somatic symptom reporting could be accounted for by both the influence of cultural expectations and the stigma of symptom reporting (31). A study on somatisation in 3,132 participants in Los Angeles found no effect of ethnicity on somatisation indexes of male participants. The authors proposed that denial and minimisation of symptoms were likely explanations, particularly in older Mexican-American men and that this may be related to "machismo" and stoicism, which were identified as common traits in this group (48). It has been reported that there are significant differences in somatic symptoms in African Americans compared to whites who had similar levels of psychosocial function, using the Global Assessment Scale (GAS) and MOS (Medical Outcomes Study) mental functioning scales, in that African Americans reported poorer general health and greater impairment on the MOS physical functioning scales (49).

It is important to point out that one of the criteria for diagnosing depression is that the symptoms cause a problem for the patient. The way in which this problem is experienced can differ according to ethnicity,

which appears to act as a proxy measure for a combination of factors which include attitudes towards illness, understanding of mental health, stress, community support and coping resources.

- **Co-morbidity and ethnicity**

  Controversial findings exist on the relationship between type 2 diabetes and depression. A 2010 study found that after controlling for demographic and diabetes related factors, white Europeans with type 2 diabetes had nearly 60% higher adjusted odds of being diagnosed with depression compared to South Asians with type 2 diabetes (50). Suggested explanations for the results are differences in presentation or identification of depressive symptoms between these two ethnic groups. However, a more recent study of white European and South Asian participants showed that depressive symptoms were not significantly more prevalent in people with type 2 diabetes or impaired glucose regulation (51). There are distinct and overlapping risk factors for depression in individuals with type 1 and type 2 diabetes. Risk factors for depression in type 1 diabetics are said to include female gender, diabetes-related complications, and co-morbidities. Risk factors for depression in type 2 diabetes are reported to include younger age, diabetes-related complications, co-morbidities, insulin use and deprivation (50).

Changes in society affect the rate of depression

Changes in economic conditions affect the prevalence of depression. The rate of depression recorded in English general practices was decreasing before the economic recession. The rate of depression in men increased following the recession, in line with increasing unemployment (52).

Adverse life events are precipitating factors for depression. Adverse life events may occur at a population or an individual level and a history of such events must be taken into consideration when diagnosing MDD.

Differences in the rate of depression may be caused by factors other than sex, age and culture

Where treatment for depression is not readily available this may be connected with a low rate of diagnosis because people may choose not to seek medical intervention. A low uptake of available treatment may also be due to the social stigma which surrounds mental illness. There may be a low rate of diagnosis in males because males are less likely to visit their GP than females. Consequently MDD may be diagnosed and treated at different rates in different populations for reasons other than the true rate of incidence of depressive symptoms.

The WHO has demonstrated the effectiveness of depression treatment in several countries with varying availability of resources and has demonstrated that where treatment is delivered it was effective (53). However, in places where there are inadequate resources and social stigma the majority of people in need of treatment for depression do not receive it. As a result, globally fewer than 50% of cases are treated. In some countries, fewer than 30% of cases in most regions and less than 10% of total cases are treated (53).

Treatment aims

Depression can present with a range of symptoms and a spectrum of intensities but the goal of treatment remains the same, namely remission of MDD. Remission consists of: minimal to no residual symptoms, restored function and low scores on scales used to track depression severity in research settings e.g. a score of < 7 on the 17-item Hamilton Depression Rating Scale (HAM-D) or a score of < 10 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (54).

Residual symptoms may include anxiety and irritability, depressed mood, feelings of guilt and loss of interest in activities, asthenia, difficulty falling asleep at night and physical symptoms.

Remission is a difficult milestone to identify. The symptoms of depression vary between patients and over the course of each individual's disease. Judd et al. noted that "MDD combined minor depressive or dysthymic disorder, and sub-syndromal or sub-threshold depressive symptoms (which) commonly alternate

over time in the same patients as a symptomatic continuum of illness activity of a single clinical disease" (55).

Judd later defined the end of a MDE as follows. "Four consecutive weeks of asymptomatic recovery and the beginning of a stable well state with improved psychosocial function. Residual symptom resolution is a continuation of an active state of the episode, not the end of an MDE" (56).

- **Remission with no residual symptoms reduces the risk of relapse for MDD**

  It is important to identify remission and transition from an MDE to residual symptoms correctly because resolution of an MDE with the continued presence of residual symptoms poses a greater risk of relapse (another MDE) and predicts a more severe, chronic, relapsing form of the disease (54). Patients with residual symptoms relapsed three times as fast as those who were asymptomatic at remission (55). Almost three times as many patients without residual symptoms at remission remained well compared to those with residual symptoms (57). Following a depressive episode, residual symptoms represent an active form of the disease and are a marker for the rate of onset of the next MDE. In such cases there is a need for continued management (55).

  Patients with severe depression are more likely to have residual symptoms. Duration of prior illness, dysthymia and dose of treatment drug do not affect the risk for residual symptoms (57).

- **Some Indications for adequate and appropriate treatment choices**

  At present, there are shortcomings in nearly every aspect of treating depression – diagnosis, delivery of treatment to those who need it and delivery of adequate treatment. This is illustrated by the National Comorbidity Survey Replication in the USA which showed that only 51.6% of 12-month cases of MDD received treatment. Treatment was adequate in only 41.9% of these cases, resulting in 21.7% of 12-month MDD being adequately treated. Sociodemographic correlates of treatment were less numerous than those of prevalence (22). A study of 790 patients who presented with one major depressive episode found that 46.7% of patients had residual symptoms following 8 to 12 weeks of antidepressant treatment (58).

