15.1 GENERAL PRINCIPLES

➢ Depression is a common problem in patients with advanced cancer.¹, ², ³, ⁴
➢ Depression often is undetected, undertreated, or treated at a stage when there is insufficient time for medication to be effective.¹, ², ⁴
➢ In patients with advanced cancer it may be very difficult to distinguish depression from physical symptoms of their illness and/or adjustment to significant life changes.¹, ²
➢ Hopelessness, feelings of guilt and worthlessness, lack of self esteem, loss of energy, insomnia and appetite disturbance are characteristic symptoms of depression.²
➢ Anhedonia is the marked loss of pleasure, interest and enjoyment in normally pleasurable activities. If present it is helpful in differentiating major depression from the ‘normal’ reaction to major physical illness and may help to identify those patients who may respond to antidepressants.⁵
➢ Many of the antidepressants available currently have acceptable side effect profiles and are usually well tolerated. Depressed patients may benefit from treatment with antidepressant medication even within the last weeks of life.², ⁴

15.2 GUIDELINES

15.2.1 Diagnosing depression

➢ Brief screening measures may be useful for identifying depression. The NICE guidance on management of depression recommends the use of at least 2 questions regarding mood and interest e.g.
   ➢ During the last month, have you often been bothered by having little interest or pleasure in doing things?
   ➢ Have you felt low, depressed or hopeless?
   ➢ Do you want help with the way you are feeling?⁴, ⁶, ⁷, ⁸ [Level 3]

➢ Alternatively consider using specific screening tools such as the Hospital Anxiety and Depression Scale (HADS) or the Edinburgh Depression Scale (EDS). The validated cut-off thresholds for palliative care patients should be used.⁴ [Level 3] The Brief Edinburgh Depression Scale (BEDS) has been developed as a screening tool in patients with advanced cancer.⁴, ⁹, ¹⁰, ¹¹ [Level 3]

➢ Table 15.1 gives the ICD-10 criteria for depression.¹¹, ¹²
The severity of depression may be determined by considering the actual symptoms experienced by patients. Further details can be seen in Table 15.2.\cite{1,11,12} [Level 4]

Patients who are depressed should be questioned about suicidal thoughts or intent. Antidepressant use has been associated with thoughts and intent of self harm particularly in patients <30 years old. Assessment of suicidal risk is particularly important when treatment is commenced or the dose adjusted.\cite{1,2,6,13} [Level 4]

If a patient expresses thoughts or intent of suicide, the issues and meaning behind this should be fully assessed. Optimising physical symptom control and psychological support in such patients is particularly important and it is important to consider increased support from the primary health care team, including direct contact. If a patient is assessed to be at considerable immediate risk of harm to themselves or others, urgent referral to mental health services should be arranged.\cite{6} [Level 4].

### Table 15.1 ICD-10 Criteria for depression\cite{11,12} [Level 4]

<table>
<thead>
<tr>
<th>Clinical significance</th>
<th>Mild depression</th>
<th>Moderate depression</th>
<th>Severe depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>Duration of at least 2 weeks.</td>
<td>Duration of at least 2 weeks.</td>
<td>Duration of at least 2 weeks.</td>
</tr>
<tr>
<td>Severity (see Table 15.2 below)</td>
<td>Two of most typical symptoms plus two of the other symptoms.</td>
<td>Two or three of most typical symptoms plus three of the other symptoms. If four or more of the somatic symptoms are present the episode is diagnosed.</td>
<td>All three of typical symptoms plus at least four other symptoms of severe intensity.</td>
</tr>
</tbody>
</table>

### Table 15.2 Symptoms of depression\cite{1,11,12} [Level 4]

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Other symptoms</th>
<th>Somatic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood.</td>
<td>Reduced concentration and attention.</td>
<td>Loss of interest or pleasure in activities that are normally enjoyable.</td>
</tr>
<tr>
<td>Loss of interest.</td>
<td>Reduced self esteem and self-confidence.</td>
<td>Lack of emotional reactivity to normally pleasurable surroundings and events.</td>
</tr>
<tr>
<td>Reduced energy levels leading to increased fatigue and reduced activity.</td>
<td>Bleak and pessimistic views of the future.</td>
<td>Waking 2 hours or more before usual waking time.</td>
</tr>
<tr>
<td>Ideas or acts of self harm or suicide.</td>
<td>Diminished appetite.</td>
<td>Objective evidence of psychomotor retardation or agitation.</td>
</tr>
<tr>
<td>Disturbed sleep.</td>
<td>Weight loss.</td>
<td>Marked loss of appetite.</td>
</tr>
<tr>
<td>Marked loss of libido.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
15.2.2 Treatment of depression

