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# The development of evidence-based European guidelines on the management of depression in palliative cancer care

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## ABSTRACT

Depression is common in cancer patients, particularly those with advanced disease. It is associated with adverse outcomes such as increased pain, disability and poorer prognosis. Our aim was to produce a European evidence-based clinical guideline on the management of depression in patients receiving palliative care to inform practice, establish policy, promote European consensus and ultimately improve patient outcomes. Recommendations were devised using the best available evidence. Where evidence was absent or equivocal, Delphi consensus methods were implemented to elicit and refine expert opinion. Evidence was graded according to the process proposed by GRADE. The resulting guideline has three main sections: (1) prevention; (2) detection, diagnosis and assessment; and (3) treatment. The prevention section outlines strategies such as optimal palliative care and support, effective communication and information-giving. The detection section provides recommendations on symptoms, screening, diagnosis and severity assessment. The treatment section gives guidance on treatment decisions including choice of psychological therapy and antidepressant medication. This is the first comprehensive, evidence-based guideline on managing depression in palliative care. It has the potential to improve patient outcomes by enabling clinicians to access and implement evidence-based knowledge quickly and easily.

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## 1. Introduction

Depression is common among patients with cancer and particularly those receiving palliative care. A systematic review by Hotopf et al. in 2002 found a median prevalence of 15% for major depression in advanced disease.<sup>1</sup> Depression compounds the physical consequences of advanced disease. It is associated with disability, pain and fatigue,<sup>2–4</sup> and there is evidence that depressed patients have poorer prognosis and higher mortality in a range of physical illnesses.<sup>5–7</sup> Detecting depression in palliative care is difficult as somatic symptoms (e.g. poor appetite, sleep disturbance and fatigue) may be due

to depression, advanced disease or medical treatment.<sup>8</sup> Also, depression is difficult to distinguish from normal fear and distress,<sup>9</sup> which often accompany terminal illness. In patients with advanced disease, the coexistence of multiple symptoms makes drug interactions more likely and treatment more complicated. Though antidepressants have been shown to ease depression in physically healthy people, there is doubt about whether they are appropriate for terminally ill patients.<sup>10</sup> Psychological therapy is the other recommended treatment for depression,<sup>11,12</sup> but questions surround its feasibility, acceptability and availability in palliative care.<sup>13,14</sup>

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In 2009, the UK National Institute for Health and Clinical Excellence (NICE) published recommendations for the management of depression in people with a chronic health problem. This guideline covered primary, secondary and tertiary care but specified that palliative care was outside its remit.<sup>11</sup> Depression in palliative care poses particular challenges and clinicians need clear guidance on improving outcomes at the end of life. A pragmatic report from the European Association of Palliative Care (EAPC) in 2001 highlighted the problem of under-detection and under-treatment of depression in palliative care. This report called for collaboration between palliative care and mental health professionals and integration of clinical experience and scientific evidence in order to establish best practice.<sup>15</sup>

The European Palliative Care Research Collaborative (EPCRC) was established through the EAPC Research Network in 2006, with funding from the European Commission.<sup>16,17</sup> The collaborative brought together 11 centres in six European countries, with the aim of improving the management of cachexia, pain and depression through translational research. The scientific work within the EPCRC spans three main strands: (1) genomics, (2) symptom assessment and classification, and (3) guideline development and dissemination. Clinical practice guidelines were developed to assist palliative care professionals in managing each of the three symptoms – pain, cachexia and depression. This paper outlines the development of the EPCRC depression guideline and provides a summary of its key recommendations.

## 2. Materials and methods

The guideline was developed in accordance with the methods of the National Institute for Clinical Excellence (NICE).<sup>18</sup> Recommendations were devised using the best available evidence. Where evidence was absent or equivocal, Delphi consensus methods were implemented to elicit and refine expert opinion. The quality of evidence and the strength of recommendations were determined using the GRADE system.<sup>19</sup>

### 2.1. Scope and purpose

The guideline aimed to provide evidence-based recommendations on managing depression in palliative care to inform clinical practice, establish policy, promote European consensus and ultimately improve patient outcomes.

