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## Review

# Depression and the older medical patient—When and how to intervene

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## ABSTRACT

Depression in the elderly, particularly those with chronic physical health problems, is a common, but complex problem. In this paper we review the research literature on both the epidemiology and management of depression in the older medical patient. After a general overview of depression in the elderly, we discuss some of the particular issues relevant to depression and co-morbid physical illness amongst elderly patients. Depression can be difficult to diagnose in medically unwell older adults, particularly when there is substantial overlap in symptomatology. The epidemiology and evidence base for the treatment of depression in a number of chronic health problems common in an older adults population are then discussed, specifically cardiac disease, cerebrovascular disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, and Parkinson's disease. For many of these conditions there is emerging evidence that treatments can be effective in reducing depressive symptoms. However, these potential benefits need to be balanced against the often-increased risk of adverse events or interactions with medical treatments. Although co-morbid depression is consistently associated with poorer medical outcomes, there is limited evidence that standard anti-depressive therapy has additional benefits in terms of physical health outcomes. Collaborative care models appear particularly well suited to medically unwell older adult patients, and may provide more generalised benefits across both mental and physical health measures.

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**1. Introduction and methods**

There has been a growing recognition of the prevalence and impact of depression in older patients, particularly those with physical illness. This paper reviews the recent literature on depression in the medically ill older patient, focusing on both epidemiological and management studies. After a general overview of depression in the elderly (and specifically in the physically ill), we focus on a number of conditions for which comorbid depression is prevalent in this age group. Where possible, we have focused on studies specifically investigating older patients; however many relevant studies of these conditions have also included some middle aged subjects.

**2. Depression in the elderly**

*2.1. Epidemiology*

Large scale epidemiological surveys report that depression affects about 5% of those 65 and older [1]. There has, however, been recent concern regarding clinicians' ability to correctly identify which older adults are depressed, with validation studies using structured interviews only confirming major depressive episodes in about 18% of older adults whom clinicians felt may be depressed [2]. This is much poorer than similar studies of younger adults, presumably because of the difficulty differentiating depression from non-specific symptoms associated with ageing and many common medical problems.

Despite difficulties with identification, depression in the elderly is associated with greater morbidity and mortality. The increased mortality has been highlighted by Almeida et al. [3] who examined death rates in males aged 68–88 years. They found that the adjusted mortality hazard of men with clinically significant depression was significantly elevated (at 1.98) with rates rising as the severity of symptoms increased: from 1.39 for those with questionable symptoms to 3.32 for those with severe depression.

*2.2. Management*

Mitchell and Subramaniam [4] found in a systematic review of depression in old age compared to middle age, that while there did not appear to be any clinically significant difference in response or remission rates to antidepressants and ECT, older patients appeared to be at higher risk of relapses into further episodes.

The benefit of antidepressants in older patients was confirmed in a meta-analysis by Kok et al. [5]. Analysing 51 randomised controlled trials (RCTs) of antidepressants in the acute treatment of depression, they found that all classes of medications were more effective than placebo in achieving response, with no demonstrable differences in either response or remission rates between the various classes of antidepressants. Furthermore, there were no differences in effectiveness in the more severely depressed patients. The numbers needed to treat (NNT) for response and remission were 6.7 and 14.4, respectively.

The safety of antidepressants in this age group was examined in a UK cohort study of depressed patients over 65 years from 570 general practices [6]. Compared to no antidepressants, SSRI antidepressants were associated with greater rates of falls (hazard ratio [HR] 1.66) and hyponatraemia (HR 1.52). SNRIs and mirtazapine were also associated with increased risk of all-cause mortality (HR 1.66), attempted suicide (HR 5.16), stroke (HR 1.37), fracture (HR 1.64) and epilepsy (HR 2.24). Almeida et al. [3] also found that adjusted mortality rates increased with use of antidepressants irrespective of current depressive symptoms. It is not possible to determine from these reports whether the increased deaths on those with antidepressants reflected the more severe depression in those prescribed antidepressants, or was an effect of the antidepressants *per se*. The higher death rates reported by Coupland et al. [6] with the SSRIs and SNRIs may be explained by these 'less toxic' antidepressants being used more commonly in patients with concurrent serious physical illnesses (such as cardiac disease).

In addition to antidepressants and ECT, psychological treatments have also been shown to be effective in older depressed

subjects, either as a stand-alone treatment or as a component of a stepped-care programme [7].

