Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis

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Abstract
Depression can exacerbate symptoms associated with life-threatening illness and increase disablement and distress. In palliative care, depression occurs in a context of multiple symptoms, which complicates detection and treatment. While systematic reviews of antidepressants have been conducted in specific life-threatening diseases, no previous study has synthesized the evidence in palliative care. The objective of this study was to determine the efficacy of antidepressants for the treatment of depression in palliative care. MEDLINE, EMBASE, PSYCINFO and Cochrane trials registers were systematically searched to identify randomized controlled trials comparing antidepressants and placebo for the treatment of depression in palliative care. The primary outcome was efficacy assessed at three time-points. Twenty-five studies were included in the review. At each time-point antidepressants were more efficacious than placebo: 4–5 weeks odds ratio (OR) 1.93 (1.15–3.42) \( p = 0.001 \); 6–8 weeks OR 2.25 (1.38–3.67) \( p = 0.001 \); 9–18 weeks OR 2.71 (1.50–4.91) \( p = 0.001 \).

This review provides evidence that antidepressants are effective in treating depression in palliative care. Their superiority over placebo is apparent within 4–5 weeks and increases with continued use. It is probable that the effect sizes yielded in this review overestimate the efficacy of antidepressants due to biases such as selective reporting and publication. Nevertheless, the magnitude and consistency of the effect suggests genuine benefit.

Keywords
Palliative care, life-threatening illness, depression, antidepressants

Introduction
Depression is common in patients receiving palliative care, with around 15% having major depression ascertained by diagnostic interview.\(^1\) Aside from the emotional suffering inherent in the diagnosis, depression may exacerbate the physical effects of advanced disease, such as pain,\(^2,3\) fatigue, poor appetite and sleep disturbance.\(^4\) Depression in physical illness hinders adherence to treatment\(^5,6\) and is a risk factor for high health service costs.\(^7,8\) It is associated with increased disability,\(^9,10\) poor prognosis\(^11\) and (for at least some diseases) higher mortality.\(^12-14\)

Clinicians are cautious about diagnosing and treating depression in palliative patients.\(^15,16\) In patients with advanced disease it is difficult to determine whether somatic symptoms, such as fatigue and sleep disturbance, are due to depression, physical illness or medical treatment.\(^17,18\) Further, life-limiting illness inevitably invokes some fear and sadness, and normal and disordered distress are particularly difficult to distinguish in this context.\(^19\) Thus clinicians are in a dilemma; on the one hand, distress is not always a symptom of mental disorder and medicalizing normal sadness can stigmatize patients, shroud the true source...
of their suffering, and impede provision of appropriate support and symptom control; on the other hand, ignoring the diagnosis of depressive disorder may reduce the patient’s chance of receiving effective treatment, for example, antidepressants. Studies suggest that clinicians are unsure whether antidepressants are appropriate in the context of concomitant physical illness. A recent study based in UK primary care showed that depressed patients with a concurrent physical illness receive fewer antidepressant prescriptions than depressed patients who are physically healthy, and the 1999 survey of Lloyd-Williams et al. found that terminally ill patients with depression were prescribed antidepressants so late that they often died before the medication had time to take effect. Systematic reviews have shown that antidepressants are effective in treating depression in physically healthy populations. There is also evidence that antidepressants are effective in treating depression in physically ill people. Gill and Hatcher’s Cochrane review in 2000 found that antidepressants were superior to placebo in treating depression in physical illness. The authors of the present review recently updated Gill and Hatcher’s original study. The revised Cochrane review included many more trials and patients than the original version and confirmed that antidepressants are effective and acceptable to physically ill people with depression. There have also been some systematic reviews of antidepressants in specific life-threatening diseases. The Ghazi-Noori et al. Cochrane review of therapies for depression in Parkinson’s disease found insufficient data on the effectiveness and safety of antidepressants to recommend their use in this population. A Cochrane review of treatments for depression in dialysis patients identified only one trial, which showed no difference in depression scores between the treatment and control groups. The majority of drug trials included in Rodin and colleagues’ systematic review of depression in cancer patients found no significant difference between treatment and control groups on depression measures. Thus, existing systematic reviews of antidepressants in specific life-threatening diseases have yielded inconclusive results. Further, no study has sought to synthesize the evidence on antidepressants for depression in palliative care. Depression in palliative care occurs in a context of co-morbidity. The coexistence and interaction of multiple symptoms and treatments complicates the management of depression in this population. Moreover, in palliative care, time is often short. Clinicians need to take account of the patient’s prognosis and the time required for potential treatments to take effect. Because of these unique challenges, it is important to establish whether antidepressants are an effective and acceptable treatment for depression in palliative care. We conducted a systematic review and meta-analysis of antidepressants in palliative care in order to determine their appropriateness for this population. The trials included in this review were a subset of trials included in the authors’ recent Cochrane review of antidepressants for depression in physically ill people that were conducted in patients with a life-threatening physical illness. The efficacy, acceptability and tolerability of antidepressants and placebo were compared. Speed of onset of therapeutic action is particularly pertinent to palliative care. By analysing efficacy outcomes at three time-points we aimed to give an indication of how early antidepressants work. We also examined quality of life and functional status to assess whether antidepressants impact upon these domains.

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.