The patient group addressed was all patients receiving palliative care. The intended audience was all health professionals involved in the provision of palliative care.

### 2.2. Guideline development and expert groups

Two groups were constituted:

- (1) A guideline development group of seven professionals from the EPCRC consortium was appointed to coordinate the project.
- (2) An expert group was constituted to help identify clinical priorities, provide expert opinion and critically discuss and develop the guideline recommendations. It

comprised two patient representatives and 29 professionals with knowledge and experience of depression in palliative care. Expert nominations were sought via the European Association of Palliative Care (EAPC) board, the EAPC website and other palliative care associations in Europe. To capture social, cultural and disciplinary differences in practice and opinion, experts were recruited from a range of disciplines and countries.

### 2.3. Preliminary literature scoping

Preliminary scoping of EMBASE, MEDLINE and PSYCINFO was undertaken to gain an overview of the literature and identify key issues to be addressed in the guideline. In palliative care, somatic, social and psychological factors interact to precipitate, perpetuate or protect against depression. In appreciation of these complexities and the holistic principles of palliative care, we adopted an inclusive approach and sought to provide guidance on all aspects of the management of depression in palliative care. We identified three overarching themes: (1) prevention, (2) detection, diagnosis and assessment, and (3) treatment.

### 2.4. Evidence review

Systematic review of the literature relevant to each theme was impractical due to funding and time constraints. The guideline development and expert groups agreed that treatment should be prioritised, and a Cochrane review was undertaken to examine the efficacy of antidepressants in people with physical illness and those needing palliative care.<sup>20,21</sup> For other aspects of the management of depression in palliative care, only the best existing evidence was identified: thus if strong evidence (e.g. from an RCT or meta-analysis) was available to answer a specific question, weaker evidence (e.g. cross-sectional surveys, case series) was not sought and appraised.

### 2.5. Delphi study

The Delphi method was used to elicit and evaluate expert opinion on contentious issues where evidence was equivocal or absent. Delphi is a consensus technique used for problem-solving and decision-making. It is a feasible and effective method for assessing expert agreement on clinical questions and it is increasingly used in research.<sup>22</sup> We used the Delphi method to ascertain and refine expert opinion on the following contentious clinical questions:

- (1) Which symptoms are most useful in diagnosing depression in palliative care?
- (2) Which screening tool is most effective in detecting depression in palliative care?
- (3) Which psychological therapy is most appropriate for treating depression in palliative care?
- (4) Which antidepressant is most appropriate for treating depression in palliative care? Experts were requested to rate their level of agreement with proposed items on a scale from 0 to 10 and to annotate their ratings with com-

ments. The anonymised comments and median and range of ratings were reported to the experts, with a request for them to rate the items again in light of the results of the first round. The final summary scores were used to inform recommendations for the guideline.

## 2.6. Consultation

Best practice recommendations were drafted on the basis of existing evidence, and the Delphi studies and Cochrane review conducted by the guideline development group. The guideline was circulated among the expert group for comment and criticism and then published on the EPCRC website for wider consultation. National and international professional associations were contacted and requested to comment on the recommendations and forward to their members for further feedback. During the 6 month consultation period a total of 70 comments were received from 18 health professionals. Respondents were from a range of countries (United Kingdom (UK), Norway, Spain, the Netherlands, New Zealand, Canada and India) and a range of disciplines (palliative medicine, nursing, psychology, psychiatry, oncology, general practice, chaplaincy and clinical governance). Comments received during the 6-month consultation period were collated and considered by the guideline development group, who then revised and refined the recommendations in light of the feedback received.

## 2.7. Grading evidence

For each section of the guideline, the Guideline Development Group drafted evidence summaries for key recommendations. The quality of the evidence and the strength of recommendations were graded according to the process proposed by GRADE.<sup>19</sup>

## 3. Guideline content

The following section briefly summarises the guideline's key recommendations.

