A REVIEW OF THE EPIDEMIOLOGY OF MAJOR DEPRESSIVE DISORDER AND OF ITS CONSEQUENCES FOR SOCIETY AND THE INDIVIDUAL

Anna McKeever[1], Mark Agius[1,2] & Pavel Mohr[3]

[1]*Clare College Cambridge, Cambridge, UK*
[2]*Department of Psychiatry, University of Cambridge, Cambridge, UK*
[3]*National Institute of Mental Health Prague, Czech Republic*

SUMMARY

Depression is a common and debilitating disease that affects people from adolescence to old age. The impact of depression extends beyond the individual with depressive symptoms. Depression adversely affects the mental and physical health, and the social and financial welfare of the individual and society.

We will address how factors including sex, age, ethnicity and societal changes affect the prevalence of depression, consider common co-morbid conditions and highlight the lessons learned from treating depression.

Key words: *depression – epidemiology – sex – age – ethnicity – treatment - cost*

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DEFINING DEPRESSION

Before we begin discussing the epidemiology of depression, it is necessary to define depression and its related conditions. This is necessary because, like all mental illnesses, the diagnosis of depression depends entirely on symptoms, so that the collection of symptoms which signifies the illness needs to be defined before any epidemiological study can be carried out.

The medical condition known as depression is described as consisting of 'Depressive Episodes' [DE] in the official WHO classification of disease (WHO 2010).

Depressive episodes, according to WHO [ICD-10] (WHO 2010) include both those caused by genetic or other endogenous factors and also those caused by reaction to life events. Therefore, the distinction between Endogenous and reactive depression is abolished. All patients must experience depressive symptoms for 14 days in order for the patients to be said to have a depressive episode. A depressive episode may last weeks or months.

If a patient has low mood for less than two weeks after an untoward life event, this is 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. Furthermore, depressive symptoms include:

Weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day;

- Insomnia or hyper insomnia;
- Psychomotor agitation or retardation;
- Fatigue or loss of energy nearly everyday;
- Feelings of worthlessness, excessive or inappropriate guilt;

- Diminished ability to think, concentrate or indecisiveness;
- Recurrent thoughts of death, suicidal ideation without a specific plan, or a suicide attempt with a specific plan for committing suicide (American Psychiatric Association 2013).

In a Mild depressive episode, F32.0, Two or three of the above symptoms are usually present. The patient will usually be distressed by the symptoms but should be able to continue with most activities.

In Moderate depressive episode F32.1 Four or more of the above symptoms are usually present while the patient is likely to have great difficulty in continuing with ordinary activities.

In a severe depressive episode without psychotic symptoms, F32.2, all the above symptoms are present. In a severe depressive episode, several of the above symptoms are marked and distressing, typically including loss of self-esteem and ideas of worthlessness or guilt. Suicidal thoughts and acts are common and a number of "somatic" symptoms are usually also present. If psychotic symptoms are present, then the patient is said to have F32.3 'Severe depressive episode with psychotic symptoms' (WHO 2010).

Many patients suffer recurrent episodes of Depression. Such patients are said to suffer recurrent depressive disorder F33. This is a disorder characterized by repeated episodes of depression as described for depressive episode (F32.-), without any history of independent episodes of mood elevation and increased energy, which is otherwise known as mania or hypomania. The first episode may occur at any age from childhood to old age, the onset may be either acute or insidious, and the duration varies from a few weeks to many months. The risk that a patient with recurrent depressive disorder will

have an episode of mania never disappears completely, however many depressive episodes have been experienced. If such an episode does occur, the diagnosis should be changed to bipolar affective disorder (F31.) (WHO 2010). 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 (WHO 2010).

Therefore, it is clear that, in order to decide whether a patient is suffering from a depressive episode, it is necessary to define when a patient has responded to treatment, when the episode has remitted, and when a relapse, which is a new episode, has occurred.

Response to treatment is the initial improvement in symptoms once treatment occurs. The end of a MDE (Major Depressive Episode), or remission, is described as "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." (Rockville 1993). Hence a relapse occurs if the depressive symptoms reccur after four weeks have passed from remission.

WHY EXAMINE
THE EPIDEMIOLOGY OF MDD?

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 predicts that by 2020, major depressive disorder (MDD) will be second only to ischemic heart disease in terms of disability experienced by sufferers (Murray 1996). Depressive symptoms often start at a young age (Thapar 2012) and are often recurring (Limosin 2004, Yiend 2009, Katon 2001).