Methods

Eligibility criteria

We identified randomized controlled trials comparing antidepressants and placebo in the treatment of depression in palliative care. The term ‘palliative’ traditionally described end-of-life care, but in recent years has been extended to encompass the care of people who have a life-threatening illness but are not imminently dying. This shift in meaning is reflected in the World Health Organization’s (WHO) 2002 definition of palliative care as the prevention and relief of suffering in patients with a life-threatening illness. We used this definition to identify relevant trials for the review. The term ‘life-threatening’ is ambiguous and there is no consensus about which diseases are life-threatening. We included in the review trials of antidepressants in cancer, renal failure, chronic obstructive pulmonary disease (COPD), chronic heart failure, Parkinson’s disease, multiple sclerosis and HIV/AIDS. These are all progressive illnesses which benefit from palliative care.

All types of antidepressant were eligible for inclusion. Trials in which antidepressants were prescribed primarily to treat symptoms other than depression (e.g. pain) were excluded. Only those trials in which depression was a primary outcome were included in the review.

The participants were adults above 18 years of age with depression in the context of a life-threatening illness. Depression included diagnoses of Major Depressive Disorder, Adjustment Disorder and Dysthymic Disorder based on standardized criteria (such as the DSM-IV or the ICD-10), and/or
according to a score above a certain cut-off on validated tools (such as the Hamilton Rating Scale for Depression [HDRS], the Montgomery-Åsberg Depression Rating Scale [MADRS] or the Hospital Anxiety and Depression Scale [HADS]).

**Outcomes**

The primary outcome was efficacy assessed using dichotomous and continuous measures of depression. The dichotomous outcome ‘response to treatment’ is defined conventionally and widely reported as a 50% or greater improvement in depressive symptomatology according to a validated scale, such as the HDRS, the MADRS or the HADS. Continuous measures were expressed as mean depression score values and standard deviations, according to a validated scale. To examine onset of therapeutic action, outcomes were assessed at three time-points: 4–5 weeks, 6–8 weeks and 9–18 weeks from randomization.

The secondary outcomes were acceptability, tolerability, quality of life and functional status. Acceptability was assessed by comparing the number of drop-outs in patients receiving antidepressants and patients receiving placebo. Tolerability was assessed by comparing the number of adverse events. The frequency of the 10 most commonly reported adverse events was assessed. Adverse events data were entered into the meta-analysis only if it was possible to make a direct comparison between treatment and placebo groups (e.g. if adverse events data were recorded as the number of participants experiencing the adverse event over a specified time period). Where the size of the group was specified in relation to the adverse event this was recorded; otherwise, the initial sample size was used as the denominator. Quality of life and functional status were examined by comparing mean scores on validated assessment scales when these were used and reported.

**Search strategy**

Established methods were used to identify all placebo controlled trials of antidepressant treatment for depression. The Cochrane Depression Anxiety and Neurosis Group completed a search of their register of trials. A supplementary search of standard bibliographic databases (MEDLINE, EMBASE, PSYCINFO – all years) was conducted. Reference lists of included studies and related reviews were scanned, and national, international and pharmaceutical industry trials registers were searched to identify any unpublished data. The search was updated twice during the course of the review (last search December 2009).

The search strategy comprised three groups of keywords:

1. Depress* or Dysthymia or “Adjustment Disorder*” or “Mood Disorder*” or “Affective Disorder*” or “Affective Symptoms”
2. (Antidepress* or “Monoamine Oxidase Inhibitors” or “Selective Serotonin Reuptake Inhibitors” or “Tricyclic Drugs” or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or Befloxatone or Benactyzine or Brofaromine or Bupropion or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Desipramine or Dibenzipin or Diclofensine or Dothiepin or Doxepin or Duloxetine or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Fluvoxamine or Idazoxan or Imipramine or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Maprotiline or Medifoxamine or Melitracen or Metapramine or Mianserin or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nomifensine or Nortriptyline or Nortriptyline or Opipramol or Oxalofazone or Oxaprotidine or Oxaprotiline or Pargyline or Paroxetine or Phenelzine or Piribedil or Pirindolol or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Reboxetine or Rolipram or Sertraline or Setiptiline or SSRIs or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Tranlycypromine or Trazodone or Trimagline or Venlafaxine or Vilozazine or Viprazine or Vizamidine)
3. Placebo*.

Within each group the keywords were combined using or. The resultant three groups were then combined using and.

**Data collection**

The authors assessed all potentially eligible studies generated from the literature search using the inclusion criteria stated above. The titles and abstracts of trials were screened to determine whether they might meet the eligibility criteria. If it was not clear from the title or abstract that the study should be rejected, the full text of the article was obtained and reviewed. This process was conducted independently by two authors (AE and KV) to reduce the possibility of relevant reports
being rejected. Any disagreements about selection criteria were resolved by discussion with MH, in consultation with IH. Two authors (AP and LR) independently extracted data onto a specially designed, standardized data extraction form. Data were extracted on study setting, diagnostic criteria used, number and characteristics of participants allocated, intervention and outcome measures, risk of bias, adverse events, drop-outs and depression scores. Any divergence in the data extracted was discussed, and consensus reached under the supervision of MH and IH.