### 3.1. Prevention

Good palliative care is of itself a key strategy for preventing and alleviating depression at the end of life. A recent RCT published in the *New England Journal of Medicine* showed that metastatic lung cancer patients who received early palliative care had improved mood and quality of life, as compared with those receiving standard oncological care.<sup>23</sup> Palliative care integrates physical, psychological, social and spiritual care to control symptoms and distress and optimise quality of life.<sup>24,25</sup> All health professionals caring for patients with advanced disease can apply these holistic principles. However, patients with complex or multiple needs should be referred to a specialist palliative care service that can offer additional support and expertise. [Table 1](#) summarises recommendations on prevention.

#### 3.1.1. Listening and communication

There is evidence that open, effective communication promotes coping and psychological adjustment to advanced

disease. Skills such as active listening, patient-centred consulting, open-ended questioning and appropriate response to cues have been found to increase the ability of palliative care professionals to elicit emotional concerns and detect distress before depression develops.<sup>26–29</sup>

#### 3.1.2. Information

There is wide variation in the type and amount of information individuals wish to receive. It is important to determine patients' desired level of information and involvement in decisions and regularly review their preferences to capture changes that may occur at each phase of care.<sup>30,31</sup> Providing patients with appropriate information on the nature, course and treatment of their illness promotes satisfaction with care and improves psychosocial outcomes.<sup>32–35</sup> Health professionals should also advise patients about the range of support services available to them (e.g. counselling, complementary therapies and peer support and community groups).<sup>11,30,33,36</sup>

#### 3.1.3. Optimal palliative care and support

There is a strong association between depression and other symptoms common in advanced disease, such as pain and fatigue.<sup>37,38</sup> Effective assessment and treatment of patients' physical symptoms is integral to palliative care and a prerequisite for preventing and treating depression.<sup>33,39</sup> Psychosocial support is also intrinsic to palliative care. Clinicians should assess patients' ability to cope and help them to retain a sense of purpose and control – for example, by engaging in support networks (social clubs, community groups and faith groups) and staying physically active.<sup>40</sup> Such support helps patients maintain social roles and relationships, preserving self-worth and improving mood.<sup>41,42</sup> The experience of progressive incurable illness can increase spirituality<sup>43</sup> and some patients experience existential distress as death approaches.<sup>44</sup> Palliative care providers should assess patients' spiritual needs and arrange support from an appropriate spiritual advisor if desired.<sup>44,45</sup> Clinicians should also consider the needs and concerns of family members and caregivers, and where possible provide practical and psychological support.<sup>46,47</sup>

#### 3.1.4. Identification of 'at risk' groups

It is important that clinicians are aware of risk factors for depression in palliative care, such as history of depression, absence of social support, concurrent life stresses, chronic pain, poor performance status and advanced disease at diagnosis.<sup>48,49</sup> Early referral to specialist palliative care has been found to improve quality of life and mood<sup>23,50,51</sup> and may be particularly valuable for individuals identified as at risk of depression.

## 3.2. Detection, diagnosis and assessment

The high prevalence of depression in people with advanced disease attests to the need for heightened awareness and attention to depressive symptoms.<sup>1,52,53</sup> In palliative care time is often short, so early detection and diagnosis of depression and regular reassessment is imperative.<sup>54</sup> [Table 4](#) sum-

**Table 1 – Prevention of depression in palliative care: evidence and recommendation summary.**

| Prevention  | Quality of evidence  | Strength of recommendation   |
|---|--|--|
| <i>Recommendation 1</i><br>Clinicians should communicate with palliative care patients in an open, non-judgemental, patient-centred manner and actively enquire about their concerns and feelings | <i>Moderate</i><br>Consistent evidence from non-randomised studies | <i>Strong</i><br>Moderate quality evidence; low risk of harm; consistent with patient preferences and clinical opinion |
| <i>Recommendation 2</i><br>In accordance with patients' wishes, clinicians should provide information on the nature, course and treatment of their illness, and appropriate sources of support    | <i>Moderate</i><br>Consistent evidence from non-randomised studies | <i>Strong</i><br>Moderate quality evidence; low risk of harm; consistent with patient preferences and clinical opinion |
| <i>Recommendation 3</i><br>Clinicians should consider referral to specialist palliative care for improved symptom control and psychosocial support  | <i>High</i><br>Evidence from well-conducted RCTs                   | <i>Strong</i><br>High quality evidence; low risk of harm; some evidence of cost-savings                                |

marises recommendations on detection, diagnosis and assessment.