MDD and other mood disorders impose
a significant and increasing burden on society

Depression has a destructive impact on the individual with depressive symptoms and also, as a consequence of their altered functionality, on society as a whole. The extent of this burden is demonstrated by the amount of disability attributed to MDD, the economic impact of MDD and the social impact of MDD. In 2001,

neuropsychiatric conditions accounted for almost 30% of the world's total years lived with disability, of which 11% was attributable to unipolar major depressive disorder (Greden 2001). It appears that the size of the 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 (Ustün 2004). Treatment resistant depression causes the greatest disability and hence economic and social impact (Greden 2001). It is of concern that, these data are likely to be an underestimate of the extent of the strain MDD imposes on society (Wittchen 2011).

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

The cost of mood disorders in Europe in 2010 was €113.4 billion. This includes both the direct healthcare costs and the non-medical costs (approx. 60%) as well as the costs associated with patients' production losses (approx. 40%) (Gustavsson 2011). A study on the total annual cost of depression in Catalonia showed that a large percentage of the costs were outside of direct healthcare expenses. 21.2% of the total cost (€735.4 million) was due to direct costs, including primary care (5.6%), mental health specialized care (1.1%), hospitalization (0.8%) and pharmacological care (13.7%), while 78.8% of the total figure represented indirect costs due to productivity losses. 3.7 million work days were lost to temporary disability for depression, costing €199.6 million. Furthermore, permanent disability and mortality attributed to suicide also accounted for significant losses (Salvador-Carulla 2011). Furthermore, Employees with depression cost US employers an excess of $31 billion dollars per year compared with employees without depression. Most of this lost productive time was attributed not to absence from work, but to reduced performance while at work (presentee-ism) (Stewart 2003).

It is reported that the presence of somatic symptoms such as pain or fibromyalgia with significant psychiatric symptoms increases the disease burden (Greenberg 2003). The authors therefore have suggested that earlier intervention in depression with somatic symptoms might be warranted due to its significantly greater economic impact.

In addition to the economic stress caused by unmanaged MDD, Kessler et al have shown that persons with Major Depressive Disorder (MDD) suffer from significant functional impairment in their home life, work, relationships and social functioning (Kessler 2003).

Major Depressive Disorder
in adults is costly to children.

Poor management of depression in society has an adverse impact that extends beyond the individual person with psychiatric symptoms. Children of low-income depressed women at a general practice have been reported to have a three-times greater risk of serious emotional problems compared with children of non-depressed mothers. Many mothers in the study were

not being treated for their depression (Weissman 2004). In a study with 72% of mothers displaying severe depression, 45% of their children had a lifetime psychiatric disorder, including disruptive behaviour (29%), anxiety (20%), and depressive disorders (19%). A history of maternal suicide attempts with comorbid panic disorder was associated with a 3-fold increase in odds of depressive disorders in the offspring. Previous maternal suicide attempts and comorbid agoraphobia was associated with an 8-fold odds increase. Particular consideration needs to be given to the mental health of children with depressed mothers (Pilowsky 2006).

A family history of depression may provide a genetic (Guffanti 2016) or environmental basis for an increased susceptibility to psychiatric conditions. Thus, maternal depression may be an environmental trigger for psychiatric illness. Burke suggests that poor parenting, marital discord, modelling, and environmental factors all contribute to the development of psychiatric symptoms in children with affected mothers. Furthermore, this study also notes a significant affect on the male partners of mothers with postnatal depression (Burke 2003).

As well as psychiatric effects, physical disturbances have been observed in children with depressed mothers. Maternal depression in the prenatal and postnatal period predicted restricted growth and diarrhoea in a community sample of infants. (Rahman 2004) On the other hand, treating maternal depression can improve the physical and mental health of their offspring, as well as improving the health of the mother.

Depression is under-detected by patients and doctors

Clinically significant depressive symptoms have been shown to be prevalent among primary care patients in the U.S. While 20.9% of primary care patients have clinically significant depressive symptoms, only 1.2% of primary care patients cited depression as the reason for their visit. (Zung 1993) Patients with Major Depressive Disorder may present with only physical chief complaints. In an international study of 1146 patients with major depression, 69% reported only physical symptoms as the reason for their physician visit. (Simon 1999) In another study, 76% of patients diagnosed with depression or anxiety had "somatic presentations" (physical complaints) (Kirmayer 1993) Thus, patients with Major Depressive Disorder (MDD) may deny emotional symptoms and instead present with somatic symptoms. Simon and his colleagues 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 (Simon 1999). Addressing the stigma surrounding mental health can reduce patients' denial of psychological symptoms and could improve the inadequate rate of diagnosis and delivery of treatment to individuals with depressive symptoms (Bagayogo 2013).