  The goal of treating MDD should be complete remission with no residual symptoms because of the high morbidity and mortality associated with residual symptoms. In terms of the use of antidepressants, one proposed strategy for achieving complete remission may be a multi-receptor targeting treatment strategy. Thus it has been proposed that long-term antidepressant therapy targeting serotonergic and noradrenergic systems provides greater efficacy and remission rates than single target drug treatments (59). In such a strategy, both physical and psychiatric symptoms should be treated because pain reduction correlates with a higher remission rate even after accounting for improvement in emotional symptoms. For this reason it has been suggested that somatic symptoms may be more effectively managed with a medication which targets both serotonergic and noradrenergic receptors (60).

  Paykel et al. have shown that tricyclic antidepressants are not effective in mild depression. Tricyclics do have a real effect on core depressive symptoms, despite there being also a marked placebo effect, in more severe 'mild to moderate' cases (61). It has been suggested that it is cost effective to add an SSRI to supportive care in cases of 'mild to moderate' depression. Evidence for this comes from a study of patients treated with an SSRI and supportive care versus those treated with supportive care alone, although the additional benefit seen in patients in the former group may be due to a placebo effect (62).

  Screening for and treating depression in the workplace has been found to be cost-effective for employers. From the perspective of the employer, psychotherapy is the most cost-effective treatment option for MDD (63). For health-care systems, combined antidepressant and cognitive therapy is more expensive than antidepressant therapy alone, but these costs were offset by the considerable reduction of productivity loss from the social perspective (64). As a consequence, it is generally accepted that while treatment with cognitive or supportive therapy alone is adequate for mild depression, and should be carried out in primary care, a combination of cognitive behavioural therapy and an adequate dose of antidepressant for a sufficient period of time, generally stated as six months, is appro-

priate treatment for a moderate to severe depressive episode. This is known as the 'Paykel and Priest rule' (65). Most moderate-to-severe episodes of depression are treated in primary care by this method.

Cases of resistant depression, defined as cases resistant to two different antidepressants with no response to six weeks of treatment with either antidepressant, should be referred to secondary care. This model of treatment is referred to by the National Institute for Health and Care Excellence (NICE) as the 'stepped care model' (66).

Several studies have investigated the utility of antidepressant therapy for treating depressive symptoms in dementia and related syndromes. In patients with Alzheimer disease, antidepressants were not found to be more effective than placebo at relieving depressive symptoms (67). The use of antidepressants in these patients was associated with an increased risk of adverse events (68). Mirtazapine and sertraline were not cost-effective for treating depression in dementia. However unpaid (family) carer costs were lower when dementia patients with depression were treated with mirtazapine than with sertraline or placebo. The positive effect of mirtazapine may have been to reduce sleep disturbances and anxiety rather than relieve depressive symptoms (69).

- **Some potential benefits of treating depression in patients with stroke and ischaemic heart disease**

Treating elderly patients for diagnosed MDD reduced the cost of medical services. Depressive symptoms were common, persistent, and were associated with a significant increase in the cost of general medical services in an elderly cohort. Expense increased across every component of healthcare costs and were not accounted for by an increase in specialty mental health care (35).

There is a complex and poorly understood interplay between depression and the development and resolution of other medical conditions. It is clear that reducing the rate of depression may improve patient outcomes in a variety of clinical scenarios. MDD increases morbidity and mortality from other medical conditions and the risk of depression is greatly increased in the presence of other recognised adverse clinical variables at baseline (70).

Despite being younger and having fewer chronic conditions, a higher three-year mortality risk was seen in patients with post-stroke depression and other mental health diagnoses after hospitalisation for an ischaemic stroke. In stroke patients, co-morbid depression increased risk of death by 13%. However, the mechanism is unknown (71).

Co-morbid depression increases morbidity and mortality in patients with ischaemic heart failure and heart failure secondary to non-ischaemic dilated cardiomyopathy (DCM) (70). Depression increases the risk of cardiac mortality and morbidity in patients with coronary heart disease (CHD). It has been suggested that this was related to antidepressant cardiotoxicity, as well as the association of depression with cardiac risk factors such as cigarette smoking, hypertension, diabetes, reduced functional capacity, the association of depression with greater coronary disease severity, non-adherence to cardiac prevention and treatment regimen, lower heart rate variability (HRV) reflecting altered cardiac autonomic tone, increased platelet aggregation and inflammatory processes. All these are potential mechanisms for the differences but it is to be concluded that further research is needed to determine how depression increases risk for cardiac morbidity and mortality (72).

It is unclear if depression can be included as an independent risk factor for CHD. A meta-analysis confirmed that depressive symptoms increase the risk of mortality in CHD patients. Risk of dying is twice that of non-depressed patients two years after the initial assessment. This negative prognostic effect persists in the long-term and after adjustment for other risk factors. Within the first six months, depressive disorders were found to have no significant effect on mortality (73). However, a 2006 meta-analysis of 6,362 events among 146,538 participants in 54 observational studies concluded that depression could not yet be established as an independent risk factor for CHD because there was incomplete and biased availability of adjustment for conventional risk factors and severity of coronary disease (74).

Conclusion

In 2012 the World Health Organization Global Burden of Disease Survey ranked depression as the 4th leading cause of disability worldwide. The management of depression remains an important challenge for both primary care and specialist services. Greden et al. (13) identified factors contributing to this challenge and to the morbidity of depression: "widespread prevalence; relatively early symptom onset; severe under-diagnosis and under-treatment; genetic vulnerabilities and precipitation or accentuation by relatively unavoidable stressors; a longitudinal pattern of frequent recurrences with increasing frequency, severity, and consequences unless treated with maintenance strategies; inadequate prioritization of recurrence prevention among clinicians". This paper has examined the epidemiology of depression. Acknowledging and understanding factors that influence the prevalence of depression should help us to develop measures that decrease the impact of this condition on the individual and on society in the future.

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