Data analysis
For dichotomous data, we calculated odds ratios (ORs) with 95% confidence intervals (CIs). For continuous data, we calculated standardized mean differences (SMDs), using available mean values and their standard deviations, together with 95% CIs. Data were pooled in meta-analyses using Review Manager 5.0. A random effects model was used. Risk of bias was judged independently by two reviewers using the Risk of Bias table approach recommended in the Cochrane Handbook.48 The tool addressed six domains – sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases. In addition we used the Van Tulder 11-item Quality Assessment Scale for RCTs to attain a summary score to serve as a cut-off for inclusion in a sensitivity analysis restricted to trials at low risk of bias. Only trials scoring above 6/11 on the Van Tulder scale were included in the risk of bias sensitivity analysis.49 If neither continuous nor dichotomous outcome variables were reported, we contacted the authors to ask for these data. Participants who withdrew from the study before endpoint were assumed not to have responded to treatment. Where baseline depression scores and standard deviations were given, but dichotomous outcomes were not provided, we imputed the number of responding participants by assuming depression scores were normally distributed and calculating the number of participants below half the baseline score. This is a validated imputation method with empirical support.50 We calculated missing standard deviations by using the mean standard deviation from the other studies using the same depression scale. To ensure that substitute standard deviations related to a similar stage of treatment, we calculated two mean standard deviations: one from outcomes reported up to eight weeks, and one from outcomes reported after eight weeks. The chi² test and I² were used to investigate heterogeneity. The chi² test assessed whether observed differences in the results of the included trials were compatible with chance alone, The I² described the percentage of variability in effect estimates due to heterogeneity rather than chance, thus providing a measure of the impact of heterogeneity on the meta-analysis. Funnel plots were used to examine potential bias due to selective publication and other small study effects. Subgroup analysis was performed by class of antidepressant to explore the comparative efficacy and acceptability of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).

Sensitivity analyses were undertaken to test whether the main findings were influenced by design effects of the included studies (e.g. variations in definition of depression, reporting of data and risk of bias). These included exclusion of studies with high risk of bias, exclusion of studies with imputed data and comparison of intention-to-treat and completer efficacy analyses. The efficacy of antidepressants in trials which used broad and narrow definitions of depression was also compared. Trials using a narrow definition of depression were defined as those which only included patients with a diagnosis of Major Depressive Disorder (MDD), based on standardized diagnostic criteria (DSM-IV/ICD-10). Trials using a broad definition of depression were defined as those which also included patients diagnosed with Adjustment Disorder (AD) and dysthymia, as well as patients whose score on a validated scale (such as the HDRS or MADRS) was indicative of a depressive disorder. In palliative care, Major Depression, Adjustment Disorder and milder mood disorders are particularly difficult to differentiate. DSM-IV and ICD-10 diagnoses are based on an essentially arbitrary number of presenting symptoms, and the extent to which these categories represent discrete pathologies requiring different management remains unclear. This sensitivity analysis enabled us to test whether response to treatment differed in the trials which included patients who did not meet diagnostic criteria for MDD.

Results
Results of the search
The search of MEDLINE, EMBASE, PSYCINFO and the Cochrane clinical trials registers provided a total of 2215 references. A further 15 studies were identified through other sources, such as pharmaceutical industry websites. After adjusting for duplicates 2018 references remained. The titles of these references were scanned: 1877 were not relevant to the review and were discarded. The abstracts of 141 records were screened, and 68 full-text articles were assessed for eligibility. Of these, 25 studies were eligible for inclusion in the review. See flow diagram (Figure 1).
Included studies

Table 1 presents the characteristics of the 25 included studies. Seven were trials of antidepressants in HIV/AIDS,\textsuperscript{51–57} six were in Parkinson’s disease,\textsuperscript{58–63} four were in cancer,\textsuperscript{64–67} three were in COPD,\textsuperscript{68–70} two were in multiple sclerosis,\textsuperscript{71,72} two were in end-stage renal failure\textsuperscript{73,74} and one was in chronic heart failure.\textsuperscript{75} Twenty-one studies contributed data to the meta-analysis of antidepressant efficacy.

Risk of bias

Risk of bias was assessed using the domain-based quality assessment tool recommended by Cochrane. Of the 25 included studies, only six (24%) reported sufficient information to determine that intervention allocations were adequately concealed. Five (20%) reported sufficient information to determine that an adequate method of sequence generation was performed. Eight studies (32%) reported sufficient information to determine that blinding of participants and key study personnel was ensured and unlikely to have been broken. Incomplete outcome data were judged to have been adequately addressed in 13 studies (52%). Study protocols were available for very few trials, therefore risk of bias from selective outcome reporting was difficult to assess. The funnel plot of response to treatment at 6–8 weeks was asymmetrical with a gap in the bottom left corner of the graph (see Figure 2). This represents a scarcity of smaller negative trials and indicates selective publication of small studies with statistically significant effect. A similar pattern was seen at 4–5 weeks, but at 9–18 weeks there were more small negative studies and publication bias was less apparent.

Efficacy

Both the response to treatment efficacy analysis and the mean depression score efficacy analysis yielded statistically significant effects favouring antidepressants over placebo. The size and precision of the effects observed in these analyses did not differ appreciably. Response to treatment is reported as the primary efficacy outcome because a greater number of studies contributed dichotomous data. At every time-point, antidepressants were superior to placebo in reducing depressive symptoms. The majority of trials contributed outcome data at 6–8 weeks (see Figure 3). The difference in efficacy between antidepressants and placebo increased over
The effect size was smallest at 4–5 weeks from randomization (OR 1.93, CI 1.15–3.42) increasing at 6–8 weeks (OR 2.25, CI 1.38–3.67), and again at 9–18 weeks (OR 2.71, CI 1.50–4.91) (see Table 2). The effects yielded by the different studies were generally consistent. At 4–5 weeks $\chi^2=4.24$ ($df=4$, $p=0.37$) and $I^2=6\%$, indicating that little of the variability in effect estimates was due to heterogeneity rather than sampling error (chance). A greater number of trials contributed data to the 6–8 week analysis, and more heterogeneity was detected at this time-point ($\chi^2=18.45$, $df=11$, $p=0.07$; $I^2=40\%$). At 9–18 weeks $\chi^2=5.89$ ($df=6$, $p=0.44$), and $I^2=0\%$.