Treatment of Depression is often inadequate

It has been demonstrated that treatments for depression are under-used and are often withdrawn prematurely. Since effective long-term treatment relieves the disease burden, this practice is detrimental to patient welfare and to society (Lecrubier 2001).

Kessler et al (Kessler 2003) reported on a group of patients who had suffered from depression over the last twelve months. Of these, 48.4% received no treatment while 51.6% received treatment. Of those who received treatment, 58.1% received inadequate treatment according to guidelines while 41.9% received adequate treatment according to guidelines, so that only 21.6% of the whole group received appropriate treatment. The situation has been reported as quite similar in the UK, where Tylee and Donaghue (Donoghue 1996) reported that as many as 88% of prescriptions for older tricyclic antidepressants are prescribed by GPs at doses below those recommended by the consensus guidelines. Newer antidepressants such as the SSRIs were reported as being prescribed at an appropriate dosage, although in both cases treatment was prescribed for a shorter time than that recommended by guidelines. Maintained drug treatment or CBT are more effective than episodic treatment at reducing the number of DALYs due to MDD (Vos 2004).

Increasing treatment of depression reduces the disease burden

The rate of diagnosis of cases of MDD is increasing as patients and clinicians become better at recognizing depression. Treatment of diagnosed depression is associated with a decrease in disease burden (Lecrubier 2001). The decrease in disease burden as depression is recognized and treated is a strong argument for addressing the problems of under-diagnosis and inadequate treatment. The economic burden of depression in the US rose by 7% from 1990 to 2000, despite an over 50% increase in the proportion of depression sufferers who received treatment. (Greenberg 2003) Untreated depression poses a greater economic threat than treating depression. The cost of depression in Sweden increased from €1.7 billion in 1997 to €3.5 billion in 2005. The cost to society nearly doubled in this time period because of a significant increase in indirect costs due to sick leave and early retirement. Direct costs remained relatively stable (Sobocki 2007).

Treating Major Depressive disorder reduces health care costs in the elderly. Depressive symptoms are common in older adults and 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 did not account for the increase in expenses (Unützer 1997).

Understanding the epidemiology of MDD is a step towards improving the currently unsatisfactory rates of diagnosis and treatment. Studying MDD in populations

may provide insight into the pathogenesis of depression, reveal the existence of sub-disorders and inform treatment strategies to target those most at risk. Improving the understanding of depression in society will help to reduce the stigma surrounding mental health that contributes to the problems faced in successful treating MDD.

SEX AND HORMONAL CHANGES AFFECT THE RISK OF DEPRESSION

MDD is approximately twice as common in females (Kessler 1996, 1994) Women are 1.7 times more likely than men to report a lifetime history of MDE. (Burt 2002, Gater 1998) This study by Burt et al suggests that the lifetime rate of major depression is up to 2.7 times greater in females than males (Burt 2002). This difference begins in early adolescence and persists through the mid-50s (Burt 2002). Several hormonal shifts are associated with changes in the risk of depression. The onset of puberty marks the beginning of increased risk for depression in women (Burt 2002). Pregnancy does not increase the risk for depression (Burt 2002). Women with a history of depression are at risk of recurrent episodes if antidepressant medication is discontinued during pregnancy (Burt 2002). Postpartum hormonal changes increase the incidence of depression (Burt 2002). The post-partum period is listed as a risk factor for MDD in the American Psychiatric Association DSM-IV. Women transitioning through peri-menopause, particularly those with psychiatric histories, report depressive symptoms (Burt 2002).

Women have a higher rate of 12-month depression than men (Kessler 1993). This is mostly 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 (Kessler 1993).

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 (Gater 1998).

AGE AFFECTS PREVALENCE OF DEPRESSION

Risk of depression changes with age, notably at adolescence and ages that align with reproductive hormone changes as mentioned above (Burt 2002). 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 (Kanowski 1994). This suggests that the age related changes in the incidence of depression occur because of particular hormonal and social changes that occur in our lives, rather than gradual biological changes that occur over the course of our lifetime. Increasing age is correlated with increased risk of a number of diseases, including cardiovascular diseases. Furthermore, depression adversely affects the prognosis of patients with co-morbidities (Discussed below).

