The Management of Depression in Palliative Care

EUROPEAN CLINICAL GUIDELINES

Developed on behalf of the European Palliative Care Research Collaborative

DISCLAIMER

This guideline was produced after carefully considering the available evidence and evaluating the opinion of experts with specialist knowledge and experience. Every effort has been made to ensure the accuracy of this text. Nevertheless, the recommendations contained in the guideline reflect the judgment of the EPCRC guideline development group and expert panel. The guideline should be taken into account when making clinical decisions, but it does not override the individual responsibility of healthcare professionals to make decisions appropriate to their local context and the circumstances of individual patients. The authors do not assume any legal liability or responsibility for the accuracy or completeness of any information herein disclosed.

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Competing interests

MH 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. LR, AP and IH do not have any competing interests. No competing interests were declared by the members of the expert group.

Contents

Executive summary

Background

- Depression is common in palliative care. As well as causing emotional suffering, depression is associated with increased pain and fatigue, reduced treatment adherence, poorer prognosis and higher mortality in a range of physical illnesses.

Aim

- To produce a European clinical guideline for the management of depression in palliative care, to inform clinical practice, establish policy, promote European consensus and ultimately improve patient outcomes.

Guideline development

- 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 guideline was developed in accordance with the methods of the National Institute for Clinical Excellence (NICE).

Recommendations

1. Prevention

Good palliative care is of itself a key strategy for preventing depression at the end of life. Palliative care integrates physical, psychological, social and spiritual care to control symptoms and distress and optimise quality of life.

- Communication is crucial. Listen to patients' problems, preferences, questions and concerns.
- Provide appropriate information according to patients' wishes.
- Assess and manage patients' physical symptoms (e.g. pain, breathlessness, fatigue).
- Provide psychosocial support and facilitate coping strategies (e.g. staying active, maintaining support networks).
- Identify patients at high risk of depression, provide additional support and monitor closely.
- Refer patients with complex needs to a specialist palliative care service that can offer additional
  support and expertise

2. Detection, diagnosis and assessment

The high prevalence of depression in palliative care attests to the need for heightened awareness and attention to depressive symptoms. Detecting depression in palliative care is particularly challenging as somatic symptoms, such as fatigue and insomnia, may be due to depression, advanced disease or medical treatment. Also, depression in palliative care is difficult to distinguish from normal fear and sadness which often accompany terminal illness.

- Low mood, loss of interest, hopelessness and suicidal ideation are key symptoms of depression.
- Discuss mood as part of the patient's routine symptom assessment.
- Validity of assessment must be balanced against brevity so as not to burden frail patients.

- Screening tools (e.g. the HADS) are helpful in detecting depression.
- However, screening is not diagnostic. If depression is suspected undertake a clinical interview
- Diagnose depression according to standardised, validated diagnostic criteria (e.g. DSM-IV).
- Assess the number, severity, context and duration of symptoms, and the degree of functional impairment.
- Consider alternative diagnoses (e.g. delirium, dementia, drug reactions, hypothyroidism).
- Consider contributory factors (e.g. pain, financial difficulties, family conflict, social isolation).
- Use a validated assessment scale to measure severity of depression and response to treatment.
- Assess and sensitively explore suicidal thoughts, plans and access to means.
- If the patient is severely depressed or the diagnosis is uncertain, refer to a mental health specialist.

3. Treatment

In patients with depression without physical disease, psychological therapy and antidepressant drugs are the mainstay of treatment. In palliative care evidence is scarce, but there is little ground to suggest a radically different approach is required. Important issues to consider include; the patient's diagnosis, prognosis, symptoms, possible contraindications and personal preferences.

- For mild depression provide good palliative care, consider guided self-help or a brief psychological intervention, facilitate effective communication and social support.
- For moderate depression also commence antidepressant or psychological therapy.
- For severe depression also manage suicide risk and refer to a mental health specialist.
- For treatment resistant depression, provide antidepressants and psychological therapy, assess compliance; refer to a mental health specialist who can consider other options.

- Provide patients with information about all treatment options.
- Listen to patients' preferences and consider the experience and outcome of previous treatment.
- Consider patients' likely life expectancy and the time required for treatment to be effective.
- Review the patient for side effects in the first week of antidepressant treatment.
- Repeat assessment of mood every 2 weeks to monitor response to treatment.

- Cognitive Behavioural Therapy (CBT) focuses on identifying and restructuring dysfunctional thought patterns. It is the most widely used and evaluated psychological therapy.
- Problem-solving therapy is a short, focused intervention that helps patients identify, discuss and resolve specific problems. Its brevity makes it a good choice for palliative patients.
- Other therapies (e.g. interpersonal therapy, couple therapy, group therapy, mindfulness-based therapy) may be beneficial for patients with advanced disease, but the evidence-base is limited.
- Psychological therapies are usually delivered over a period of 6-8 weeks. In palliative care, brief
  interventions may be preferable due to the poor prognosis and frailty of patients.
- Creative therapies (e.g. music and art therapy) may benefit palliative patients by supporting emotional and spiritual expression and promoting relaxation, pain control and wellbeing.

- There is no strong evidence indicating that any one antidepressant is preferable over others.
- Choice of antidepressant should be guided by patient preference, symptoms, contraindications and side effects (including those that may be beneficial).
- Studies suggest mirtazapine, sertraline and citalopram are among the most effective and well tolerated antidepressants, and these may be good choices for palliative care patients.
- Tricyclic antidepressants may be helpful for patients with neuropathic pain

- Consider drug interactions and contraindications in light of the patient's physical disease and concurrent medication; refer to national prescribing guidelines.

Background

Depression is common in palliative care. Prevalence estimates indicate that about 15% of palliative care patients meet criteria for major depressive disorder and many more experience depressive symptoms (1). Depression compounds the physical consequences of advanced disease. It is associated with disability, pain and fatigue (2-4), and there is evidence that depressed patients have poorer prognosis and higher mortality in a range of physical illnesses (5-7). 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 (8). Also, depression is difficult to distinguish from normal fear and distress (9), which often accompany terminal illness. In patients with advanced disease, the coexistence of multiple symptoms makes drug interactions more likely and treatment more complicated.