### 3.2.1. Symptoms, psychological assessment and screening

Persistent low mood, loss of interest in everyday activities, feelings of hopelessness, worthlessness or guilt and suicidal ideation are key symptoms of depression in palliative care. It is also important to be aware of non-verbal cues indicative of depression, such as slumped posture, lack of movement, flat affect and reduced emotional reactivity.<sup>55</sup> Somatic symptoms commonly associated with depression (e.g. appetite change, fatigue, sleep disturbance, psychomotor slowing and loss of libido) may be due to physical disease or treatment and are, therefore, less useful in making a diagnosis of depression in palliative care.<sup>8,53,56</sup> Clinicians should be aware of possible cultural variations (ethnic, regional, age-related) in the presentation of depression. For example, patients from groups that stigmatise depression may be more likely to present with somatised distress. A diagnosis of depression may be viewed as shameful, so sensitivity and reassurance is required.<sup>30</sup>

Clinicians should ask about mood as part of routine assessment. Patients may be more relaxed and open if depression is considered in the context of a general conversation about coping, in which they feel able to tell their story, feel heard and understood.<sup>57</sup> Assessment of depression should be accompanied by an assessment of anxiety, as these symptoms are strongly associated.<sup>11,58</sup>

There is mixed evidence on the ability of screening tools to improve depression outcomes.<sup>59,60</sup> Nevertheless, it is unlikely that screening for depression causes patients harm and many palliative care services use screening tools to aid detection of depression due to the frequency of cases in this population. Commonly used depression-specific screening tools include the Hospital Anxiety and Depression Scale (HADS),<sup>61–67</sup> the Brief Edinburgh Depression Scale (BEDS),<sup>68</sup> a two item screening tool assessing low mood and loss of interest,<sup>63,69–71</sup> and the single item 'Are you depressed?'<sup>63,70,72–74</sup> (see Table 2). Screening tools must balance validity of assessment against brevity. To avoid burdening very frail patients, clinicians should consider using a generic symptom assessment

scale that includes one or more questions about depression (e.g. the Palliative care Outcome Scale (POS)<sup>75,76</sup>).

### 3.2.2. Diagnosis and severity assessment

If depression is suspected, a clinical assessment should be undertaken. This should involve a thorough psychiatric history and an assessment of the intensity of depressive symptoms, the duration of the episode and the degree of functional impairment.<sup>11</sup> Depression should be diagnosed according to validated diagnostic criteria (e.g. DSM-IV<sup>77</sup> or ICD-10<sup>78</sup>). A standardised, validated assessment scale should be used to measure the severity of depression and monitor response to treatment. The HADS was developed to quantify depression and anxiety in medical patients. It can be used for assessment of severity and response to treatment as well as for screening and case-finding. Because the HADS was designed for use in medically ill populations it excludes somatic symptoms (e.g. sleep disturbance and poor appetite), which can confound diagnosis of depression in physically ill people. This makes it an appropriate tool for use in palliative care.<sup>64</sup> The Hamilton Depression Rating Scale (HDRS) was designed to measure the severity of depression and evaluate the efficacy of treatment.<sup>79</sup> Though this tool does include somatic symptoms, a recent study provided support for the reliability and validity of the HDRS in a large sample of terminally ill cancer patients.<sup>80</sup> The Beck Depression Inventory (BDI)<sup>81</sup> is another commonly used severity assessment scale, sensitive to change,<sup>82</sup> and validated in palliative care populations.<sup>66</sup>

It is crucial that clinicians consider alternative diagnoses for the presentation as misdiagnosis may prevent patients receiving appropriate treatment. Examples of differential diagnoses include delirium, dementia, Parkinson's disease, hypothyroidism, uncontrolled pain, cerebral metastases and adverse drug reactions. It is also important to consider contributory factors, which if addressed might alleviate the patient's depressive symptoms. Contributory factors may be biological (e.g. hypercalcaemia, uncontrolled physical symptoms, drugs causing depression – e.g. steroids), psychological (e.g. spiritual distress, anger relating to diagnostic delay) or social (e.g. family conflict, isolation, poor living conditions). Another challenge is distinguishing depressive disorder from

