

Depression, cardiac mortality and all-cause mortality

Jeremy Seymour & Tony B. Benning

SUMMARY

Depression is an illness that kills. The links between depression and medical illness are well established and bi-directional, but evidence is mounting that depression increases mortality as well as morbidity in adults, particularly older adults. We examine the evidence that the increase in mortality in depression applies to all-cause mortality as well as cardiac mortality, and describe plausible physiological theories for the association. We conclude that excess mortality arising from depression is a major public health problem that is largely unrecognised and needs to be addressed by a range of clinicians.

DECLARATION OF INTEREST

None.

mortality caused by undertreated depression is given insufficient recognition as a public health problem. The article focuses on organic rather than psychosocial aspects.

Dying of a broken heart: historical background

It was first reported in the early 1960s that widowers became depressed following spousal bereavement and had a high risk of dying, often of heart disease, in the year after bereavement (Young 1963). This stimulated research into the possibility that depression may itself increase mortality. Colin Murray Parkes performed a detailed analysis of bereavement in a series of studies in London and Boston and coined the phrase ‘dying of a broken heart’ (Parkes 1969). He suggested that the heart was damaged physiologically by the stress of grief-related depression. He concluded that widowers in their first year of widowhood were at a greater risk of death – usually from heart disease – than their married counterparts.

Medical illness in depression

People with depression often have poor medical health (Wells 1989), and a range of factors is likely to contribute to this. Depression is not conducive to a healthy lifestyle: individuals may neglect their health owing to negative cognitions and poor body image; they may not adhere to medication; and they are more likely to smoke or drink to excess to control or mask their symptoms. The link between depression and poor medical health is likely to be mediated in part via the endocrine system. The association between depression and dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis and hypercortisolaemia has long been recognised. A further area that has attracted increasing interest is the relationship between depression and diabetes. Studies in patients with established diabetes suggest that depression leads to poor glycaemic control and an increased risk of complications such as retinopathy and neuropathy (De Groot 2001). An emerging hypothesis is that depression might itself be a risk factor for the development of type 2 diabetes. The abnormalities in HPA-axis regulation referred to above lead to increased cortisol secretion, which may in turn lead

Jeremy Seymour is a Consultant in Old Age Psychiatry and is an Honorary Senior Lecturer at the University of Sheffield. His interests are in liaison old age psychiatry and in developing mental health services for older people, and he is a member of the Executive Committee of the Royal College of Psychiatrists’ Faculty of the Psychiatry of Old Age.

Tony B. Benning is a Specialist Registrar in Psychiatry on the Sheffield and North Trent Higher Training Scheme and is currently based in Barnsley. He has completed higher specialist training in general adult psychiatry and liaison psychiatry. His special interests include clinical neuropsychiatry, liaison psychiatry and neurodevelopmental disorders such as Asperger syndrome.

Correspondence Dr Jeremy Seymour, Michael Carlisle Centre, Nether Edge Hospital, Osborne Road, Sheffield S11 9BF, UK. Email: jerry.seymour@sct.nhs.uk

Depression is the most common major mental illness, with a 6–11% lifetime prevalence of major depression, a figure that is at least double for less severe forms of depression (Simon 1995). There is abundant evidence that depression is underdiagnosed and undertreated across the age range. The reasons for this are complex (Glasser 1997) and are likely to be related to doctor, patient and societal factors. There is a debate as to whether some general practitioners (GPs) and psychiatrists regard treating depression in its milder forms as ‘medicalising misery’ (Parker 2007). When depression and physical illness coexist, it is likely that physical symptoms contribute to underdiagnosis of depression. Symptoms of illnesses such as coronary heart disease, asthma, cancer, Parkinson’s disease and multiple sclerosis mimic depressive symptoms, such that doctors may wrongly assume them to be attributable to the medical condition rather than to depression. For example, weight loss, anorexia, anergia and poor sleep occur in both depression and many medical conditions. Manifestations of neurological illness may pose particular diagnostic challenges: consider, for example, the difficulties in distinguishing flattening of affect from Parkinsonian mask-like facies, or psychomotor retardation from the bradykinesia of Parkinsonism.