In 2009, the 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 (10). 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 (11).

The European Palliative Care Research Collaborative (EPCRC) was established through the EAPC Research Network in 2006, with funding from the European Commission (12). 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. This clinical practice guideline was developed on behalf of the EPCRC to assist health professionals in managing depression in palliative care.

Guideline development

1 Scope and purpose

1.1 Overall objective

- To produce a European clinical guideline for the management of depression in palliative care, on behalf of the European Palliative Care Research Collaborative (http://www.epcrc.org). The guideline will provide evidence-based recommendations on managing depression in palliative care to inform clinical practice, establish policy, promote European consensus and improve patient outcomes.

1.2 The patient group

- Patients receiving palliative care.

1.3 The target audience

- All health professionals involved in the provision of palliative care.

1.4 Rigour of development

- A Guideline Development Group was constituted, comprising clinicians and researchers based at King's College London. This group was responsible for coordinating guideline development and writing the guideline.

- An Expert Group was constituted to help identify clinical priorities, offer opinion and critically discuss and develop the guideline. The Expert Group was multi-national and multi-disciplinary, including patient representatives and professionals from palliative care, clinical psychology, psychiatry, general practice, psychiatric pharmacy, social work, oncology and chaplaincy. Key clinical questions considered important to patients and clinicians were identified by the Expert Group to define the scope of the guideline.

- Evidence for these guidelines was provided by review of the Cochrane Library, Medline, PubMed, Embase and other guidelines.

- A Cochrane review of antidepressants for depression in physical illness and a systematic review of antidepressants for depression in palliative care were conducted by the Guideline Development Group to inform the guideline recommendations.

- The Delphi Method was used to ascertain and refine expert opinion on contentious aspects of clinical practice.

- During a six month consultation period, national and international professional associations were contacted and requested to forward the recommendations to their members for comment. The guideline was then revised in light of the feedback provided.

- For each section of the guideline (prevention, assessment, treatment) the Guideline Development Group drafted evidence summaries for key recommendations. The quality of evidence and the strength of recommendations were graded according to the process proposed by GRADE (see appendix) (13).

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Recommendations

1 Prevention

Good palliative care is of itself a key strategy for preventing depression at the end of life. All patients should be able to benefit from the palliative care approach which integrates physical, psychological, social and spiritual care to control symptoms and distress and optimise quality of life. All health professionals involved in the provision of palliative care can apply these holistic principles. However, many patients who have complex or multiple needs will require referral to a specialist in palliative care with additional knowledge and expertise. Communication is crucial - between services, between health professionals, between patients and health professionals, and between patients and their families. Actively listening, empathizing and asking open-ended questions encourage patients to express their problems and preferences, in turn enabling health professionals to provide appropriate and effective information and support. Effective assessment and control of physical symptoms, such as pain and fatigue, is integral to palliative care and a prerequisite for preventing depression. It is important that clinicians are aware of risk factors for depression in palliative care, such as lack of social support and poor performance status. Identifying patients 'at risk' facilitates increased psychosocial support and sensitivity to the symptoms and signs of depression.

1.1 Listening and communication

- Listen to patients' problems, preferences, questions and concerns. Hear their story (14-16).
- Determine their desired level of information and involvement in treatment decisions (16, 17).
- In accordance with patients' wishes, discuss the disease and care plan and involve them in treatment decisions (16, 18).
- Communicate in an open, engaging and non-judgmental manner (15, 16, 19-22).
- Avoid using clinical language or jargon without explanation (23).
- Assess the quality of relationships with significant others, family roles, conflicts, and how these have changed as a result of the illness. Facilitate communication between family members (24, 25).
- Ask patients about their needs at key stages, including upon diagnosis and at the beginning and end of treatment (10, 26).
- If patients wish, discuss and where possible support, their preferences about place of care and death (27).
- Ensure discussions take place in settings in which the confidentiality, privacy and dignity of the patient are respected (10, 28).
- There should be close collaboration between primary and secondary physical health services, palliative care and mental health services, where appropriate (10, 11, 27, 28).
- Ensure patients are aware of ongoing communication and collaboration within the

multidisciplinary team.

1.2 Information

- Provide patients and their families with information on the nature, course and treatment of their illness, and the use and side effects of medication (10, 18, 22, 27, 29, 30).

- There is wide variation in the amount and type of information patients wish to receive, and individual preferences may change over time. Review patients' desire for information at each phase of care (31).

- Provide information in the appropriate language and audio format if possible (31).

- Discuss this information in light of patients' individual circumstances (27).

- Inform patients about the range of local support available to them – which may include counselling, telephone helplines, self-help organizations and complementary therapies (31, 32).

- Advise patients and their families where to seek financial and practical support (e.g. advice on housing and employment issues, state benefits, mobility (e.g. disabled parking), help with personal care, cleaning and shopping) (27, 28, 31).

- Inform patients about self help, peer support and community groups (including religious/ spiritual groups) available to them (10, 27, 31, 32).

1.3 Optimal palliative care and support

- Ensure that patients' physical symptoms (e.g. pain, fatigue, breathlessness) are being assessed and managed effectively (10, 31).

- Take account of psychosocial needs as well as physical ones (33-35).

- Consider referral to specialist palliative care for symptom control, physical, emotional, social and spiritual support, as early referral may reduce depression and improve quality of life (36-38).

- Address potential deficits in social support which might be present in patients whose disabilities could impair opportunities to socialize (e.g. dysphasic, deaf, poor mobility) (35).

- Assess patients' coping strategies. Where necessary, facilitate the development of new effective strategies to help them regain a sense of control (e.g. staying active, taking a walk, engaging in social relationships, finding meaning in events) (24, 25, 39) .

- People facing advanced disease may withdraw from previously helpful support networks and activities. Encourage patients to draw on previous social and cultural networks (e.g. community group, faith groups, social clubs).