**Table 2 – Commonly used depression-specific screening tools.**

| Screening tool  | Sensitivity | Specificity |
|---|-------------|-------------|
| Single-item<br>'Are you depressed?'   | 0.42–0.86   | 0.74–0.92   |
| Two-item<br>'During the last month, have you been bothered by feeling down, depressed or hopeless?'<br>'During the last month, have you been bothered by having little interest or pleasure in doing things?' | 0.91–1.00   | 0.57–0.86   |
| Hospital Anxiety and Depression Scale<br>14 items, 7 for anxiety, 7 for depression. Excludes somatic symptoms   | 0.68–0.92   | 0.65–0.90   |
| The Brief Edinburgh Depression Scale<br>6 items covering guilt, insomnia, fear, sadness, inability to cope and thoughts of self-harm  | 0.72        | 0.83        |

Note: single item and two items can be found within composite outcome scales, such as the Palliative Outcome Scale or the Edmonton Symptom Assessment Schedule

**Table 3 – Characteristics of depression versus appropriate sadness.**

| Depression                                       | Sadness                                       |
|--|---|
| Feels outcast and alone                          | Able to feel intimately connected with others |
| Feeling of permanence                            | Feeling that some day this will end           |
| Regretful, rumination on 'irredeemable' mistakes | Able to enjoy happy memories                  |
| Extreme self-depreciation/self loathing          | Sense of self worth                           |
| Constant and unremitting                         | Comes in waves                                |
| No hope/interest in the future                   | Looks forward to things                       |
| Enjoys few activities                            | Retains capacity for pleasure                 |
| Suicidal thoughts/behaviour                      | Will to live                                  |

normal sadness relating to declining health and fear of death. Patients who are sad usually retain some hope for the future and still derive satisfaction from relationships. Sadness tends to fluctuate, whereas depression is more constant and characterised by self-loathing and a sense of permanence (see Table 3).

Patients who do not meet criteria for major depression may still benefit from psychological support and referral to specialist palliative care. If there is uncertainty about the diagnosis, or if the patient is severely depressed or suicidal, they should be referred to a mental health specialist. Clinicians should ask patients directly about suicidal ideation and intent and be particularly vigilant during high risk periods such as initiation of antidepressant treatment.<sup>83</sup>

### 3.3. Treatment

In physically healthy people with depression, psychological therapy and antidepressant drugs are the mainstay of treatment. In palliative care, evidence is scarcer, but there is little ground to suggest a radically different approach is required. Table 6 summarises recommendations on treatment.

#### 3.3.1. Mild, moderate, severe depression

The type and intensity of treatment provided to palliative care patients with depression depends on the duration and severity of symptoms (see Table 5).

#### 3.3.2. Short prognosis

Given the high prevalence of delirium in patients near the end of life, clinicians should first consider whether there is an organic cause for agitation and distress.<sup>84</sup> Agitation should be treated symptomatically and benzodiazepines or neuroleptics prescribed if indicated. Some clinicians report benefit from psychostimulants for depression in patients with short life expectancy. However, we do not recommend the use of psychostimulants due to there being strong evidence of adverse effects and inadequate evidence of efficacy.<sup>85</sup> For patients with short prognosis, the threshold for treatment resistant depression should be lowered from 6 weeks to 4 weeks.

#### 3.3.3. Choice of psychological therapy

Cognitive behavioural therapy (CBT) is the most widely used and evaluated psychological therapy for depression. It focuses on identifying and restructuring dysfunctional thought patterns. Randomised controlled trials have demonstrated the effectiveness of CBT in physically ill populations,<sup>86</sup> but there is still a scarcity of studies in palliative care.<sup>87–89</sup> Another therapy increasingly used in palliative care is problem-solving therapy – a short, focused intervention that helps patients work out steps to resolve specific problems occurring in their lives. Though there is limited data on the efficacy of problem-solving therapy,<sup>90</sup> its simplicity and brevity make it a popular choice in palliative care. Other therapies that may help alleviate depressive symptoms in palliative patients include interpersonal therapy, couple therapy, group therapy, guided