**Table 1.** Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Intervention</th>
<th>Participants</th>
<th>Duration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumenfield 1997</td>
<td>Renal failure (on dialysis)</td>
<td>20mg fluoxetine</td>
<td>14 (7 fluoxetine, 7 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Borson 1992</td>
<td>COPD</td>
<td>nortriptyline 1mg/kg body weight</td>
<td>36 (18 nortriptyline, 18 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Costa 1985</td>
<td>Cancer</td>
<td>Mianserin (dose modified)</td>
<td>73 (36 mianserin, 37 placebo)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Devos 2008</td>
<td>Parkinson’s disease</td>
<td>Desipramine 20mg Citalopram 20mg</td>
<td>46 (17 desipramine, 15 citalopram, 16 placebo)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Ehde 2008</td>
<td>Multiple sclerosis</td>
<td>Paroxetine 10-40mg</td>
<td>42 (22 paroxetine, 20 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Elliot 1997</td>
<td>HIV</td>
<td>Paroxetine 10-40mg Imipramine 50-200mg</td>
<td>75 (25 paroxetine, 25 imipramine, 25 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Gottlieb 2007</td>
<td>Chronic heart failure</td>
<td>Paroxetine 12.5-25mg daily</td>
<td>28 (14 paroxetine, 14 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Leentjens 2003</td>
<td>Parkinson’s disease</td>
<td>Sertraline 25-100mg</td>
<td>12 (6 sertraline, 6 placebo)</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Light 1986</td>
<td>COPD</td>
<td>Doxepin 25-150mg</td>
<td>12 (6 doxepin, 6 placebo)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Mauri 1994</td>
<td>HIV</td>
<td>Fluvoxamine 100-150mg</td>
<td>26 (16 fluvoxamine, 10 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Menza 2009</td>
<td>Parkinson’s disease</td>
<td>Nortriptyline 25-75mg Paroxetine 12.5-37.5mg</td>
<td>52 (17 nortriptyline, 18 paroxetine, 17 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Musselman 2006</td>
<td>Breast cancer</td>
<td>Desipramine 25-200mg Paroxetine 20-40mg</td>
<td>35 (11 desipramine, 13 paroxetine, 11 placebo)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Palmer 2002</td>
<td>COPD</td>
<td>Citalopram 20-40mg</td>
<td>27 (15 citalopram, 12 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Pervin 2006</td>
<td>End-stage renal disease (on dialysis)</td>
<td>Escitalopram (dose not stated)</td>
<td>62 (32 escitalopram, 30 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Rabkin 1994</td>
<td>HIV</td>
<td>Imipramine 50-300mg</td>
<td>97 (50 imipramine, 47 placebo)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Rabkin 1999</td>
<td>HIV</td>
<td>Fluoxetine 20mg</td>
<td>120 (81 fluoxetine, 39 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Rabkin 2004</td>
<td>HIV/AIDS</td>
<td>Fluoxetine 20mg</td>
<td>85 participants (46 fluoxetine, 39 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Razavi 1997</td>
<td>Cancer</td>
<td>Fluoxetine 20mg</td>
<td>91 (45 fluoxetine, 46 placebo)</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Schiffer 1990</td>
<td>Multiple sclerosis</td>
<td>Desipramine 25mg</td>
<td>(14 desipramine, 14 placebo - excluding 2 drop-outs)</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Targ 1994</td>
<td>HIV</td>
<td>Fluoxetine 20mg</td>
<td>20 (10 fluoxetine, 10 placebo)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Van Heeringen 1996</td>
<td>Breast cancer</td>
<td>Mianserin 30-60mg</td>
<td>55 (28 mianserin, 27 placebo)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Weintraub 2009</td>
<td>Parkinson’s disease</td>
<td>Atomoxetine 80mg</td>
<td>55 (28 atomoxetine, 27 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Weiser 2004</td>
<td>Parkinson’s disease</td>
<td>Mirtazapine 30mg</td>
<td>20 (10 mirtazapine, 10 placebo)</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Wermuth 1998</td>
<td>Parkinson’s disease</td>
<td>Citalopram 10-20mg</td>
<td>37 (18 citalopram, 19 placebo)</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Zisook 1998</td>
<td>HIV</td>
<td>Fluoxetine 20mg-60mg</td>
<td>47 (25 fluoxetine, 22 placebo)</td>
<td>7 weeks</td>
</tr>
</tbody>
</table>

*Duration refers to the trial end-point. Many trials reported data at multiple time-points and were therefore included in more than one analysis.

**Figure 2.** Funnel plot of response to treatment at 6–8 weeks.
indicating that any variability in effect estimates was due to chance not heterogeneity.