- The experience of progressive incurable illness can increase spirituality (40) and some patients experience existential distress as death approaches (41). Assess patients' spiritual needs and arrange support from an appropriate spiritual advisor (e.g. chaplain) if desired (42-44).

- Caring for a person with advanced disease can be physically and emotionally stressful. Be aware of the needs and concerns of family members and caregivers, and where possible provide psychological and practical support (45-47).

1.4 Identification of "at risk groups"

- Risk factors for depression in palliative care:

Personal or family history of depression (48, 49)
Concurrent life stresses (e.g. recent bereavement) (50)
Absence of social support (51, 52)
Younger age (53, 54)
Patients with advanced disease at diagnosis (54)
Poorly controlled symptoms (24, 55)
Poor performance status or physical disabilities (54)

- If a patient is at high risk of depression, intensify support given (e.g. refer to specialist palliative care (38)), monitor closely and consider psychological intervention (35, 56).

Prevention: evidence and recommendation summary

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

2 Detection, diagnosis & assessment

Given the prevalence of depression in palliative care, it is advisable to attempt to identify cases in all patients. Some health professionals use a depression screening tool to do this; others ask patients about mood as part of a general symptom assessment. There is mixed evidence on the ability of screening tools to improve patient outcomes. However, it is unlikely that screening for depression will cause patients harm, and due to the frequency of depression in this population, many palliative care services do screen patients. In introducing screening, it is important to ensure that clinicians are able to perform competent clinical assessment, treatment and referral as appropriate. Validity of assessment must be balanced against brevity, so as not to burden frail patients with prolonged questioning. Diagnosing depression in palliative care is challenging. Depression is particularly difficult to differentiate from normal distress in this population, as advanced disease often invokes fear, sadness or spiritual distress. Health professionals must balance the risk of medicalising normal distress with the risk of under-detecting and under-treating depression. A further challenge is that the somatic symptoms of depression (e.g. fatigue, insomnia, poor appetite) mimic those of advanced disease, making it difficult to determine whether such symptoms are due to depression or physical illness. In addition, there are a number of differential diagnoses which can be confused with depression. Misdiagnosis may cause the underlying problem to be overlooked and prevent the patient receiving adequate treatment. If there is any doubt about the diagnosis, assessment should be undertaken by an experienced psychiatrist.

2.1 Signs & symptoms

- The high prevalence of depression in palliative care attests to the need for heightened awareness and attention to patients' mood (1, 57, 58).

- Typical presentations which should lead to an assessment of depression (59):

Persistent low mood, tearfulness and distress
Loss of interest or pleasure in daily activities, social withdrawal
Feelings of hopelessness, helplessness, worthlessness or guilt
Suicidal thoughts, plans or actions, including requests for physician assisted suicide/ euthanasia

- Physical symptoms commonly associated with depression (e.g. appetite/ weight change, changes in sleep pattern, loss of energy, fatigue, psychomotor slowing, loss of libido, diminished concentration, intractable physical symptoms or symptoms disproportionate to the degree of disease) may be due to physical illness or treatment, and are therefore less useful in making a diagnosis (8, 55, 59, 60).

- Be aware of non-verbal cues (e.g. dejected demeanour, slumped posture, lack of movement, flat affect and reduced emotional reactivity) (21, 61).

- 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 (31).

2.2 Psychological assessment and screening

- Clinicians should be comfortable asking about mood as part of a routine assessment. Patients may be more relaxed and open if depression is considered in the context of a general conversation about symptoms, coping and well-being (62).

- Depression is strongly associated with anxiety, so assessment of depression should include an assessment of anxiety (10, 25). This should take into account affective symptoms (e.g. fear, dread), physical symptoms (e.g. breathlessness) and behavioural consequences (e.g. avoidance).

- Active listening (eye contact, attentive posture, summarising/ clarifying what patients have said, conveying empathy and interest) encourages patients to disclose feelings/ concerns (63).

- Listen not just for symptoms and signs, but let patients tell their story and feel heard and understood (14).

- Informal caregivers can play an important role in detecting depression. Ask patients' family members or carers about their mood (31).

- Consider screening for depression among people with advanced cancer and patients receiving palliative care (64, 65).

- Screening tools may be helpful in detecting possible cases of depression, but evidence that they improve depression outcomes is lacking (66). Screening tools are not diagnostic in confirming caseness and should not be used as a substitute for the clinical interview (62, 64).

- Screening should always be complemented by training and a comprehensive management strategy (62, 67, 68).

- Commonly used depression specific screening tools:

Screening tool	**Sensitivity**	**Specificity**
Single-item "Are you depressed?" (69-73)	0.42-0.86	0.74-0.92
Two-item "During the last month, have you been bothered by feeling down, depressed or hopeless?" "During the last month, have you been bothered by having little interest or pleasure in doing things?" (71, 72, 74, 75)	0.91-1.00	0.57-0.86
Hospital Anxiety and Depression Scale (HADS) (72, 76-81) 14 items, 7 for anxiety, 7 for depression. Excludes somatic symptoms.	0.68-0.92	0.65-0.90
The Brief Edinburgh Depression Scale (BEDS) (82) 6 items covering guilt, insomnia, fear, sadness, inability to cope and thoughts of self-harm.	0.72	0.83

- To avoid burdening patients, consider using a generic symptom assessment scale that includes one or more questions on mood and/ or depression (e.g. the Edmonton Symptom Assessment Scale (ESAS) (83) the Palliative care Outcome Scale (POS) (84-86), or an overall quality of life scale (e.g. EORTC QLQ) (87). If the patient's response indicates depression, consider also using a depression specific screening tool or assessment scale.

- Some screening tools, such as the HADS (77), can be used to assess the severity of depression and monitor change over time (see 2.4). This can be beneficial as it avoids the need to use two different tools for screening and assessment (88).

- For patients with communication difficulties (e.g. sensory impairment, learning difficulties) consider using the Distress Thermometer (89), and asking relatives or carers about their symptoms (10).