**Table 4 – Detection, diagnosis and severity assessment: evidence and recommendation summary.**

| Detection, diagnosis and severity assessment   | Quality of evidence   | Strength of recommendation   |
|--|---|--|
| <i>Recommendation 4</i><br>Clinicians should prioritise cognitive/affective symptoms in detecting depression as physical symptoms (e.g. weight loss, fatigue) may be caused by physical disease or medical treatment             | <i>Moderate</i><br>Consistent evidence from non-randomised studies                | <i>Strong</i><br>Moderate quality evidence; consistent with clinical opinion                   |
| <i>Recommendation 5</i><br>Clinicians should consider screening for depression in palliative care patients. Screening tools may help clinicians detect depression, but evidence that they improve depression outcomes is lacking | <i>Very low</i><br>No studies of impact on depression outcomes in palliative care | <i>Weak</i><br>Low quality evidence; cost implications unclear                                 |
| <i>Recommendation 6</i><br>The psychological state of patients receiving palliative care is unstable. Clinicians should regularly review depressive symptoms to capture changes in mood  | <i>Moderate</i><br>Consistent evidence from non-randomised studies                | <i>Strong</i><br>Moderate quality evidence; consistent with clinical opinion; low risk of harm |

imagery and mindfulness-based therapy. There is a paucity of research on psychological therapy in palliative populations and more trials are needed to strengthen the evidence-based in this context. Despite this, health professionals working in palliative care do report benefit from these interventions, and it is probable that they benefit both patients with and without progressive incurable illness.

#### 3.3.4. Choice of antidepressant

The Cochrane review we conducted showed that antidepressants are more effective than placebo in treating depressed patients with physical illness, including those with 'life-threatening' physical illness.<sup>20,21</sup> Though there is no evidence that any particular antidepressant is preferable for palliative patients, a recent meta-analysis in physically well people indicated that some second generation antidepressants are marginally more effective and better tolerated than others.<sup>91</sup> We recommend, therefore, that clinicians become familiar with two or three of the better performing antidepressants (e.g. mirtazapine, sertraline and citalopram). Tricyclic antidepressants pose greater risk in overdose than SSRIs and are often contraindicated in palliative care patients due to heart disease, liver failure or prostatic hypertrophy. However, amitriptyline and other tricyclic antidepressants are potential second-line medicines, which may be useful for patients with neuropathic pain.<sup>92</sup> Given the lack of evidence for a clearly superior antidepressant, choice of drug should be based on the type of comorbid physical illness, the patient's symptom profile, potential side-effects, interactions and contraindications, clinician familiarity and patient preference.

#### 3.3.5. Before initiating treatment

Clinicians should discuss the different treatment options with the patient and take into account their preferences and the outcome of previous treatments. Patients should be informed about potential side-effects of antidepressant drugs, discontinuation symptoms, possible delay in onset of effect, and the need to take medication as prescribed, even

after remission. If there is a high risk of suicide, a limited quantity of antidepressants should be prescribed, preferably ones which are relatively safe in overdose (e.g. SSRIs).<sup>11</sup>

#### 3.3.6. Reviewing treatment

Patients should be reviewed for side-effects in the 1st week of treatment. If adverse effects occur with antidepressant treatment, clinicians should consider discontinuing treatment or switching to a different drug. A comprehensive mood assessment should be repeated every 2 weeks using a validated scale sensitive to change over time. Patients at risk of suicide should be reviewed after 1 week.<sup>11</sup>

## 4. Discussion

The translation of research findings into systematically developed guidelines has been found to improve patient outcomes by bringing evidence-based knowledge into clinical practice.<sup>93–95</sup> The EPCRC depression guideline was developed to address the lack of guidance on managing depression in patients receiving palliative care. It draws together the most current and important evidence in the field, enabling clinicians to access and implement new knowledge quickly and easily.