### 3. Depression in the elderly with comorbid physical health problems

#### 3.1. Epidemiology

Developing physical illness in old age has long been recognised as a major risk for depression [8,9]. For example, Pfaff et al. [10] demonstrated that depression was 3–4 times more likely to occur amongst older adults with the highest number of medical comorbidities and the greatest level of functional impairments.

#### 3.2. Management

##### 3.2.1. General issues

First, a number of approaches for the management of depression in the older medical patient have been explored. While the majority of studies have focused on antidepressants in this population (mainly selective serotonin reuptake inhibitors [SSRIs]), an increasing number of reports have appeared in recent years that have considered collaborative care or stepped care programmes.

Second, while most studies have examined the effect of these treatments on depressive symptoms, there has been an increasing focus on outcomes related to the physical illness itself, such as mortality and morbidity rates or measures of relevant risk factors (such as lipid levels in those with cardiac disease).

Third, the safety of antidepressant medications in the older medically ill patient has been an area of considerable focus. In some conditions, particularly cardiac illnesses, the impact of antidepressants (such as the tricyclic antidepressants [TCAs]) on mortality rates has been an area of concern. Another major issue has been the potential for significant drug interactions, such as the effects of SSRIs on cytochrome P450 enzyme (CYP450) activity and bleeding risk.

##### 3.2.2. Antidepressants

Taylor et al. conducted a systematic review and meta-analysis of studies examining the efficacy, tolerability and safety of antidepressants in depression in those with chronic physical conditions such as stroke, chronic obstructive pulmonary disease (COPD), cancer, Parkinson's disease, diabetes and cardiovascular disease [11]. They found that antidepressants demonstrated a significant advantage over placebo in respect to remission and/or response, with no differences in efficacy identified between SSRIs and TCAs. However, other reviews have reported that such medical comorbidity was a risk factor for inferior response to antidepressants and poor tolerability [4].

Caughey et al. examined a large Australian older veterans' affairs administrative claims database, concluding that 87% of those prescribed antidepressants had at least one comorbid physical condition that would raise concerns about potential drug interactions [12]. The conditions of most concern were cardiovascular diseases, arthritis, pain management and osteoporosis.

There have been a number of studies of the management of depression in nursing home patients – an older population with high rates of physical comorbidity [13]. Boyce et al. reviewed studies of the effectiveness of antidepressants in this population, concluding that despite the limited number and quality of the research, it appeared that depressed nursing home patients demonstrate a modest response to antidepressant medications [14].

##### 3.2.3. Collaborative care

There have been a number of major RCTs of collaborative or multidisciplinary care in older adults. Katon et al. undertook an

RCT of collaborative care in 214 US primary care patients with poorly controlled diabetes, coronary heart disease or both, and co-existing depression [15]. The collaborative care comprised a medically supervised nurse, working with the general practitioner, providing guideline-based, collaborative care management, with the goal of controlling risk factors associated with multiple diseases. They found that collaborative care was associated with a significant improvement in the control of the medical diseases and reduced depressive symptoms. In a randomised study of a structural multidisciplinary approach to depression in nursing home residents, Leontjevas et al. reported that this treatment programme reduced the prevalence of depression by 7% [16]. The latter treatment involved nursing staff, medical practitioners and allied health staff, and was comprised of three components: structured assessment, multidisciplinary treatment, and monitoring.

##### 3.2.4. Psychological therapies

There has been growing interest in the role of psychological therapies such as cognitive behavioural therapy (CBT) and psychoeducation in the management of comorbid depression in this population, either as monotherapy, or adjunct to antidepressant medications.

## 4. Cardiac disease

There is a complex inter-relationship between depression and coronary heart disease (CHD), with evidence for both an increase in CHD in those with depression, and increased morbidity and mortality in CHD patients who become depressed. With regard the former, the large prospective US Nurses' Health Study [17] reported on outcomes of depression in over 63,000 women without a prior history of CHD or stroke. This study found that depressive symptoms were associated a greater likelihood of the later onset of CHD events, particularly sudden cardiac death, with a specific relationship between this outcome and antidepressant use. Kimmel et al. analysing the UK General Practice Research Database, identified over 128,000 patients with a first diagnosis of depression [18]. In contrast to the Nurses' study, this study found that those prescribed SSRIs had a lower risk of myocardial infarction, particularly with longer term use. Huang et al. followed up almost 40,000 Taiwanese patients over 9 years [19]. They found that individuals who were depressed at baseline were more likely (hazard ratio 1.49) than those without depression to experience a new coronary event, but reported no association between antidepressant use and risk of coronary events.