2.3 Diagnosis

- If depression is suspected, undertake a clinical assessment.

- This should involve assessment of the severity of symptoms, the duration of the episode and the degree of impairment (10).

- Take a thorough psychiatric history. It should not be assumed that this is the first episode of depression, precipitated by being terminally ill. Patients with a history of depression are much more likely to have a further episode. Information about previous episodes of depression and previous treatments should be sought (10).

- Diagnose depression according to recognised diagnostic criteria (e.g. DSM-IV (90) or ICD-10 (91)) See Appendix.

- Example questions for clinical interview:

Low mood	Things have obviously been pretty tough for you lately. Have you felt down or depressed? Is that all the time, or does it come and go? How long does it last?
Anhedonia	Have you lost interest in your usual activities? Do you get less pleasure in things you used to enjoy? Are there any activities you enjoy doing now?
Sleep disturbance	How have you been sleeping? How does that compare to your normal sleep?
Appetite or weight change	Has there been any change in your weight or appetite?
Decreased energy/ fatigue	Have you been feeling particularly tired? Have you noticed a change in your energy levels?
Increased or decreased psychomotor activity	Have you been feeling fidgety or having trouble sitting still? Have you felt slowed down, like you were moving in slow motion or stuck in mud?
Decreased concentration	Have you been having trouble concentrating? Is it harder to make decisions than before?
Guilt or feelings of worthlessness	Are you feeling guilty or blaming yourself for things? Do you feel valued by the people in your life?
Suicidal ideation	Have you felt that life is not worth living? Do you want to go to sleep and not wake up? Have you actively planned to harm yourself?
Impairment	It sounds like you've been feeling pretty low: Is it a big problem for you? How difficult have these symptoms made it for you to get

	along with other people/ take care of things at home? Have these symptoms affected your home life?
Duration of symptoms	How long have you been feeling this way? - more than 2 weeks; more than a month?
Frequency/ stability of symptoms	Does it come and go, or do you feel this way all the time? Do you feel this way all of the time/ most of the time/ some of the time?
Psychiatric History	Have you ever had medication or therapy for your mood? Have you ever deliberately harmed yourself?

- Consider **alternative diagnoses** for the clinical presentation. These may require a different response.

  Examples of differential diagnoses are:

Delirium (may cause affective changes, agitation or withdrawal. Differentiating features include clouded consciousness, incoherent speech and involuntary movements) (92, 93).
Dementia (often associated with changes in mood and motivation. Distinguishing features include dysphasia, poor orientation and memory deficits) (92).
Ongoing physical symptoms (can cause intense distress that may be mistaken for depression, which is ameliorated when symptoms are addressed) (55).
Adverse drug reactions (depressed mood is a recognised side effect of many drugs, including steroids, and may be associated with opioid toxicity. Depressed mood may also result from harmful alcohol/ substance use or drug withdrawal (e.g. corticosteroids and alcohol). A thorough alcohol and drug history is essential (94).
Space occupying lesion (e.g. cerebral metastases) (95).
Drug induced parkinsonism causing reduced facial expression (96).
Other psychiatric disorders (e.g. psychotic disorders, anxiety disorder).
Other physical illnesses can present with depression-like symptoms (e.g. hypothyroidism, Parkinson's disease).

- Identification of an alternative explanation for the presentation may lead to the diagnosis of depression being rejected. For example, if the apparent depressive presentation is caused by hypoactive delirium, then antidepressants are best avoided. In other cases (e.g. in patients with cerebral metastases) it may be less clear that disease completely explains the depressive symptoms and treatment of depression might still go ahead.

- If there is uncertainty about the diagnosis, refer the patient to a mental health specialist.

- Consider **contributory factors**, which if addressed, may alleviate depressive symptoms.

  Examples of contributory factors include:

Biological contributory factors
Uncontrolled physical symptoms (e.g. pain)
Drugs causing or contributing to depression (e.g. steroids)
Metabolic factors contributing to or causing depression (e.g. hypercalcaemia)
Psychological contributory factors
Lack of information related to diagnosis, prognosis etc.

Anger or blame related to diagnosis, diagnostic delay etc.
Fears and preoccupation related to prognosis, fears of dying and fear of symptoms leading up to death
Concerns for the welfare of relatives after death
Recent bereavement or other losses
Existential or spiritual distress
Social contributory factors
Family conflict
Social isolation
Poor living conditions
Financial difficulties
Loss of function, roles, relationships
Concerns about place of care/ death

- These are common difficulties which contribute to depression in many patients with advanced disease. Addressing these is a core component of palliative care and central to the management of depression in this context.

- In palliative care, it is particularly difficult to distinguish depression from normal sadness relating to declining health and fear of death.

- Characteristics of depression vs. appropriate sadness (24):

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

- Take into account the patient's personality, family circumstances and history of illness and coping.

- Be mindful of recent life events/ losses which may contribute to low mood (9).

- Patients who are sad or distressed but do not meet criteria for depressive disorder may well benefit from support, information, specialist palliative care referral and psychological interventions (as for Prevention 1.1-1.4 and 3.1).

2.4 Severity assessment scales

- For patients in whom depression is suspected, use a validated assessment scale to measure the severity of depression and response to treatment (10).
- Assessment tools should be introduced with appropriate explanation and consent, as for any other assessment or procedure.
- Frequent reassessment is necessary because the psychological state of palliative care patients fluctuates (49, 55).
- Commonly used severity assessment scales include the Beck Depression Inventory (BDI) (21 items) (80, 81, 97-99), the Hamilton Depression Rating Scale (HDRS) (17 items) (81, 100, 101), and the Hospital Anxiety and Depression Scale (HADS) (14 items, 7 for anxiety, 7 for depression) (72, 76-81).