This is the first comprehensive, evidence-based clinical guideline on managing depression in palliative care. The multinational nature of our expert group meant that the guideline incorporated the knowledge, expertise and experience of experts from 10 European countries. Regional variations in policy and patient care were identified within the expert group and these were debated to determine best practice. However, guideline development was led by a UK research group and as a consequence British clinicians were over-represented in the expert group. Health care organisation and models of palliative care vary considerably across Europe and there are also important differences in public and professional perceptions, terminology and treatments.<sup>96</sup> It is possible that the guideline content reflects the British

**Table 5 – Treatment of depression in palliative care.**

|  |  |
|--|--|
| <p><i>Mild depression</i><br/>Characterised by a small number of symptoms with limited impact on the patient's everyday life</p>   | <p><i>First-line treatment</i><br/>– Refer to specialist palliative care for symptom control and psychosocial support</p> <p>– Assess quality of relationships with significant others; facilitate communication</p> <p>– Consider a guided self-help programme</p> <p>– Consider a brief psychological intervention (e.g. problem-solving therapy, brief CBT)</p> <p><i>If symptoms persist...</i><br/>– Consider using an antidepressant</p> <p>– Reassess and possibly revise the diagnosis</p>                 |
| <p><i>Moderate depression</i><br/>Characterised by a larger number of symptoms which make it difficult for the patient to function as they would normally</p>  | <p><i>First-line treatment</i><br/>– Do all recommended for mild depression</p> <p>– Initiate antidepressant medication and/or psychological therapy</p> <p><i>If symptoms persist...</i><br/>– Assess compliance to treatment</p> <p>– Consider combining antidepressant treatment and psychological therapy</p> <p>– After 4 weeks of antidepressant treatment, consider raising the dose of antidepressant or switching to a different drug</p>   |
| <p><i>Severe depression</i><br/>Characterised by a large number of symptoms which make it very difficult for the patient to carry out everyday activities. There may be psychotic symptoms, food and/or fluid refusal or severe and persistent suicidal ideation</p> | <p><i>First-line treatment</i><br/>– Do all recommended for mild depression</p> <p>– Initiate antidepressants and psychological therapy</p> <p>– Consider using a hypnotic or sedative in sleep disturbed or very distressed patients</p> <p><i>If symptoms persist...</i><br/>– As for moderate depression</p> <p>– Refer to a mental health specialist</p> <p>– Lithium augmentation, electroconvulsive therapy and anti-psychotic drugs may be considered (under supervision of a mental health specialist)</p> |

**Table 6 – Treatment of depression in palliative care: evidence and recommendation summary.**

| Treatment   | Quality of evidence   | Strength of recommendation   |
|---|---|--|
| <p><i>Recommendation 7</i><br/>Clinicians should refer patients with depression to specialist palliative care for improved symptom control and psychosocial support</p> | <p><i>High</i><br/>Evidence from well-conducted RCTs</p>                                | <p><i>Strong</i><br/>High quality evidence; low risk of harm; some evidence of cost savings</p>    |
| <p><i>Recommendation 8</i><br/>Clinicians should consider antidepressants for treatment of depression in palliative care</p>  | <p><i>High</i><br/>Consistent evidence from RCTs of efficacy in treating depression</p> | <p><i>Strong</i><br/>High quality evidence; consistent with clinical opinion</p>                   |
| <p><i>Recommendation 9</i><br/>Clinicians should consider psychological therapy for treatment of depression in palliative care</p>                                      | <p><i>High</i><br/>Evidence from RCTs of efficacy in reducing depressive symptoms</p>   | <p><i>Strong</i><br/>Consistent with clinical opinion and patient preference; low risk of harm</p> |

bias in composition of the expert group and that some recommendations may be less applicable to countries with contrasting systems of care. In the main, though, the guideline promotes best practice appropriate to all European countries, irrespective of health care context and culture, and we hope it will help harmonise palliative care policy and practice across the continent.