In this article, we examine the consequences of undertreating depression, in terms of morbidity and mortality, and argue that the excess

to hyperglycaemic states and insulin resistance (Musselman 2003).

Depression may also harm health through secondary effects on appetite, sleep and diurnal rhythms, or lipid metabolism (Peet 2002).

The effect of age

Medical illness may accompany depression in people of all ages and all cultures, but is particularly prevalent and significant in older people. First, disability and functional disability are much more common in older people, as are common illnesses such as cancer, heart disease, diabetes and stroke (Surtees 2003). Second, older people have less 'functional reserve' with which to cope and adjust to medical illness, physiologically and psychologically, particularly if loss and disability are cumulative. For example, poorly controlled hypertension associated with depression may precipitate a myocardial infarction in an 80-year-old man, but not a 30-year-old; or subclinical hypothyroidism may precipitate a depressive episode in a 70-year-old woman, but not a 40-year-old. The lack of functional reserve in older people may be particularly important in cardiovascular disease (Strandell 1976).

Depression in medical illness

It is a robust finding in the literature that depression is more common in people with concurrent medical illness than in comparison groups who do not (Prince 1997; Braam 2005). There may even be a direct relationship, with rates of depressive symptoms increasing incrementally with increasing severity of medical comorbidity (Covinsky 1999). The strong association between depression and medical illness has been found in all populations studied: primary care/community samples (Braam 2005), people in residential care (Eisses 2004), hospital in-patients (Moffic 1975) and in different cultures (Ormel 1994).

The complex aetiological relationships between depression and medical illness has been extensively reviewed (Rodin 1986; Charlson 2002). Here we will focus on three areas – medical depression, iatrogenic depression and depression related to psychosocial factors – and then consider the special case of depression and cardiac illness.

Medical depression

In people with medical conditions such as hypothyroidism or Cushing's disease, depression may primarily be an 'organic affective illness' resulting from hormonal/endocrinological disorders related to their condition. Other examples of organic affective disorders include post-stroke

depression and vascular depression (Alexopoulos 1997).

The particularly high rates of depression seen in other neurological conditions, such as Parkinson's disease, Huntington's disease and multiple sclerosis, support the suggestion that physiological or local structural factors may be important. Studies in community populations of patients (Chwastiak 2002) confirm the findings of studies undertaken in more specialist settings (Ron 1989). Neuroimaging studies support the claim that the high rates of depression in multiple sclerosis are, at least in part, explained by neurostructural factors. For example, a magnetic resonance imaging study involving people with multiple sclerosis compared 21 participants fulfilling the criteria for major depression with 19 participants without depression. The participants with depression had more hyperintense lesions in the left inferior medial frontal region and greater atrophy of left anterior temporal regions. These structural abnormalities accounted for 42% of the depression variance (Feinstein 2004). It is interesting to note that these lesions are in neuroanatomical regions similar to those implicated in depression associated with other neurological conditions – the literature on depression following stroke also implicates left frontal regions (Robinson 1984).

Iatrogenic depression

Drugs used to treat medical illness that cross the blood–brain barrier may themselves cause depression by direct actions on brain neurochemicals in predisposed individuals. The list of drugs recognised as causing depression is extensive and includes β -blockers, corticosteroids, immunosuppressants (such as β -interferon and acyclovir), calcium channel blockers, levodopa, thiazide diuretics and anticonvulsants such as phenytoin.

Depression and psychosocial factors

Depression may follow medical illness as a consequence of social losses, for example loss of independence/autonomy, earning power or sex life. Medical illness can also adversely affect self-esteem, body image and sense of identity. The extent of these psychological effects may be modified by the individual's personality and previous (childhood) experience of illness. Pathological mourning and loss were of course central to Freud's theory of the genesis of depression.

Depression in cardiac illness

Cardiac illness seems to be a special case with respect to its interactions with depression – or perhaps it has just been the subject of more

research. The heart does not operate in isolation and, obviously, cardiac dysfunction links in with the hypothesis of vascular depression (Alexopoulos 1997).

There is overwhelming evidence, confirmed by two systematic reviews (Rugulies 2002; Van der Kooy 2007), that depression is strongly associated with ischaemic heart disease, heart failure and myocardial infarction. This seems to apply to depressive symptoms as well as to major depression (Wulsin 2003).