2.5 Suicide risk

- Ask patients with psychological distress directly about suicidal ideas and intent (10).
- Be particularly vigilant during high risk periods such as during initiation of and changes to medication and increased personal stress (10, 102).
- Assess whether patients with suicidal thoughts have adequate social support and appropriate sources of help (10).
- Ensure that patients have limited access to means (e.g. potentially harmful medication such as opiates or sharp objects) (10).
- If an antidepressant is prescribed take into account risk in overdose (10).
- Where patients present immediate risk to themselves, arrange urgent referral to a specialist mental health service (10).
- Ensure patients are aware of locally available services and have access to out of hours support (e.g. a 24 hour helpline/ palliative care on call).
- Consider hospitalisation.

2.6 Refer to mental health specialist if:

- If there is uncertainty about the diagnosis of depression (103).
- There is a past history of complex psychiatric disorder (103).
- The patient has severe or psychotic depression (19).
- The patient shows signs of suicidal ideation or intent (which might trigger emergency referral) (24).
- Depression is interfering with the patient's decisional capacity.
- The patient presents a risk to others.

- The patient does not respond to treatment (19).

Detection, diagnosis & assessment: evidence and recommendation summary

Detection, diagnosis and severity assessment:	Quality of evidence	Strength of recommendation
Recommendation 4 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.	**Moderate** Consistent evidence from non-randomised studies	**Strong** Moderate quality evidence; consistent with clinical opinion
Recommendation 5 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.	**Very low** No studies of impact on depression outcomes in palliative care	**Weak** Low quality evidence; cost implications unclear
Recommendation 6 The psychological state of patients receiving palliative care is unstable. Clinicians should regularly review depressive symptoms to capture changes in mood.	**Moderate** Consistent evidence from non-randomised studies	**Strong** Moderate quality evidence; consistent with clinical opinion; low risk of harm

3 Treatment

In patients with depression without physical disease, psychological therapy and antidepressant drugs are the mainstay of treatment. In palliative care, evidence is scarce, but there is little ground to suggest a radically different approach is necessary. Patients with severe or treatment resistant depression should be referred to a mental health specialist, and additional interventions should be considered (see 3.4). All treatment options should be discussed with patients in accordance with their wishes. If a course of antidepressant treatment is planned, contraindications and possible side effects should be considered and discussed (including those that may be beneficial). Response to treatment and side effects must be monitored regularly.

3.1 Mild depression

(characterised by a small number of symptoms that have a limited impact on the person's everyday life) (see appendix)).

First-line treatment:
Provide good palliative care; consider referral to specialist palliative care (38)
Assess quality of relationships with significant others. Facilitate communication between family members (31)
Consider a guided self-help programme that consists of provision of appropriate written materials and support (10, 27, 50)
Consider a brief psychological intervention (brief CBT, problem-solving therapy, counselling) (56, 104-106)
If symptoms persist (or the patient has a history of moderate/ severe depression)**:**
Where mild depression persists after other intervention, consider use of an antidepressant
Reassess the patient, possibly revise the diagnosis

3.2 Moderate depression

(characterised by a larger number of symptoms which make it difficult for the person to function as they would normally (see appendix)).

First-line treatment:
Do all recommended as first-line treatment in 3.1
Antidepressant medication (107, 108) and/ or CBT (109)
Given the lack of evidence indicating a clearly superior approach for moderate depression (110), treatment decisions should be based on patient and clinician preference
If symptoms persist:
Assess compliance to treatment
If the patient has taken the antidepressant as prescribed, but has not responded to treatment after 6

weeks, consider gradually increasing the dose (if there are no significant side effects), or switching to a different antidepressant of the same or different class. If switching antidepressants, be aware of potential interactions between antidepressants (111)
Consider combining antidepressant treatment and psychological therapy (112)
Reassess the patient's psychosocial environment, e.g. family/marital relationships

3.3 Severe depression

(characterised by a large number of symptoms which make it very difficult for the person to carry out everyday activities. There may be psychotic symptoms, food or fluid refusal or severe and persistent suicidal ideation (see appendix)).

First-line treatment:
Do all recommended as first-line treatment in 3.1
Antidepressant medication and psychological therapy (112, 113)
Refer to mental health specialist (103)
Manage suicide risk
Consider using a hypnotic or sedative in sleep disturbed or very distressed patients
For patients with severe agitation or anxiety, additional treatment with benzodiazepines is an option, though with long-term use there may be a risk of cognitive impairment and dependence. Consider using medication with a long half-life (e.g. diazepam) (114)
If symptoms persist :
Assess compliance to treatment
Consider switching to a different antidepressant of the same or different class, or adding another antidepressant (111, 115)
For patients with psychotic depression, consider treating with anti-psychotics as well as antidepressants
Under the supervision of a mental health specialist, lithium augmentation (116) or electroconvulsive therapy may be considered (117)

3.4 Treatment resistant depression

(characterised by depression which has not responded to at least one course of antidepressant given at full dose for at least 6 weeks).

Assess compliance to treatment
Refer to a mental health specialist who can consider a wider range of treatment options (103)
Consider switching antidepressant or adding another antidepressant (e.g. mirtazapine and venlafaxine) (111, 115)
Under the supervision of a mental health specialist, lithium augmentation (116) or electroconvulsive therapy may be considered (117)

3.5 Short prognosis

Given the high prevalence of delirium in patients with short prognosis, consider first if there is an organic cause for agitation and distress. Treat agitation symptomatically; consider use of benzodiazepines or neuroleptics
Some clinicians report benefit from using psychostimulants in depressed patients with a short life expectancy. However there is evidence of significant adverse effects and insufficient evidence of efficacy to recommend psychostimulants for treatment of depression (118)
For patients with short prognosis, the threshold for treatment resistant depression should be lowered to 4 weeks

3.6 Before starting treatment:

- Give patients and carers appropriate information on the nature of depression and the different treatment options. Keep use of technical language to a minimum (see 1.1, 1.2) (15, 18).
- Listen to patients' preferences and consider the experience and outcome of previous treatment/s.
- Consider the likely prognosis and time required for treatment to be effective.
- Conduct a baseline severity assessment using an appropriate validated measure of depression (see 2.4).
- Where patients have some depressive symptoms but do not reach the threshold for diagnosis of Major Depressive Disorder, it is reasonable to provide general palliative care, without starting specific treatments for depression (see 1.3 & 3.1). Such patients should be monitored and reassessed regularly.
- There should be close collaboration and regular communication between primary and secondary physical health services, palliative care and mental health services, where appropriate (119, 120) .
- Ensure patients are aware of ongoing communication and collaboration within the multidisciplinary team (31).
- Establish a clear agreement between all professionals on the responsibility for monitoring and treatment; this should be shared with patients and their families (see 1.1) (10).
- Health professionals should be trained in delivering psychotherapeutic interventions. Those less experienced should receive regular supervision (121, 122).