Tension between the depth and breadth of information provided in the guideline was debated at the beginning of project when the expert group rejected the option of producing treatment guidelines in favour of a comprehensive clinical guideline that could also assist palliative care providers in preventing, detecting and assessing depression. This broad scope necessitated a pragmatic approach to reviewing relevant literature. Given finite time and funding and the large number of recommendations included in the guideline, we could not undertake a systematic literature review for each. Rather, we appraised the strongest and most relevant evidence. Thus, if strong evidence (e.g. RCT or meta-analysis) was available to answer a specific question, weaker evidence (e.g. cross-sectional surveys, case series) was not sought. Similarly, if evidence from palliative care populations existed, studies in patients with less advanced physical illness were not appraised. In addition, we conducted a systematic review on the efficacy of antidepressants for treating depression in people with physical illness generally,<sup>20</sup> and those with a life-threatening condition.<sup>21</sup> This Cochrane review showed that antidepressants are effective and acceptable for both – providing high quality, up-to-date evidence for the treatment section of the guideline.

An issue that arose during development of the guideline was how to formulate evidence-based recommendations where evidence was lacking. We found a paucity of high quality evidence on improving depression outcomes in palliative populations. Obstacles to conducting randomised controlled trials in palliative care are well documented and include ethical concerns about vulnerability and consent, and practical difficulties such as recruitment, attrition and compliance.<sup>97,98</sup> Where there was no evidence in palliative care on which to base guideline recommendations, we extrapolated data from well-conducted studies in cancer patients with less advanced disease. Many parallels exist in the experience of depression in patients receiving palliative and curative cancer care, and interventions must address the same interrelated problems of physical and emotional suffering. Moreover, there is growing advocacy for palliative care to be introduced earlier in the disease trajectory – as an adjunct to curative care rather than an alternative.<sup>23</sup> Whilst many aspects of the management of depression in palliative care can be informed by research on patients with curable disease, some are distinct and require research in patients who are terminally ill. A recent systematic review identified eight studies showing that palliative care patients are interested in participating in studies and may even benefit from doing so.<sup>99</sup> The data suggest that the views of terminally ill patients are similar to patients participating in trials in the oncology setting and call into question the special scrutiny afforded to palliative care research. Further, studies in palliative care are achieving increasingly large sample sizes, suggesting that practical limitations can also be overcome.<sup>23,53</sup>

Such developments hold promise for future studies that can address the evidence gaps identified in the EPCRC depression guideline. One research priority is to determine the optimal method of detecting depression in palliative care. Screening is advocated as a systematic and cost-effective way to improve identification of depression in this population but there is a lack of evidence supporting its efficacy.<sup>59</sup> Randomised controlled trials are needed to test the impact of screening on depression outcomes. RCTs in palliative patients are also required to address unresolved issues relating to treatment of depression at the end of life. The guideline recommends that antidepressants should be considered for treating depression in palliative care, but there were too few trials to determine a ‘first choice’ antidepressant for patients with advanced disease. Trials comparing the efficacy and acceptability of specific drugs for specific diseases are needed. Similarly, whilst there is some evidence supporting psychological therapy for treatment of depression in palliative care, there remains a dearth of data on the comparative efficacy and acceptability of different types of therapy.

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## Contributions

L.R.: coordinating guideline development – including expert group meetings, Delphi study, Cochrane review, guideline consultation, literature review, writing recommendations, grading evidence. A.P.: identifying clinical priorities, conducting Cochrane review. M.H.: winning peer review funding for project; supervision of guideline development – including expert group meetings, Delphi study, Cochrane review, guideline consultation, literature review, writing recommendations, grading evidence. I.J.H.: winning peer review funding for project, supervision of guideline development – including expert group meetings, the Delphi study, Cochrane review, guideline consultation, literature review, writing recommendations, grading evidence. All authors contributed to writing this paper. L.R. and I.J.H. are co-guarantors.

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Aaronson, The Netherlands Cancer Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St. George's University of London; Mari Lloyd Williams, University of Liverpool. Project management: Stein Kaasa, Ola Dale and Dagny F. Haugen, NTNU.

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### Conflict of interest statement

M.H. is an independent expert witness (instructed by the claimants' solicitor) in a group litigation on the potential for paroxetine to cause adverse events on withdrawal of treatment. L.R., A.P. and I.J.H. do not have any competing interests. No competing interests were declared by the members of the expert group.

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