Carney et al (2005) report that dysregulation of the autonomic nervous system may put people with depression at an increased risk of heart disease. For example, elevated plasma levels of catecholamines have been found in medically well but currently depressed individuals. The authors refer to studies of patients with depression and coronary heart disease in whom there is concurrent evidence of autonomic dysfunction, including elevated heart rate, low heart-rate variability, exaggerated heart-rate responses to physical stressors, high variability in ventricular repolarisation and low baroreceptor sensitivity.

The central role of the vagus (Latin for 'wanderer') nerve in mediating complex neuro-visceral relationships between mood and cardiac disease is increasingly appreciated. Heart rate and heart-rate variability is modulated by vagal tone and there is increasing evidence that vagal tone is itself influenced by a range of variables, including exercise, mood and activity in the prefrontal cortices (Thayer 2000).

Might depression and ischaemic heart disease be sharing a common pathogenesis? Physiological links between depression and heart disease are summarised in Box 1.

Depression and mortality

There is a weight of literature to support the possibility that depression kills patients (Wulsin 2002) and this literature is reviewed below. We will subdivide this section to consider depression and all-cause mortality and depression and cardiac mortality, and then examine issues of severity of depression and the effects of age.

Depression and all-cause mortality

Wulsin et al (1999) conducted a systematic review of the mortality of depression, examining 57 studies from 1966 to 1996. Of these studies, 51% reported a positive association between depression and all-cause mortality, 23% reported no association and 26% reported mixed or equivocal findings.

Research in this area has the benefit of a clear outcome measure – death – but has many potentially

confounding variables. Studies differ in terms of sampling methods, sample size, length of follow-up and medical fitness at the point of entry. There are varying methods for diagnosing depression and depression may or may not have remitted, persisted or recurred during the study period.

Schulz et al (2002) attempted to address these issues by using Wulsin et al's methodology to examine 61 later studies (published between 1997 and 2002). They analysed each study in detail for its methodological rigour and identified 24 high-quality studies, 75% of which showed an unequivocal association between depression and mortality. We will examine three of these papers in more detail to illustrate that depression increases mortality in different populations.

First, Osby et al (2001) used a case-control design to analyse data on 15 386 patients admitted to Swedish psychiatric hospitals with a first diagnosis of bipolar disorder and 39 182 patients with unipolar disorder. The age range for both groups was 15–70 years. The standardised mortality ratio was almost double (compared with non-depressed matched controls in the community) for both the bipolar and the unipolar groups.

Second, Pulska et al (1999) examined an older community population (813 participants: mean age 74.3 years, s.d. = 6.1) also using a case-control design. At the 5-year follow-up, long-standing depression (as defined by DSM-III) conferred a relative risk of mortality of 1.5, with a lower risk if the patient had recovered from depression. This was the relative risk after correcting for age, gender, smoking, physical health and functional status.

Third, Von Ammon Cavanaugh et al (2001) adopted a cohort study approach with 241 medical in-patients (mean age 49.9 years, s.d. = 17.1) for a much shorter follow-up period. Of their sample, 8.3% died but, the study having controlled for severity of medical illness, 30% of patients with current major depression died v. 6% of non-depressed controls.

BOX 1 How does depression increase cardiac mortality?

There are three main hypotheses, which are not mutually exclusive.

- The stress-diathesis model – overstimulation of the HPA axis in depression leads to sustained release of adrenaline (overriding normal feedback mechanisms), sustained increases in blood pressure and hence damage to intima of coronary vessels.
- Reduced heart-rate variability – reduced heart-rate variability represents an imbalance between sympathetic and parasympathetic nervous systems and occurs in depression. If the heart rate and cardiac output are unable to respond to a sudden increase in demand (through stress or exercise), arrhythmias and sudden death may follow.
- Serotonin and platelet aggregation – abnormalities in serotonin metabolism in depression enhance platelet aggregation in coronary arteries, leading to myocardial infarction and death.