Table 2 shows the effect observed at each timepoint for each sensitivity analysis. Excluding trials judged to be at high risk of bias increased the effect size at 4–5 weeks, but diminished the effect at later time-points. The results of the intention-to-treat and completer analyses were similar, and excluding trials with imputed data did not appreciably alter the size of the effects observed. At 4–5 weeks, the effect observed in trials which used a narrow definition of depression (MDD only) was greater than that observed in trials which used a broader definition of depression. In contrast, at later time-points greater effect sizes were
yielded in those trials which defined depression more broadly.

Of the 25 studies included in the review, 13 compared an SSRI with placebo, four compared a TCA with placebo, and four three-armed trials compared a SSRI and a TCA with placebo. Subgroup analysis was performed to assess the efficacy of the two main classes of antidepressant – TCAs and SSRIs. Both classes of antidepressant were more efficacious than placebo, but before nine weeks the effect was statistically significant for only TCAs (see Table 3). There were also two trials of mianserin (a tetracyclic antidepressant), one trial of mirtazapine (a noradrenergic and specific serotonergic antidepressant) and one trial of atomoxetine (a selective noradrenaline re-uptake inhibitor). Mirtazapine and mianserin were grouped together due to having a similar mode of action. At 6–8 weeks there was one trial using mirtazapine (n = 20) and one trial using mianserin (n = 55). The combined OR of these two trials was 3.56 (1.24–10.23), which exceeds the effect size found for SSRIs and TCAs at the same time-point.

Four trials did not provide data amenable to meta-analysis. Two of these were reported as abstracts only, and two did not report outcome data with sufficient clarity to enable inclusion in the meta-analysis. Pervin and colleagues’ 2006 study of escitalopram for treatment of Major Depression in patients with end-stage renal disease showed a greater decrease in HDRS compared with placebo, eight weeks from randomization (n = 30). The 1997 trial by Blumenfeld et al., also in renal failure, reported that ‘the mean change from baseline on all depression scale measurements was greater in the active group than in the placebo group at the mid-study point’. However, this trial included only 14 patients, baseline depression scores and standard deviations were not reported, and at endpoint there was little difference in depression scores between the two groups. The other trials not included in the meta-analysis assessed the efficacy of antidepressants in COPD. Light et al. (1986) found no difference in depression scores between patients taking doxepin and patients taking placebo. Palmer et al. (2002) found that citalopram was more effective than placebo in patients with mild to moderate depression, but there was no difference in severely depressed patients.

Acceptability

Acceptability was assessed by comparing the number of drop-outs in the treatment and placebo groups (see Table 4). At the earlier time-points there was no difference in drop-out between the two groups. At 9–18 weeks, fewer patients receiving placebo withdrew from study compared with patients treated with an antidepressant (OR 2.09, CI 1.02–3.31). Subgroup analysis by class of antidepressant at 6–8 weeks showed little difference between the odds of drop-out in trials of SSRIs and TCAs. At 9–18 weeks, the odds of dropping out of study were greater for patients treated with a TCA than for patients treated with placebo. At 4–5 weeks there were too few TCA trials to warrant meta-analysis.

Tolerability

Tolerability was assessed by comparing the number of adverse events in the treatment and placebo groups (see Table 3.)
### Table 4. Acceptability: number of drop-outs

<table>
<thead>
<tr>
<th>Time since randomisation</th>
<th>Primary analysis</th>
<th>Subgroup analysis (class of antidepressant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TCA</td>
</tr>
<tr>
<td>4-5 weeks</td>
<td>*OR 1.00 (0.25–4.07)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>$p = 1.00$, $I^2 = 74%$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 trials, 212 patients</td>
<td></td>
</tr>
<tr>
<td>6-8 weeks</td>
<td>OR 1.08 (0.65–1.81)</td>
<td>OR 1.30 (0.52–3.24)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.76$, $I^2 = 37%$</td>
<td>$p = 0.57$, $I^2 = 22%$</td>
</tr>
<tr>
<td></td>
<td>10 trials, 597 patients</td>
<td>3 trials, 153 patients</td>
</tr>
<tr>
<td>9-18 weeks</td>
<td>OR 2.09 (1.02–4.31)</td>
<td>OR 2.28 (0.70–7.39)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.05$, $I^2 = 0%$</td>
<td>$p = 0.17$, $I^2 = 15%$</td>
</tr>
<tr>
<td></td>
<td>6 trials, 228 patients</td>
<td>2 trials, 86 patients</td>
</tr>
</tbody>
</table>

*For acceptability OR > 1 favours placebo.