The impact of depression on older patients with heart disease and the appropriate means of treating this represent the most developed literature on the management of depression in the older medically ill patient. The main areas of focus have been on depressed patients with myocardial infarction or cardiac failure.

### 4.1. Myocardial infarction

#### 4.1.1. Epidemiology

Major depressive disorder (MDD) occurs in about 15–20% of patients with myocardial infarction or angina [20]. There has been a major interest in this comorbidity in view of the repeated observation dating from the early 1990s [21] that patients with MDD following a myocardial infarction have a major increase in both mortality and poor cardio-vascular outcome. This recognition has led to recommendations of routine screening for depression in those with coronary artery disease [22], although this has not been without controversy [23].

While the association between depression and poor outcomes in this population is now well-established, the mechanism is as

yet not established, with some data indicating that the mediating factor may be inactivity [24] and others proposing decreased heart rate variability (HRV), enhanced platelet activation [25] or increased inflammatory markers or hypothalamic pituitary adrenal axis (HPA) activity [20].

#### 4.1.2. Management

The majority of treatment studies in depressed patients with myocardial infarction have focused on the effect of antidepressants on both depressive and cardiac outcomes. A number of large randomised placebo-controlled trials have been published since the early 2000s, the most prominent of which has been the SADHART trial (Sertraline Antidepressant Heart Attack Recovery Trial) [26]. Systematic reviews of these trials [23,27] have concluded that antidepressants – including sertraline, fluoxetine, citalopram and mirtazapine – are superior to placebo in modestly reducing depressive symptoms, but do not appear to lead to improved cardiac outcomes. Intriguingly, several trials have reported that cardiac [28] and all-cause mortality [29] are increased in those who are non-responsive to antidepressant treatments or who are insufficiently treated. It is difficult to reconcile the latter reports with the broader treatment literature indicating no overall benefit of antidepressants on cardiac outcomes and mortality rates.

In general, TCAs are usually proscribed in those with myocardial infarction in view of their effects on cardiac conduction and increased propensity to hypotension. The major safety issue with serotonergic antidepressants is the increased risk of bleeding [30].

There have also been a number of controlled trials of psychological treatments such as CBT in depressed CHD patients (e.g. ENRICH – Enhancing Recovery in Coronary Heart Disease Patients; [31]). These have similarly demonstrated reduced depressive symptoms without demonstrable effect on cardiac outcomes.

In contrast to these findings, randomised controlled trials of collaborative care have demonstrated improvements in both depressive symptoms and medical outcomes [15]. A randomised controlled study of collaborative care in 400 depressed patients with diabetes or heart disease in general practice in Australia, using practice nurses as case managers [32], found significantly improved depression and treatment intensification, sustained over 12 months.

## 4.2. Chronic heart failure

### 4.2.1. Epidemiology

Depression is common in heart failure, with one meta-analysis reporting a prevalence of 21.5% of patients experiencing clinically significant depression [33]. Rates of depression are higher in those with more severe heart failure, and mortality rates and secondary cardiac events are higher in those with depression [34].

### 4.2.2. Management

Unlike the situation with myocardial infarction, depression treatment outcomes are poor in those with cardiac failure. The largest randomised controlled trial compared sertraline and placebo (SADHART-CHF; [35,36]) amongst 469 patients and found no significant difference with respect to either depression scores or cardiac outcomes. One other trial of citalopram was also negative [37]. Veien et al. reported a 50% increase in mortality risk in those prescribed antidepressants in a Danish clinical database, though it is possible that those with depression represented a group with more severe heart failure [38]. The study of Diez-Quevedo et al. found no association between antidepressant use and mortality rates [34].

## 5. Cerebrovascular disease

### 5.1. Epidemiology

Depression is common in patients with stroke, with a prevalence of almost 20% in inpatients and 23% in outpatients [39]. A population-based study of subjects aged 85 years and older in Scandinavia [40] found that 43% of those with a history of stroke were depressed. A history of both stroke and ongoing depression was associated with greater 5-year mortality compared with stroke alone. It was previously believed that the location of a stroke was important in the aetiology of post-stroke depression, but recent systematic reviews have found no evidence for this [41], though physical disability, stroke severity and cognitive impairment have been found to be consistent predictors of depression [42].