ETHNICITY AFFECTS THE PREVALENCE OF DEPRESSION

There is an unequal risk of depression across ethnic groups in the UK. British South Asian women have higher rates of depression than their white counterparts (Waheed 2015). 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 excess South Asian odds were mostly accounted for by comorbidities. The increased prevalence in Black Caribbean participants was mostly explained by socio-economic disadvantage (Williams 2015). Determining an explanation for these ethic differences should 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 if these differences 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 compared with White British people (Taylor 2013). However, Commander et al found that there was no difference between South Asian and White people in their understanding of their illness or what they perceived to be the cause of their symptoms. Differences in diagnosis and treatment of depression between South Asian and White populations may be due to disparities in the availability of treatment, rather than cultural differences in identification and perception of disease. (Commander 2013) Thus the pathways to care of different groups who suffer depression may be affected differently.

There are complex racial and ethnic variations in somatic symptoms associated with depression due to social and cultural factors that influence how individuals seek medical attention (Bagayogo 2013).

Physical symptoms 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 a diagnosis of a mood or

anxiety disorder by two-fold to three-fold. A greater number of physical symptoms is associated with a higher likelihood of depressive disorders and greater loss of functionality (Kroenke 1994). Unexpectedly, a study found that depression diagnoses were more common in Punjabis with low scores for somatic symptoms compared with their English counterparts (Bhui 2004). Ethnic and gender variation in somatic symptom reporting may be accounted for by the influence of cultural expectations and stigma of symptom reporting (Bagayogo 2013). A study on somatization in 3132 participants in Los Angeles found no effect of ethnicity on somatization indexes of male participants. The authors proposed that denial and minimization of symptoms were likely explanations, particularly in older Mexican-American men and may be related to "machismo" and stoicism, which were identified as common traits in this group. (Escobar 1987) Brown C et al found 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. African Americans reported poorer general health and greater impairment on the MOS physical functioning scales (Brown 1996).

It is significant to note that one of the criteria for diagnosing depression is that symptoms cause a problem for the patient. This may be identified at different stages 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, as well as community support and coping resources.

Co-morbidity and ethnicity

There are controversial findings 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 (Ali 2009).

Suggested explanations for the results were 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 DM or impaired glucose regulation (Aujla 2010).

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 include female gender, diabetes related complications, and comorbidities. Risk factors for depression in type 2 diabetics were reported to include younger age, diabetes related complications, comorbidities, insulin use and deprivation (Ali 2009).

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 prior to the economic recession. The rate of depression in men increased following the recession, in line with increasing unemployment. (Kendrick 2015). Adverse life events are precipitating factors for depression. Adverse life events may occur at a population or an individual level and such events should be considered in the diagnosis of MDD.

Differences in the rate of depression may be due to 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, since people may choose not to seek medical intervention. A low uptake of available treatment may be due to the social stigma surrounding mental illness. There may be a low rate of diagnosis in males as males are less likely to visit their GP than females. Therefore 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 have demonstrated the effectiveness of depression treatment in several countries with varying resource availability and showed that where treatment is delivered it was effective (Markus 2012). However, where there are inadequate resources and social stigma, the majority of people in need of treatment for depression do not receive it. Globally fewer than 50% are treated. In some countries, fewer than 30% in most regions and less than 10% of cases are treated. (Markus 2012)

TREATMENT AIMS

As depression presents with a range of symptoms and spectrum of intensities, it is important to consider the goal of treatment. Remission is the goal of treatment of MDD. This consists of: minimal to no residual symptoms, restored function and low scores on scales used to track depression severity in research settings e.g. 17-item Hamilton Depression Rating Scale (HAM-D) score ≤ 7, Montgomery-Åsberg Depression Rating Scale (MADRS) score < 10. (Judd 1998) 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 an individual's disease. Judd et al. noted that the symptoms of "MDD, combined minor depressive or dysthymic disorder, and subsyndromal or subthreshold depressive symptoms commonly alternate over time in the same patients as a symptomatic continuum of illness activity of a single clinical disease."(Judd 2016) Judd later identified the end of a

MDE as "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." (Judd 2016).

Remission with no residual symptoms reduces the risk of relapse for major depressive disorder

It is important to identify remission and transition from 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. (Judd 2000) Patients with residual symptoms relapsed 3 times as fast compared to those who were asymptomatic at remission. (Judd 2015) Almost 3 times as many patients without residual symptoms at remission remained well compared to those with residual symptoms. (Paykel 1995) 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 major depressive episode. In such cases there is a need for continued management (Judd 2016). 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 (Paykel 1995).