Depression and cardiac mortality

The evidence linking depression with cardiac mortality is even stronger than that linking it with all-cause mortality. Depression increases cardiac mortality in community samples, medical out-patients undergoing exercise testing, out-patients with cardiac failure, post-myocardial infarction patients and patients undergoing coronary-artery bypass grafting (references available from the authors). Two methodologically rigorous studies are particularly worthy of mention. In one, Penninx et al (2001) recruited 2847 community participants with a mean age of 70 years in a cohort study. Diagnosis of depression was rigorous, using a self-reported rating scale plus a diagnostic interview schedule. During the 4-year follow-up, 18% of the sample died, with both major and minor depression increasing cardiac mortality, irrespective of cardiac disease at baseline. Controlling for age, gender, smoking and medical comorbidity, the relative risk of cardiac mortality was 3.0–3.9 for major depression and 1.5–1.6 for minor depression.

In the other, Frasure-Smith et al (1999) studied 896 post-myocardial infarction patients with a mean age of 59 years. Only 4% had cardiac mortality at 1-year follow-up but applying a multivariate analysis gave an odds ratio of 3.7 for cardiac mortality in the depression group.

Although there is heterogeneity in the severity of depression in these studies, taken overall they suggest that depression increases the standardised mortality ratio for patients who die from cardiac disease by a factor of at least 1.5–2.0.

Is it only major depression that increases mortality?

Although the link between major depression and increased mortality is established (Wulsin 1999; Schulz 2002), are less severe forms of depression also linked to increased mortality? ‘Mild depression’ and ‘depressive symptoms’ are terms associated with nosological confusion, and in some studies it is clear that depression has been ‘diagnosed’ merely on the basis of cut-off points on simple self-reported rating scales such as the Geriatric Depression Scale. In large-scale epidemiological studies, where a wealth of cardiological outcome data is collected and researchers may have little experience of diagnosing depression, one wonders about the sophistication of depression diagnosis. Nonetheless, in Schulz et al’s exhaustive review (2002), there are several good-quality studies linking less severe forms of depression with increased mortality, and a study by Ahto et al (2007) increases this evidence.

Overall, it can be concluded from cohort and case-control studies that the link between

depression and mortality is strong for major depression, but is also present in minor depression/depressive symptoms. Not surprisingly, there are some methodologically rigorous studies that do not report such an association – interested readers are referred to the paper by Schulz et al (2002).

Is increased mortality in depression a problem only for older people?

Most research has been conducted in older populations, although a substantial body of high-quality research has established a link in younger people too. Schneider et al (2001) followed up 354 psychiatric in-patients aged 18–80 for 5 years, and found that all forms of affective disorder increased mortality compared with a control group after controlling for age, gender, demographics and psychiatric comorbidity. Osby et al (2001) studied 54 568 individuals with depression or bipolar disorder aged 15–70 from the Swedish in-patient register and found that the standardised mortality ratio was increased across the age range.

It can be concluded that depression and mortality should be an issue of concern for all psychiatrists, not just old age psychiatrists.

Why should depression increase all-cause mortality? First, depression may pre-date and be a marker for medical illness. For example, an individual may present with depression, but have occult pancreatic cancer underlying it. Second, self-neglect, poor adherence to medication, alcohol misuse and so on may predispose the patient to pulmonary embolus or fatal infections such as pneumonia. Schulz et al (2000) coined the term ‘motivational depletion’ to denote the ‘giving up and fading away’ that can occur at the end of life in people with medical illness who become depressed. Third, depression adversely affects immunity, T-lymphocyte function and immune surveillance, which may affect cancer survival and survival from infection (Leonard 1990).

Depression and mortality: an unrecognised public health problem?

A possible explanation of the underrecognition of mortality arising from depression is that depression rarely, if ever, appears on death certificates of people who die from natural causes, and such cases rarely attract the interest of the coroner. Suicide due to depression is, however, recorded, although in the sections described above, suicide mortality has been excluded.

Depression and suicide

Suicide is a tragedy for all concerned, particularly when it occurs in association with a treatable mental

illness such as depression. Completed suicide is a relatively rare event in the UK, accounting for approximately 5000 of the 600 000 annual deaths (0.8%), and its incidence is falling (Harris 1997; Kapur 2006). In numerical terms, if depression is increasing the standardised mortality ratios in cardiac and all-cause mortality, deaths from natural causes associated with depression must be a numerically greater public health problem than depression-related suicide.