### 5.2. Management

There have only been a limited number of placebo-controlled trials of antidepressants in patients with post-stroke depression [43–45]. A Cochrane review [45] of these studies found a significant but small effect of medications (though not psychotherapy), but a high rate of adverse effects, particularly neurological (seizures, fall and delirium). In light of the risk of adverse effects, the authors of that Cochrane review gave only “tentative” support for the use of antidepressants in this population, though both American and European treatment guidelines continue to support their use [42].

## 6. Cancer

### 6.1. Epidemiology

Depression is commonly associated with cancer [46]. A recent major meta-analysis [47] found rates of major depression of 16% in oncology and haematology inpatient and outpatient settings. Some aspects of cancer may increase the risk of depression; for example older patients with metastases were 2.2 times more likely to be depressed, while those with cognitive impairment were 3.6 times more likely [48].

### 6.2. Treatment

A recent systematic review and meta-analysis identified nine RCTs of antidepressants in the treatment of depressive symptoms in patients with cancer, finding a significant effect size for antidepressants (mainly SSRIs or mianserin) compared to placebo [49]. Unfortunately, most studies were small, allowing for only limited confidence in the findings. Three studies involved patients with breast cancer, one involved gynaecological cancers, and the other two involved a range of cancers.

A number of psychosocial treatments have been trialled in the management of depression and anxiety in cancer [44,50]. These include psychoeducation, problem-solving therapy, CBT and interpersonal therapy (IPT) which can often be delivered by trained cancer care nurses. Evidence from RCTs and meta-analyses (e.g. [51]) suggest that such therapies only have small effect sizes.

From a clinical perspective, Torta and Ieraci [52] have provided a very practical guideline for the use of antidepressants in cancer patients. They advise taking into account the following when deciding upon a particular antidepressant: (i) the specific symptoms due to the cancer, e.g. avoiding medications affecting gut motility in colon cancer; (ii) the stage of the cancer, e.g. sedation may be problematic at some stages, but beneficial at others; (iii) the risk of additive side effects in those on chemotherapy, e.g. dry mouth or nausea; and (iv) pharmacokinetic and pharmacodynamics issues, e.g. interaction of the analgesic tramadol with



**Table 1**  
Summary of prevalence of depression and efficacy of antidepressants and psychotherapy for common medical disorders in old age (see text for references).

Medical condition	Estimated prevalence of depression (%)	Evidence for efficacy of antidepressants	Antidepressants to avoid	Role of psychotherapy
Myocardial infarction	15	++	TCAs	Evidence for CBT, collaborative care
Chronic heart failure	21.5	–	TCAs	Few studies
Cerebrovascular disease	20–43	+	TCAs	Not effective
Cancer	16	+	Avoid TCAs if impaired gut motility; avoid SSRIs with tramadol; avoid SSRIs with tamoxifen	Small effect sizes for psycho-education, problem solving therapy, CBT, IPT
Chronic kidney disease	20–23	+	TCAs may cause urinary retention	Few studies
COPD	41	+	Nil specific	Some evidence for CBT; increased efficacy of psychological/lifestyle treatments which include an exercise component
Parkinson's disease	8–17	No evidence for antidepressants, but pramipexole is efficacious	Nil specific	Few studies

Antidepressant efficacy: –, nil; +, limited; ++, moderate-strong. TCAs, tricyclic antidepressants.

serotonergic antidepressants, and the effect of CYP450 2D6 inhibiting antidepressants on the metabolism of tamoxifen. They also provide particular guidance about specific antidepressant classes in various cancer management scenarios.

## 7. Chronic kidney disease

### 7.1. Epidemiology

A recent meta-analysis estimated that the prevalence of interview-defined depression for those with chronic kidney disease (CKD) was 20%, with those on dialysis having a higher prevalence of 23% [53]. As with many chronic diseases, the reasons for this high level of co-morbidity are likely to be mixed, but factors such as shared social and biological risk factors and the dramatic impact of renal failure and dialysis on independence and quality of life are likely to be of major importance [54]. Depression in CKD has been shown to be associated with multiple poor outcomes, including more frequent and longer hospitalisations, decreased treatment compliance and higher mortality rates [55–59]. Unfortunately, despite these associations, rates of detection and treatment of depression in patients with CKD remain low [60].