### Table 5. Tolerability: number of adverse events

<table>
<thead>
<tr>
<th>Time since randomisation</th>
<th>Primary analysis</th>
<th>Subgroup analysis (class of antidepressant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TCA</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>*OR 2.05 (1.29–3.26)</td>
<td>OR 5.33 (2.23–12.73)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.003$, $I^2 = 0%$</td>
<td>$p = 0.0002$, $I^2 = 16%$</td>
</tr>
<tr>
<td></td>
<td>12 trials, 546 patients</td>
<td>7 trials, 203 patients</td>
</tr>
<tr>
<td>Constipation</td>
<td>OR 1.30 (0.49–3.46)</td>
<td>OR 0.89 (0.12–6.87)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.60$, $I^2 = 30%$</td>
<td>$p = 0.91$, $I^2 = 67%$</td>
</tr>
<tr>
<td></td>
<td>7 trials, 337 patients</td>
<td>4 trials, 115 patients</td>
</tr>
<tr>
<td>Nausea</td>
<td>OR 1.51 (0.63–3.63)</td>
<td>OR 1.23 (0.45–3.35)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.36$, $I^2 = 59%$</td>
<td>$p = 0.40$, $I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>11 trials, 504 patients</td>
<td>3 trials, 83 patients</td>
</tr>
<tr>
<td>Dizziness</td>
<td>OR 1.23 (0.62–2.44)</td>
<td>OR 2.41 (0.66–8.81)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.55$, $I^2 = 0%$</td>
<td>$p = 0.18$, $I^2 = 46%$</td>
</tr>
<tr>
<td></td>
<td>9 trials, 595 patients</td>
<td>4 trials, 271 patients</td>
</tr>
<tr>
<td>Headache</td>
<td>OR 1.50 (0.58–3.86)</td>
<td>OR 1.07 (0.42–2.75)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.40$, $I^2 = 57%$</td>
<td>$p = 0.88$, $I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>10 trials, 447 patients</td>
<td>4 trials, 105 patients</td>
</tr>
<tr>
<td>Insomnia</td>
<td>OR 0.58 (0.10–3.29)</td>
<td>OR 0.29 (0.03–3.36)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.54$, $I^2 = 53%$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 trials, 240 patients</td>
<td></td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>OR 1.92 (0.80–4.65)</td>
<td>OR 2.70 (0.74–9.80)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.15$, $I^2 = 0%$</td>
<td>$p = 0.31$, $I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>5 trials, 242 patients</td>
<td>2 trials, 71 patients</td>
</tr>
<tr>
<td>Hypotension</td>
<td>OR 2.37 (0.67–8.35)</td>
<td>OR 1.40 (0.24–8.11)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.18$, $I^2 = 0%$</td>
<td>$p = 0.71$, $I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>4 trials, 174 patients</td>
<td>3 trials, 83 patients</td>
</tr>
<tr>
<td>Sedation</td>
<td>OR 1.18 (0.39–3.50)</td>
<td>OR 1.77 (0.50–6.33)</td>
</tr>
<tr>
<td></td>
<td>$p = 0.77$, $I^2 = 18%$</td>
<td>$p = 0.38$, $I^2 = 0%$</td>
</tr>
<tr>
<td></td>
<td>3 trials, 166 patients</td>
<td>2 trials, 74 patients</td>
</tr>
<tr>
<td>Appetite change</td>
<td>OR 0.84 (0.30–2.40)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>$p = 0.75$, $I^2 = 4%$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 trials, 132 patients</td>
<td></td>
</tr>
</tbody>
</table>

*For tolerability OR > 1 favours placebo.*
Table 5). The frequency of the 10 most commonly reported adverse events was assessed. Dry mouth was more frequently reported by patients treated with an antidepressant than by patients treated with placebo. This effect was strongest among patients treated with a TCA. Nausea was more common in patients treated with an antidepressant than in patients treated with placebo, though this effect was only statistically significant in patients treated with an SSRI. More patients treated with a TCA reported dizziness than did patients treated with placebo. Sexual dysfunction, hypotension and headache were more likely to be reported by patients taking an antidepressant, though these effects were not statistically significant. Insomnia was reported less frequently by patients taking an antidepressant. There was no difference in the frequency of constipation, sedation or appetite change between patients treated with antidepressant and patients taking placebo.

Quality of life

Only four studies included in the review reported quality-of-life outcomes. Each of these studies reported greater improvements in measures of quality of life in the treatment group than in the control group. The studies used different scales to assess quality of life (Spitzer Quality of Life Index [SQOLI], Endicott Quality of Life Enjoyment and Satisfaction Questionnaire, Medical Outcomes Study 36-Item Short Form Survey [SF-36], Minnesota Living with Heart Failure Questionnaire [MLWHFQ], MS Quality of Life Inventory [MSQLI]), and so the results are not readily comparable. The difference in improvement in quality of life between treatment and placebo groups was non-significant, except in the general health domain of the SF-36 in Gottlieb and colleagues’ 2007 trial. These results should be interpreted with particular caution due to the risk of reporting bias.

Functional status

Three studies included in the review reported outcome data related to functional status. Wermuth et al. reported no difference between citalopram and placebo groups in scores on the Unified Parkinson’s Disease Rating Scale (UPDRS), which evaluates motor impairment and physical disability in patients with Parkinson’s disease. Ehde et al. assessed the impact of fatigue on functioning in multiple sclerosis and found a greater improvement in the treatment group than in control, though the difference was not statistically significant. Borson (1992) also reported a greater improvement in function in patients receiving an antidepressant, based on two measures (Sickness Impact Profile [SIP], Pulmonary Functional Status Instrument [PFSI]). Again, given that so few studies reported them, it is likely that functional status outcomes were selectively reported.

Discussion

This review provides evidence that depression in patients with a life-threatening illness can be effectively treated with antidepressants. Antidepressants were superior to placebo using both dichotomous and continuous efficacy data. The effect favouring antidepressants was statistically significant at each time-point, increasing in size over time. There was little evidence of heterogeneity, indicating consistency in the effects yielded by the individual studies. The number needed to treat (NNT) was calculated to determine how many patients must take an antidepressant in order for one to benefit. At 4–5 weeks the NNT was 9 (95% CI 4.3–81.0); therefore one additional person would be expected to respond to treatment for every nine patients taking antidepressants instead of placebo for 4–5 weeks. The NNT decreased over time: 6–8 weeks NNT = 6 (95% CI 3.9–8.8); 9–18 weeks NNT = 5 (95% CI 2.9–9.9), indicating that there may be a delay in the onset of action of antidepressants in this population. It may be instructive to compare the NNT we observed with that of other common medical treatments. For example for radiotherapy for breast cancer the NNT was estimated to be 8, and the flu vaccine was found to have NNT of 12. Thus the NNT for antidepressants in palliative care is comparatively low, suggesting a clinically important effect.