Suicide reduction has been a government target in the UK since 1990 and has met with some success. However, the government has invested little in mental health policy areas relevant to reducing mortality arising from depression, switching its attention to obesity as a major public health issue.

Is the treatment of depression contributing to increased mortality in patients with depression?

This question could be rephrased: Are antidepressants and other psychotropic drugs cardiotoxic and therefore contributing to the observed increase in mortality in depression? Twenty years ago, when tricyclic antidepressants and electroconvulsive therapy were the mainstays of treatment, this was a very pertinent question. Tricyclic antidepressants are known to increase the QT interval and trigger arrhythmias in predisposed individuals with ischaemic heart disease, and antipsychotics used to treat depression are also potentially cardiotoxic (O'Brien 2003). The cardiac risks of venlafaxine, which emerged after 10 years of post-marketing surveillance, should warn against complacency. However, there is a massive body of evidence that selective serotonin reuptake inhibitors (SSRIs) and other modern antidepressants, such as mirtazapine and duloxetine, are safe (Anderson 2001). The SADHART trials suggest that sertraline is non-cardiotoxic even in patients recovering from myocardial infarction (Glassman 2002). A Cochrane review found that antidepressants improved the outcome in medically ill patients with depression (Gill 2000).

A final strand of evidence for the safety of antidepressants comes from the Leiden 85-plus Study. Vinkers et al (2004) identified all 705 people over 85 years old living in the Dutch city of Leiden and recruited 500 of them to a follow-up study. Depressive symptoms (defined by a score >4 on the Geriatric Depression Scale) were present in 118 participants, but none was receiving antidepressants. At follow-up, all-cause mortality among these 118 at baseline was double that among those who had not been depressed (and cardiac mortality was more than double, consistent with previous literature). The significance of this study is that treatment of depression/toxicity of antidepressants

could not be a factor in the increased mortality, as no participants were receiving treatment for depression or being prescribed antidepressants.

Does treating depression reduce mortality?

There is little doubt that treating depression in people with concurrent medical illness reduces morbidity (Gill 2000; MacHale 2002) but does it reduce mortality? The intuitive answer is 'Yes, of course', particularly as SSRIs may restore reduced heart-rate variability and attenuate platelet activation (Serebruany 2003) in depression, i.e. SSRIs may have a cardioprotective effect. A case-control study of 5336 patients treated with fluoxetine, sertraline or paroxetine conferred a significantly reduced odds ratio of 0.59 for myocardial infarction (Sauer 2003). However, the literature on all-cause mortality is not clear-cut, as few long-term prospective studies have been done owing to the potential complexity of ethical study designs and confounding variables. Two large-scale studies, MIND-IT (Van Melle 2007) and ENRICH (Berkman 2003) looked specifically at treating depression in post-myocardial infarction patients and failed to show that mortality improved. The interpretation of these negative findings has been that the studies were insufficiently powered or were too late in the day to alter prognosis after heart damage (Korszun 2007). At present, however, there is insufficient evidence to be certain that treating depression improves mortality, particularly in people who have had a myocardial infarction.

Treatment of depression in medical illness – clinical practice

If one accepts that untreated or inadequately treated depression increases morbidity and mortality at all ages, what implications does this have for clinical practice? A statement such as 'untreated depression may kill you' is not useful in negotiating treatment alternatives with vulnerable, depressed, medically ill patients but patients do need to be aware of the risks of non-treatment.

Improving the assessment and treatment of depression in primary care is a high priority,[†] as this is where most underdiagnosis occurs. Our observation is that there is little evidence that GPs are adopting the stepped model of care advocated in National Institute for Health and Clinical Excellence (NICE) guidance on depression (National Collaborating Centre for Mental Health 2004) and further research is needed to determine why GPs are reluctant to implement practice guidelines (Kendrick 2000). A promising avenue of development is the concept of managing depression as a chronic disease (Rost 2002).

[†]For a related discussion see Lester H (2005) Shared care for people with mental illness: a GP's perspective. *Advances in Psychiatric Treatment*, 11: 133–9; Burns T (2005) Shared care, individual expertise. Invited commentary on... Shared care for people with mental illness. *Advances in Psychiatric Treatment*, 11: 139–41. Ed.