### 7.2. Management

Treating depression in CKD patients poses particular challenges. Generally, antidepressant medications are highly protein bound, hepatically metabolised and not removed significantly by dialysis [60]. This makes the relative activity and mode of excretion of metabolites of these drugs difficult to predict. Further concerns include anticholinergic effects, including urinary retention (TCAs) [60,61], accumulation of toxic metabolites (serotonin–noradrenaline reuptake inhibitors [SNRIs]) [61], and increased risk of bleeding (SSRIs) [62]. Despite these concerns, a number of small trials have suggested relative safety and efficacy of a number of antidepressants, including citalopram and fluoxetine, provided that dose reductions are made in line with the estimated glomerular filtration rate [54]. To date it remains unclear if treating depression in CKD will improve renal outcomes.

## 8. Chronic obstructive pulmonary disease (COPD)

### 8.1. Epidemiology

Fan et al. found that 41% of COPD subjects had at least mild to moderate depressive symptoms, with the most severely depressed

being at increased risk of respiratory hospitalisation [63,64]. Those with the highest depression symptom scores had a significantly increased 3-year mortality rate (odds ratio [OR] 2.7) and were more likely to experience dyspnoea and have a low body mass index. Few patients had received treatment for depression.

### 8.2. Management

There have been few trials of treatments for depression in patients with COPD [65]. Fritzsche et al. reviewed the published trials of antidepressants and psychological treatments for these co-occurring conditions [66]. They found a limited number of small placebo controlled trials of TCA and SSRI antidepressants which were suggestive of some benefit. Similarly, they reported evidence from a relatively small literature of the value of psychological therapies including CBT.

One of the practical difficulties with antidepressant treatments for subjects with COPD appears to be adherence, with Pirraglia et al. reporting lower rates of adequate antidepressant compliance in the first few months of treatment for patients with COPD compared to other medical disorders in a US Veterans Affairs pharmacy database [67]. A recent meta-analysis [68] of complex psychological and/or lifestyle interventions which included an exercise component has reported that these treatments significantly improve symptoms of depression and anxiety in people with COPD, highlighting the importance of promoting physical activity in this population.

## 9. Parkinson's disease

### 9.1. Epidemiology

Major depression is commonly associated with Parkinson's disease with a prevalence of 8–17% (depending upon the population studied [69]). Differentiation between depression and Parkinson's disease can be difficult as patients with Parkinson's disease without depression may also manifest with similar symptoms of psychomotor retardation and reduced facial expression. Depression has been reported to be more prevalent in those with more advanced Parkinson's disease and in those with associated dementia [69].

### 9.2. Management

There have been few trials of antidepressant medications in depressed subjects with Parkinson's disease. Rocha et al. were able to identify five placebo-controlled trials, but meta-analysis

failed to demonstrate a definite beneficial effect [70]. There has been increasing interest in anti-Parkinsonian drugs in the management of depression in this condition. In the largest trial of such medications, Barone et al. [71] randomly assigned 296 patients to either the dopamine agonist pramipexole or placebo, finding a significantly greater reduction in depressive symptoms with pramipexole, mainly through a direct antidepressant effect.

## 10. Conclusions

Depression amongst older adults with physical illness is a common, but complex problem. It can be difficult for clinicians to identify which patients are depressed, with many common features of depression easily confused with non-specific symptoms of old age or co-morbid physical illness. However, correctly diagnosing depression in this patient group is vital as it can have a dramatic impact on quality of life and is consistently shown to be associated with poorer physical health outcomes. As outlined in the sections above and summarised in Table 1, different management strategies and specific considerations are needed, depending on the particular medical condition present. For many conditions there is emerging evidence that modified depression treatments can be effective at reducing depressive symptoms, but this needs to be balanced against an elevated risk of adverse effects. Gaps remain in terms of our understanding of the biological links between depression and physical illness and, to date, there is limited evidence that standard depression treatment have additional benefits in terms of physical health outcomes. Collaborative care models appear particularly well suited to medically unwell older adult patients, and may provide more generalised benefits across both mental and physical health measures.

## Contributors

Philip B. Mitchell and Samuel B. Harvey drafted the manuscript.

## Competing interests

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