Our recent Cochrane review showed that antidepressants are superior to placebo in treating depression in people with a physical illness. It updated a previous Cochrane review of antidepressants in medical illness by Gill and Hatcher, which also concluded that antidepressants were an effective treatment for depression in physically ill people. This review of antidepressants in palliative care augments the evidence base by showing that antidepressants are also effective in treating depression in life-threatening illness. It is the first systematic review to assess the effects of antidepressants in this patient group. An interesting difference between this review and the Cochrane review is that in general physical illness the effect favouring antidepressants was largest at 6–8 weeks, whereas in life-threatening illness the efficacy of antidepressants increased over time, with the largest effect occurring at 9–18 weeks. This finding highlights the need for increased awareness and attention to depression in palliative care, so the patients can be diagnosed and prescribed treatment in time for it to have full effect. It also suggests that antidepressants should continue to be taken by patients even if there is little effect in the first few weeks.
Given that depression and normal sadness are particularly difficult to distinguish in palliative care, the question of whether antidepressants are only effective in the context of mental disorder is pertinent to this population. To explore this issue we compared antidepressant efficacy in trials which included only patients diagnosed with MDD with those which included patients with less severe depressive symptomatology. At the later time-points, the size of the effect yielded by trials which included patients who did not meet the criteria for MDD was greater than that observed in trials which restricted enrolment to patients diagnosed with MDD. This suggests that in palliative patients milder depressive disorders may be responsive to antidepressant treatment. At 4–5 weeks, the MDD trials yielded the larger effect size; however, this analysis only included two trials. Inferences about the relative efficacy of MDD and milder depressive disorders should be tempered by the fact that the trials which defined depression broadly included patients with patients with MDD as well as patients with AD and dysthymia. Future research should assess the effect of antidepressants in trials which included only patients with mild depressive disorders.

Subgroup analysis by class of antidepressant indicated that both TCAs and SSRIs are superior to placebo in treating depression in the context of a life-threatening illness. The size of this effect was greater for TCAs at every time-point, and at 4–5 weeks and 6–8 weeks the effect was statistically significant for only TCAs. This tendency towards greater efficacy with TCAs is consistent with the authors’ Cochrane review of antidepressants in physical illness, which also found larger effect sizes for TCAs, particularly at the earlier time-points. The data are compatible with TCAs having an earlier onset of action than SSRIs in patients with a life-threatening physical illness. However, there are many caveats: the comparison of SSRIs and TCAs is indirect, non-randomized, and therefore vulnerable to biases and confounding; the 95% CIs for SSRIs and TCAs overlap; and the proportion of responders in the control group was lower in the TCA trials. For these reasons we do not think our findings should be used to recommend tricycles over other antidepressants, but suggest that they should not be overlooked as a treatment option. There are insufficient data to draw conclusions regarding the comparative efficacy of the new atypical antidepressants, though the three trials using mianserin or mirtazapine did show superiority over placebo.

At 9–18 weeks, the odds of withdrawing from the study were greater for patients treated with an antidepressant than for patients taking placebo, though this effect only just reached the level of statistical significance. The number needed to harm (NNH) at 9–18 weeks’ treatment was 6, meaning that approximately six patients would need to be treated with an antidepressant to produce one drop-out that would not have occurred had they been given placebo. At the earlier time-points no difference in drop-out was observed. Subgroup analysis by class of antidepressant showed little difference between the odds of drop-out in trials of SSRIs and TCAs. Dry mouth was commoner among patients treated with an antidepressant, particularly those taking a TCA. Nausea was associated with treatment with an SSRI only.

Clinical practice implications

This review indicates that antidepressants should be considered for treating depression in palliative care. The question that remains unanswered is which antidepressant clinicians should choose. There are still too few trials to determine the efficacy and acceptability of specific antidepressants for specific diseases. Whilst our results are encouraging for TCAs there are sound reasons to favour SSRIs and other second generation antidepressants and these drugs are more frequently prescribed in the last year of life. TCAs are purported to be poorly tolerated by palliative patients, yet the indirect evidence we present shows little difference in drop-outs and adverse events between the two classes of drug. Trials directly comparing TCAs and SSRIs would be needed to confirm the superior efficacy of TCAs in this population; however, we suggest that there is a greater need to assess the onset of action and acceptability of other second generation drugs such as mirtazapine, which is already widely used in palliative care and appears from multiple treatment meta-analysis to be one of the more effective newer antidepressants.