Adequate treatment promises a better prognosis and is cost effective

There are shortcomings in nearly every aspect of treating depression – diagnosis, delivery of treatment to those who need it and delivery of adequate treatment. The National Comorbidity Survey Replication showed that only 51.6% of 12-month cases of MDD received treatment for MDD. Treatment was adequate in only 41.9% of these cases, resulting in 21.7% of 12-month MDD being adequately treated. (Kessler 2003) Socio-demographic correlates of treatment were less numerous than those of prevalence. (Kessler 2003) 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 (Mouchabac 2003).

The goal of treating MDD should be complete remission with no residual symptoms because of the high morbidity and mortality associated with residual symptoms. One proposed strategy for achieving this may be a multi-receptor targeting treatment strategy. Therefore it has been suggested that long-term anti-depressant therapy targeting serotonergic and noradrenergic systems provides greater efficacy and remission rates than single target drug treatments. (Bakish 2001) This being the case, 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 effectively managed with a serotonergic and noradrenergic targeting drug such as Duloxetine (Fava 2004).

COST-EFFECTIVE TREATMENT OF MD

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 (Paykel 1998).

It has been suggested that it is cost effective to add an SSRI to supportive care in cases of 'mild to moderate' depression. In a study of patients treated with SSRI and supportive care group vs treating with supportive care alone, although the additional benefit seen in patients in the former group may be due to a placebo effect (Kendrick 2009).

Screening for and treating depression in the workplace is cost-effective for employers. (Evans-Lacko 2016) From the perspective of employers, psychotherapy is the most cost-effective treatment option for MD (Evans-Lacko 2016).

For health-care systems, combined antidepressant and cognitive therapy proved to be more expensive than anti-depressant therapy alone, but the costs were offset by the considerable reduction of productivity loss from the social perspective (Sado 2009). 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 6 months is appropriate treatment for a moderate to severe depressive episode. This is known as the 'Paykel and Priest rule' (Paykel 1992). 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 6 weeks treatment with either antidepressant, are referred to secondary care. This model of treatment is referred to by the National Institute for Care and Clinical Excellence as the 'Stepped care Model' (NICE 2009).

Several studies have investigated the utility of anti-depressant therapy for treating depressive symptoms in dementia and related syndromes. In patients with Alzheimer's disease, anti-depressants are not more effective than placebo at relieving depressive symptoms (Banerjee 2013). The use of anti-depressants in these patients was associated with an increased risk of adverse events (Banerjee 2011). Mirtazapine and sertraline were not cost-effective for treating depression in dementia. 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 (Romeo 2013).

Benefits of treating depression

Treating elderly patients for diagnosed MDD reduced the cost of medical services. Depressive symptoms were common, persistent, and associated with a significant increase in the cost of general medical services in an elderly cohort (Unützer 1997). Expenses increased across every component of health care costs and were not accounted for by an increase in specialty mental health care (Unützer 1997).

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. Major Depressive Disorder 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 (Faris 2002). Despite being younger and having fewer chronic conditions, a higher 3-year mortality risk was seen in patients with post-stroke depression and other mental health diagnoses after hospitalization for an ischemic stroke (Williams 2004). In stroke patients, comorbid depression increased patients' risk of death by 13%. However, the mechanism is unknown (Williams 2004). Co-morbid depression increases morbidity and mortality in patients with ischaemic heart failure and heart failure secondary to non-ischaemic DCM (Faris 2002).

Depression increases the risk of cardiac mortality and morbidity in patients with coronary heart disease (CHD), Carney et al 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, and reduced functional capacity association of depression with greater coronary disease severity, nonadherence 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 (Carney 2002).

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 2 times higher than that of non-depressed patients 2 years after the initial assessment. This negative prognostic effect persists in the long-term and after adjustment for other risk factors. Within the first 6 months, depressive disorders were found to have no significant effect on mortality (Barth 2004). However, a 2006 meta-analysis of 6362 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 (Nicholson 2006).

CONCLUSION

In 2012 the World Health Organization Global Burden of Disease Survey ranked depression as the 4th leading cause of disability worldwide (Murray 1996).

Therefore depression remains an important problem for primary care today.

In 2001, Greden et al. identified "widespread prevalence; relatively early symptom onset; severe underdiagnosis 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" as factors that contribute to the morbidity of depression (Greden 2001).

This paper has highlighted and examined the epidemiology of all of these factors in order to improve understanding of them and inform decisions that will minimise their impact.

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Correspondence:

Mark Agius, MD
Clare College Cambridge, University of Cambridge
Cambridge, UK
E-mail: ma393@cam.ac.uk