3.7 Reviewing treatment

- Review patients for side effects in the first week of treatment. If adverse effects occur with antidepressant treatment, consider discontinuing treatment or changing to a different antidepressant, in accordance with patients' wishes. Consider other treatment options, such as psychological therapy.
- Repeat assessment of mood every 2 weeks.

- Patients started on antidepressants who are considered to be at risk of suicide should be reviewed after 1 week.

- Use a validated assessment scale to monitor outcome and measure change over time (see 2.3).

- Ensure that patients are involved in reviewing the efficacy of the treatment (31).

- Monitor adherence to treatment.

- Monitor for signs of restlessness (akathisia), suicidal ideas, and increased anxiety and agitation, particularly in the early stages of treatment with a selective serotonin reuptake inhibitor (SSRI). If patients become agitated following treatment with an SSRI, consider changing their antidepressant or a brief period of concomitant treatment with a benzodiazepine, followed by review (123).

3.8 Psychological therapy

- Psychological therapy is usually patients' preferred strategy for treating depression.

- There is evidence from randomised controlled trials (RCTs) that psychotherapy is useful for treating depressive states in patients with advanced disease (124, 125).

- Most psychological therapies are typically delivered over a period of 6 to 8 weeks. In palliative care, brief interventions may be preferable for many patients due to their physical health status or poor prognosis.

- RCT evidence suggests that non-mental health specialists can be trained to deliver psychological therapy (121, 122).

- Ensure that healthcare professionals providing psychological treatment are competent in the delivery of the treatment and receive regular supervision (122).

- Psychological interventions should be based on the relevant treatment manual.

3.8.1 Cognitive Behavioural Therapy (CBT)

- Cognitive Behavioural Therapy (CBT) is the most widely used and widely evaluated psychological therapy for depression.

- CBT focuses on identifying and restructuring dysfunctional thought patterns. It helps patients identify those thought patterns that trigger emotional distress, and then change these to be more realistic and constructive.

- Though there is a scarcity of studies in palliative care populations (126, 127), RCTs have demonstrated the effectiveness of CBT in physically ill people (109).

- There is evidence that CBT in palliative care can improve some outcomes (121, 124).

3.8.2 Problem-solving therapy

- Problem-solving therapy is a short, focused intervention that helps patients cope with problems they are facing in their lives.
- Together patient and clinician identify a specific problem occurring in the patient's life, discuss possible solutions, choose a strategy and work out the steps to resolution of the problem.
- Though there is limited data on the effectiveness of problem-solving therapy (128), its simplicity and brevity make it a popular choice for palliative care patients.

3.8.3 Other therapies with possible psychological benefits

Interpersonal therapy	Brief therapy focusing on the patient's personal relationships and interactions with others. Interpersonal therapy has been shown to be an effective treatment for depression (129), and there is some evidence that it decreases depressive symptoms in cancer patients (130).
Couple therapy	The patient's relationship with their partner is the focus of attention. There is some evidence of efficacy in reducing depressive symptoms in cancer patients (131). May be first-line treatment in patients with obvious relationship difficulties.
Group therapy	Places emphasis on sharing of feelings and experiences among patients with a comparable stage of disease. There is some evidence of efficacy in metastatic breast cancer patients (132). Therapy is prolonged, therefore may not be suitable for end-stage patients.
Guided imagery	Use of the mental imagery to invoke senses and feelings that bring a sense of calmness and empowerment. There is limited evidence indicating that guided imagery may improve emotional well-being in cancer patients but more research is needed (133).
Dignity therapy	An intervention aimed to help bolster patients' sense of meaning and purpose at the end of life, but contraindicated in patients with severe depression (134, 135).
Mindfulness-based therapy	There is some evidence that mindfulness-based therapy can improve the psychological well-being of cancer and palliative care patients (136).

3.8.4 Complementary therapies with possible psychological benefits

Creative therapies (e.g. music, art therapy)	May benefit palliative care patients by supporting emotional and spiritual expression, and promoting relaxation, pain control and a sense of well-being. There is evidence that art therapy reduces depressive symptoms

	in cancer patients (137). Music therapy is also associated with improvements in mood and is popular in palliative care (138, 139).
Massage therapy	A systematic review of RCTs found no robust evidence to support massage therapy for treatment of depression (140). However an RCT of aromatherapy massage showed short-term improvement in cancer patients' mood (141).
Acupuncture	A recent Cochrane review found insufficient evidence to recommend acupuncture for depression (142), though previous systematic reviews have shown benefit (143).

3.9 Antidepressant treatment

- There is strong evidence that antidepressants are effective in treating depression in people with a life-threatening physical illness (108).

- Before starting treatment with an antidepressant:

Consider possible interactions and contraindications (see 3.9.3) (10).
Discuss possible side effects with patients before initiating treatment (see 3.9.2) (18). Explain that side effects may occur before there is any therapeutic benefit (144). Advise patients to seek help if they experience distressing side effects.
Explain that craving and tolerance do not occur (10, 144).
Discuss the risk of discontinuation symptoms, and advise patients to seek advice if they experience distressing symptoms (see 3.9.4) (10).
Inform patients about the possible delay in onset of effect, the duration of treatment and the need to take medication as prescribed, and continue after remission (144).
Give patients appropriate written information (10, 144).
If there is a high risk of suicide, prescribe a limited quantity of antidepressants, preferably ones which are relatively safe in overdose (e.g. SSRIs) (10).