Aside from efficacy and acceptability, other issues impact upon choice of antidepressant. Some antidepressants have effects which may benefit patients with certain conditions or symptoms. For example, mirtazapine can cause sedation and increased appetite; citaprom may reduce agitation and anxiety, and tricyclic antidepressants, such as amitriptyline, have been shown to relieve neuropathic pain. Equally, some antidepressants adversely affect patients with particular conditions or symptoms. For example, tricyclic antidepressants are generally contraindicated for patients with heart disease or liver failure. TCAs also worsen the symptoms of prostatic hypertrophy (benign enlargement of the prostate, which can obstruct the urethra and impede urination). Thus, given the high prevalence of prostatic hypertrophy in older men (40% in men aged 60–69 years), tricyclic antidepressants may be inappropriate for many palliative care patients,
irrespective of their relative efficacy. In palliative care patients, who often have multiple comorbidities and medications, possible drug interactions may preclude treatment with particular antidepressants. For example, mirtazapine enhances the anticoagulant effect of warfarin, and fluoxetine interacts with selegiline, a drug widely used in the treatment of Parkinson’s disease. Toxicity in overdose is another important consideration in choosing an antidepressant. Tricyclic antidepressants pose greater risk in overdose than SSRIs, which may be a better choice for patients with suicidal ideation.92

On the basis of this review there is insufficient evidence to recommend a specific antidepressant for use in palliative care. In the absence of direct comparative data, choice of antidepressant should be based on patients’ preferences and symptoms, contraindications and potential interactions with other medication.

Limitations

In order to minimize the risk of selective outcome reporting, we included in the review only studies in which depression was the primary outcome. Nevertheless it is possible that study authors may have selectively reported outcomes at the time-point(s) at which the largest effect size was observed. Similarly, investigators may have used several rating scales to assess depression yet reported data only from the scale(s) that showed a positive effect.

There was great variation in the quality of the trials and the transparency of reporting. Many trials omitted methodological information used to assess study quality (such as randomization, allocation concealment, blinding and completeness of outcome data). Sensitivity analysis restricted to studies at low risk of bias diminished the size of the effect observed at 6–8 weeks and 9–18 weeks, suggesting that shortcomings in the design and conduct of included studies may have exaggerated the efficacy of antidepressants in this review. However, this sensitivity analysis included too few studies for firm conclusions to be drawn. Funnel plots for the efficacy analyses showed a scarcity of smaller studies showing no effect. This is indicative of publication bias, whereby small, negative studies are suppressed and not published. Few trials reported outcome data on quality of life or functional status, and variation in the assessment scales used hindered comparison between studies. Of those trials that reported the impact of antidepressants on quality of life and functional status, the majority found a positive effect. However, the results of these studies should be interpreted with caution due to the high risk of reporting bias.

The applicability of the results of this review to people with severe illness is limited due to restrictive trial inclusion criteria. Many trials excluded patients whose physical health was very poor; therefore the most unwell patients will not have been represented in this review. Our review defined palliative care broadly using the WHO definition, which is applicable early in the course of life-threatening illness. Some of the patient groups in this review are seldom seen in specialist palliative care services, which still provide mainly for advanced cancer patients. However, studies have shown that symptom prevalence and severity is similar in cancer and chronic non-malignant disease.93 The palliative care needs of non-cancer patients, and the benefits of introducing palliative care earlier in the disease trajectory, are increasingly being acknowledged.34 If this review had applied a narrower definition of palliative care encompassing end-stage patients only, it would have included far fewer studies. Three trials in COPD were included in the review, but all had small sample sizes and only one reported data amenable to meta-analysis. There were two studies in end-stage renal disease, but neither provided sufficient data to allow inclusion in the meta-analysis. Of the three cancer trials, one included primarily patients with metastatic disease,64 one excluded patients with a life expectancy of less than three months,66 and one included only women with stage I or II breast cancer.67 In the one heart failure trial included in the review, the majority of patients were New York Heart Association (NYHA) Functional Classification II, denoting only mild symptoms and slight limitation in ordinary activity. The dearth of data on antidepressants at the end of life demands that treatment decisions for this patient group be guided by research in populations with better prognosis. The role of disease severity and life expectancy in mediating responsiveness to antidepressant treatment requires further investigation.

Conclusions

This review provides evidence that antidepressants can ameliorate depressive symptoms in patients with a life-threatening illness. The NNT decreased from 9 at 4–5 weeks to 6 at 6–8 weeks and to 5 at 9–18 weeks, indicating that the effect of antidepressants increases with continued treatment. Early detection of depression in palliative care is therefore crucial, so that patients who may benefit from antidepressants receive treatment in time for it to have optimal effect. Antidepressants were reasonably well tolerated, though significantly more patients treated with an antidepressant experienced dry mouth than did patients treated with placebo. Antidepressants appear to be effective in reducing depressive symptoms in patients with milder mood disorders, such as AD and dysthymia, as well as in patients with MDD. Further research is required to
examine the threshold of severity at which antidepressants have benefit. This review found that both the main classes of antidepressant (TCAs and SSRIs) were effective in treating depression in patients with life-threatening illness. Due to problems such as selective reporting and publication, small sample sizes and the variable methodological quality of included studies, it is likely that the effect sizes obtained in this review exaggerate the efficacy of antidepressants in palliative care. Notwithstanding, the size and consistency of the effect favouring antidepressants suggests they do lessen depression in this patient group. Further trials are needed in order to determine the impact of antidepressants on function and quality of life, and the relative efficacy and acceptability of specific antidepressants in palliative care.

Contributions
LR: protocol development, data extraction, analysis of results, writing. AP: protocol development, data extraction. AE: initial development of protocol and screening of identified abstract. KV: screening of identified abstracts. MH: winning peer review funding for review as part of research programme; project supervisor – including of protocol, data extraction, analysis and writing. IH: winning peer review funding for review as part of research programme; project supervisor – including of protocol, data extraction, analysis and writing.

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