For in-patient psychiatrists, treatment resistance is a common issue. The priority is for prompt treatment of index episodes addressing (where possible) precipitating and perpetuating factors in depression, and ensuring effective follow-up and prophylaxis to prevent relapse. Psychiatrists need to know how to use a stethoscope; to have a working knowledge of common medical comorbidities; and to know when to refer to medical colleagues.†

For old age psychiatrists, it is fairly clear what works in terms of relapse prevention, namely lengthy continuation of antidepressants backed up by an appropriate psychotherapeutic approach (Baldwin 2002; Reynolds 2006). Complex medical comorbidities should not constrain doctors from treating depression (Gill 2000; Schultz 2007).

The unshakeable evidence linking depression with poor general health and functional disability challenges the dualistic conceptualisation of 'psychiatric illness' as a distinctly separate category from 'medical illness'. In evaluating depression and its response to treatment, all psychiatrists may become increasingly inclined to take into consideration physical and biochemical variables such as platelet aggregation factors, measures of autonomic function and heart-rate variability.

Conclusions

Depression and medical illness coexist and frequently complicate each other; depression is a strong risk factor for disability and vice versa (Box 2). There is now clear evidence in the literature that depression increases mortality (cardiac and all-cause) as well as morbidity. Although this does not necessarily apply to fit young people with milder forms of depression, it is not just older people who have increased mortality. As the lifetime prevalence of depression is so high, this is a major public health problem that is not currently recognised by government policies or targets, which perhaps need to move on from suicide prevention.

General practitioners have a key role in addressing this underrecognised problem. Physicians need to recognise depression as a risk factor on a par with hypertension, smoking or diabetes in terms

of medical morbidity and mortality, and to start treating depression according to NICE guidelines. Psychiatrists need to revisit skills in recognising and treating medical illnesses comorbid with depression.

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†This area is discussed in MacHale S (2002) Managing depression in physical illness. *Advances in Psychiatric Treatment*; **8**: 297–305; Garden G (2005) Physical examination in psychiatric practice. *Advances in Psychiatric Treatment*; **11**: 142–9. Ed.

BOX 2 Interaction of depression and medical illness

- It is overly simplistic to separate 'depression in medical illness' from 'medical illness in depression'
- Interrelationships between depression and medical illness are bi-directional and complex
- Interrelationships are mediated through the HPA axis, lipid metabolism, the immune system, the (para)sympathetic nervous systems and cardiac function

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MCQ answers				
1	2	3	4	5
a	t	a	f	a
b	f	f	a	t
b	f	b	t	b
f	t	b	t	f
c	f	c	f	c
f	c	f	c	f
d	f	d	f	d
f	d	f	d	f
e	f	e	f	e
f	e	f	e	f

<p>MCQs</p> <p>1 The following symptoms may be falsely attributed to medical illness, when in fact they are attributable to depression:</p> <ul style="list-style-type: none"> a anergia b diurnal variation in mood c loss of interest d anhedonia e hopelessness. <p>2 Depression is not a risk factor for:</p> <ul style="list-style-type: none"> a smoking b type I diabetes c diabetic neuropathy d alcohol misuse e stroke. 	<p>3 Depression is more prevalent in:</p> <ul style="list-style-type: none"> a patients taking non-steroidal anti-inflammatories than patients taking steroids b multiple sclerosis than rheumatoid arthritis c myocardial infarction than stroke d leukaemia than AIDS e right frontal stroke than left frontal stroke. <p>4 The presence of major depression:</p> <ul style="list-style-type: none"> a has a stronger link statistically with all-cause mortality than with cardiac mortality b is more likely than depressive symptoms to cause cardiac mortality c suppresses B-lymphocyte function d increases heart-rate variability e decreases platelet aggregation. 	<p>5 In depression linked to cardiac mortality:</p> <ul style="list-style-type: none"> a depression increases risk of mortality in heart-failure patients b treatment of depression unequivocally improves mortality c the SADHART trials show all SSRIs are safe post-myocardial infarction d depressive symptoms have the same impact on mortality as major depression e most cardiac patients die by suicide.
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