3.9.1 Choice of antidepressant

- There is no direct evidence from palliative care populations (or indeed the wider population of people with physical illness) to suggest that one antidepressant is preferable over others (107, 108).

- A recent meta-analysis indicated that some second generation antidepressants are marginally better tolerated and more effective than others (145). We recommend therefore that clinicians become familiar with two or three of the better performing antidepressants. We suggest that Mirtazapine, Sertraline and Citalopram are a reasonable selection for use in palliative care patients. Apart from the 15mg and 45mg preparations of mirtazapine, these drugs are all similarly inexpensive (at least in UK).

- Tricyclic antidepressants pose greater risk in overdose than SSRIs and are purported to be less well tolerated. Nevertheless, tricyclic antidepressants are potential second-line medicines, which may be useful for patients with neuropathic pain (146). For patients already taking TCAs for neuropathic pain it may be appropriate to raise the dose to treat depression rather than prescribe an additional antidepressant. Studies have shown amitriptyline to be at least as effective as SSRI comparators (147).

Drug	**Half Life**	**Forms**	**Usual Dose**
Mirtazapine (Noradrener-gic specific serotonergic antidepres-sant (NaSSAs))	20-40 hours	Tablets (30mg) Orodispersible tablets (15/30/45mg) Oral solution (15mg)	15-45mg/day (max 45mg/day) (148)
Sertraline (SSRI)	24-36 hours	Tablets (50/100mg)	50mg/day (max 200mg/day) (148)
Citalopram (SSRI)	26-40 hours	Tablets (10/20/40mg) Oral drops (40mg)	20-40mg/day (max 60mg/day) (148)
Amitriptyline (TCA)	9-36 hours	Tablets (10/25/50mg) Solution (25/50mg)	75-200mg/day (max 200mg/day) (148)

- Given the lack of evidence for a clearly superior antidepressant, treatment decisions should be based on:

Type of physical comorbid illness (149)
Symptom profile (149)
Pharmacological properties (e.g. half-life, interactions etc) (149, 150)
Potential side effects (some of which may be beneficial) (149-151)
Response to prior treatment (103)
Patient preference (103)
Clinician familiarity and preference (24)

3.9.2 Special considerations

Mirtazapine	Benefits • May increase appetite • May reduce nausea • Sedative effect may be beneficial for some patients • May have early onset of action, therefore a good choice for patients with a short prognosis • Available as orodispersible tablet • Suitable in heart failure and diabetes

	Possible side effects • Sedation, dizziness, constipation, hypertension, weight gain , oedema, orthostatic hypotension, dry mouth, fatigue, tremor, dizziness, confusion, anxiety, arthralgia, myalgia
	Cautions • Possible increased serotonergic effects when given with tramadol or venlafaxine • Enhances anticoagulant effect of warfarin
Sertraline	Benefits • Beneficial for renal impairment • First choice for recent cardiac event
	Possible side effects • Nausea, vomiting, drowsiness, dizziness, dry mouth, anorexia, dyspepsia, diarrhoea, insomnia, sweating, sexual dysfunction, agitation, hyponatraemia, pancreatitis, hepatitis, jaundice, liver failure, tachycardia, amnesia, paraesthesia, aggression, urinary incontinence, menstrual irregularities
	Cautions • Risk of ventricular arrhythmias if taken with droperidol • Increased risk of bleeding when given with aspirin
Citalopram	Benefits • Beneficial for agitated depression/anxiety, nausea • Relatively safe for patients at risk of seizures • Available as oral suspension
	Possible side effects • Nausea, vomiting, anorexia, dyspepsia, diarrhoea, dry mouth, dizziness, insomnia, sweating, sexual dysfunction, agitation, hyponatraemia, palpitation, tachycardia, postural hypotension, confusion, impaired concentration, amnesia, migraine, paraesthesia, taste disturbance, increased salivation, rhinitis, tinnitus, polyuria, micturition disorders, euphoria, abnormal dreams
	Cautions • Increased risk of bleeding when given with aspirin • Possibly greater risk in overdose than other SSRIs
Amitriptyline	Benefits • May be beneficial for patients with insomnia or neuropathic pain • If a patient is already on a low dose for neuropathic pain, it may be beneficial to increase this dose, rather than introduce another antidepressant • May have an earlier onset of action than SSRIs • There is evidence that TCAs are equally, if not more effective than SSRIs
	Possible side effects • Dry mouth, constipation, hypotension, tachycardia, urinary retention, confusion, dizziness, sleep disturbance, drowsiness, arrhythmia, abdominal pain, stomatitis, palpitation, oedema, restlessness, fatigue, mydraiasis, increased intra-ocular pressure, sexual dysfunction, nausea, sweating

	Cautions • Greater toxicity in overdose than SSRIs

- For drug interactions refer to national prescribing guidelines (e.g. the British National Formulary http://bnf.org/bnf/ in the UK (149), the Drug Commission of the German Medical Council http://www.akdae.de/35/10/67-Depression-2006-2Auflage.pdf in Germany, www.medinteract.net in Spain).

3.9.3 Physical disease contraindications of antidepressants

Cardiovascular disease	
Recent myocardial infarction	Tricyclics contraindicated
Heart block	MAOIs contraindicated
Congestive heart failure	Tricyclic: risk of postural hypotension Lithium excretion lowered by ACE inhibitors and diuretics
Hypertension	Lithium excretion reduced by diuretics MAOIs may enhance the hypotensive effect of antihypertensives. Avoid venlafaxine
Eye disease	
Glaucoma	Tricyclics, duloxetine, mirtazapine contraindicated
Genito-urinary disease	
Prostatic hypertrophy	Tricyclics worsen symptoms – risk of retention of urine due to anticholinergic action
Renal failure	Risk of toxicity from lithium
Neurological disease	
Epilepsy	All antidepressants lower seizure threshold Maprotiline contraindicated Interactions between SSRIs and anticonvulsants (raised levels of phenytoin, carbamazepine) Avoid carbamazepine with MAOIs
Cerebrovascular accident	MAOIs contraindicated
Parkinson's disease	Interaction between fluoxetine and selegiline (confusional state)
Migraine	Interaction between fluoxetine and selegiline (confusional state)
Liver failure	Decrease dose of all antidepressants If severe, tricyclics contraindicated
Gastrointestinal disease	
Upper GI tract disease	SSRIs may worsen nausea SSRIs may cause GI bleeding in at risk individuals

Lower GI tract disease	Tricyclic levels raised by cimetidine
Endocrine disease	
Phaeochromocytoma	MAOIs and moclobemide contraindicated
Hyperthyroidism	Tranylcypromine and moclobemide contraindicated Caution with venlafaxine
Blood disorders	
Agranulocytosis	Tricyclics and mianserin contraindicated
Warfarin treatment	Avoid mirtazapine
Porphyria	Avoid tricyclics

3.9.4 Discontinuing antidepressant treatment

- Some patients experience symptoms when stopping antidepressants. These may include dizziness, nausea, paraesthesia, anxiety, headaches (102).

- All antidepressants can cause discontinuation symptoms, but there is evidence that they are more frequent in some antidepressants (e.g. paroxetine and venlafaxine). Discontinuation symptoms are more likely to occur when antidepressants are stopped abruptly, but can also occur if doses are missed in shorter half life antidepressants. Patients should be advised not to miss doses if at all possible, and to seek medical advice before stopping their antidepressant (102).

- The likelihood of developing discontinuation symptoms is probably reduced if the antidepressant dose is reduced slowly before stopping (102). If discontinuation symptoms

  occur despite this, increase the dose and reduce more slowly, or consider swapping to a longer half life antidepressant (e.g. fluoxetine) and then stopping.

- It may be appropriate to discontinue antidepressant treatment in patients with very short life expectancy (hours, days). Consideration should be given to tapering the dose, or changing to a liquid preparation if this is feasible.

3.9.5 St John's wort

- Extracts of the plant *Hypericum perforatum* L. (popularly called St. John's wort) is an herbal treatment for depression which can be bought from pharmacies.

- In light of mixed evidence regarding efficacy (152, 153) and the potential for adverse interactions with many medications, use of St John's Wort in palliative care is not recommended.

- Clinicians should discuss with patients the risk of drug interactions and discourage use of St John's wort (152).

Evidence and recommendation summary

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

Appendix

Criteria for diagnosis of depression

- DSM-IV criteria:

Major Depressive Episode
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note:** Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood. (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others) (3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains. (4) Insomnia or hypersomnia nearly every day (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) (6) Fatigue or loss of energy nearly every day (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or motor retardation.

- DSM-IV severity specifiers

Mild
Few, if any symptoms in excess of those required to make the diagnosis and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.
Moderate
Symptoms or functional impairment between “mild” and “severe”
Severe Without Psychotic Symptoms
Several symptoms in excess of those required to make the diagnosis, *and* symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.
Severe With Psychotic Symptoms
Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent: Mood-congruent psychotic features: Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Mood-incongruent psychotic features: delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment. Included are symptoms such as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control.
In Partial Remission
Symptoms of a Major Depressive Episode are present but full criteria are not met, or there is a period without any significant symptoms of a Major Depressive Episode lasting less than 2 months following the end of the Major Depressive Episode.
In Full Remission
During the past 2 months, no significant signs or symptoms of the disturbance were present.

- ICD-10 criteria:

Clinical significance
Some difficulty in continuing with ordinary work and social activities, but will not cease to function completely in mild depressive episode; considerable difficulty in continuing with social, work or domestic activities in moderate depressive episode; considerable distress or agitation, and unlikely to continue with social, work, or domestic activities, except to a very limited extent in severe depressive episode
Duration of symptoms
A duration of at least 2 weeks is usually required for diagnosis for depressive episodes of all three grades of severity
Criteria
Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity in typical depressive episodes; other common symptoms are: (1) Reduced concentration and attention (2) Reduced self-esteem and self-confidence (3) Ideas of guilt and unworthiness (even in mild type of episode) (4) Bleak and pessimistic views of the future (5) Ideas or acts of self-harm or suicide (6) Disturbed sleep (7) Diminished appetite
Severity
Differentiation between mild, moderate, and severe depressive episodes rests upon a complicated clinical judgement that involves the number, type, and severity of symptoms present. The extent of ordinary social and work activities is often a useful general guide to the likely degree of severity of the episode, but individual, social, and cultural influences that disrupt a smooth relationship between severity of symptoms and social performance are sufficiently common and powerful to make it unwise to include social performance amongst the essential criteria of severity.
Mild
For mild depressive episode, two of most typical symptoms of depression and two of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.
Moderate
For moderate depressive episode, two of three of most typical symptoms of depression and at least three of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.
Severe
For severe depressive episode, all three of the typical symptoms noted for mild and moderate depressive episodes are present and at least four other symptoms of severe intensity are required.
Severe With Psychotic Symptoms
For severe depressive episode with psychotic symptoms, the criteria for a severe depressive episode are met and in additions, delusions, hallucinations, or depressive stupor are present.

GRADE scheme for rating quality of evidence and strength of recommendations

- The guideline was summarised in key recommendations on preventing, detecting and treating depression in palliative care. These are given at the end of each chapter. The quality of evidence and the strength of key recommendations were graded according to the process proposed by GRADE (13). The three chapters on prevention, detection and treatment provide more detailed step-by-step guidance on how to follow and apply the key recommendations. Recommendations stating that clinicians should 'consider' an intervention indicate the need for treatment to be individually tailored to the patient's specific needs.

- The GRADE system classifies the quality of evidence in one of four levels – high, moderate, low and very low.

Definitions of grade of evidence	
High	Further research is unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

- The GRADE system offers two grades of recommendations: "strong" and "weak". The strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh undesirable effects.

Determinants of strength of recommendation	
Factor	**Comment**
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a strong recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention – that is, the greater the resources consumed – the lower the likelihood that a strong recommendation is warranted

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