- Both pharmacological and psychological interventions should be considered. \(^1,^4\) [Level 2+].
- Patients who are prescribed antidepressants should be informed about:
  - Potential side-effects.
  - Possible delay in onset of action.
  - Likely duration of treatment.
  - Importance of compliance.
  - Possible symptoms that may be experienced on stopping or withdrawal from the antidepressant medication. \(^6\) [Level 4]
- Patients should be advised about the likely delay in onset of any beneficial effect from antidepressant medication although the length of delay is difficult to estimate. Previous guidance has suggested a delay in onset of 4-6 weeks but new evidence suggests that benefit may be seen within a shorter timescale. \(^1^5\) [Level 3]
- The dose of antidepressant medication should be increased more slowly than in physically well patients. It is important to monitor side effects and clinical response and to consider factors that may influence the response. This may include the physical condition of the patient, or treatment with drugs which may predispose to depression, such as corticosteroids. \(^1,^2,^3\) [Level 4]
- Prescribers should consider clinically significant interactions when prescribing antidepressants and should consult the British National Formulary, Appendix 1 for further guidance. \(^6\) [Level 4]
- If there is an inadequate response to the standard dose and no side-effects, the dose may be increased in accordance with the Summary of the Product Characteristics, but it may be advisable to increase the dose more slowly than in physically well patients. If there has been no response within 4-8 weeks, consider changing to an antidepressant from a different therapeutic group. \(^6\) [Level 4]
- If appropriate, antidepressants should be continued for at least 6 months after remission of a first episode of depression, to ensure adequate treatment and reduce the risk of relapse. If there are recurrent episodes, treatment should be continued for longer. \(^6\) [Level 1+]
- In patients with reduced life expectancy consider the use of psychostimulants, such as methylphenidate, where the onset of action is very rapid. \(^6,^1^4\) [Level 4] (see Guidelines on the Use of Psychostimulants).
- The Committee on Safety of Medicines (UK) advises that hyponatraemia has been associated with all classes of antidepressant drugs. \(^1^6\) [Level 3] It is more common in the elderly and may be due to inappropriate anti-diuretic hormone secretion. Hyponatraemia should be considered as a possible aetiology in all patients who develop drowsiness, confusion or fits whilst taking antidepressant medication. \(^1^6\) [Level 4]
- Information leaflets appropriate to the needs of the patient should be provided. \(^6\) [Level 4]

15.2.3 Antidepressants

General Points

- Antidepressants generally reduce the seizure threshold. Caution is required with other pro-convulsive drugs such as antipsychotics or with conditions that predispose to seizures e.g. Cerebral tumours. Tricyclics are often more problematic compared to SSRIs. Citalopram is usually considered the drug of choice in patients vulnerable to seizures. \(^2^1\) [Level 4]
- When choosing an antidepressant it is also useful to consider the available formulations other than tablets/ capsules. Fluoxetine is available as a liquid. Paroxetine comes as an oral suspension. Citalopram and escitalopram come as oral drops and mirtazapine is available as a melt. \(^2^0\) [Level 4]
Table 15.3 illustrates some antidepressants in common use. 17, 23

**Selective serotonin re-uptake inhibitors**

Selective serotonin re-uptake inhibitors (SSRIs) are not superior in efficacy to tricyclic antidepressants but there is evidence that they are better tolerated. They should be considered as first-line treatment for depression.6 [Level 1-]

SSRIs have the potential to increase the risk of bleeding from the upper gastrointestinal tract in all patients. The risk is increased for patients with other risk factors such as receiving non-steroidal anti-inflammatory agents (including aspirin), liver failure, peptic ulcer disease or oesophageal varices. 6, 17 [Level 4]

If SSRIs are co-administered with tramadol there is a theoretical risk of serotonin syndrome and therefore this combination must be used cautiously. 3 Characteristics of the serotonin syndrome include restlessness, tremor, shivering, myoclonus, confusion, convulsions and extreme cases may result in death. Other antidepressants may also trigger serotonin syndrome. Serotonin syndrome rarely occurs after taking only 1 drug with serotonergic activity and is more likely to occur when 2 or more drugs with serotonergic activity are taken together. 1,3,6,18,19 [Level 4]

**Tricyclic antidepressants**

Tricyclic antidepressants (TCA) such as amitriptyline, are an alternative option but are more likely to be associated with side effects e.g. the increased risk of cardiotoxicity; greater toxicity in overdose than agents of similar potency.6, 20 [Level 3]. Tricyclics other than lofepramine should not be prescribed for patients at high risk of serious cardiac arrhythmias or patients who have recently suffered a myocardial infarction. 20 [Level 4]. Lofepramine has a relative lack of cardiotoxicity compared to other tricyclics but should still be used with caution in such patients. 6 [Level 4]

Tricyclic antidepressants may be useful in patients who have co-existing neuropathic pain. 3, 17 [Level 4]

The side effect profiles of individual antidepressants may influence the choice of drug. Some side effects of tricyclic antidepressants, such as constipation, dry mouth, cognitive impairment and confusion, may be problematic in palliative care patients, but others, such as sedation and reduced secretions, may be helpful in certain situations. 3, 14 [Level 4]

**Venlafaxine**

Venlafaxine inhibits the reuptake of serotonin and noradrenaline, and lacks the sedative and antimuscarinic effects of the tricyclics. Venlafaxine should not be prescribed for patients who have had a recent myocardial infarction or those at high risk of serious cardiac arrhythmias. It should also be avoided in patients with uncontrolled hypertension. Blood pressure should be checked on initiation and regularly during treatment. If a sustained increase in blood pressure occurs the dose should be reduced or venlafaxine discontinued. Patients prescribed venlafaxine should also be monitored for signs and symptoms of cardiac dysfunction. Venlafaxine is more dangerous in overdose than other antidepressants of similar efficacy. 6 [Level 4]
Mirtazapine

- Mirtazapine is a noradrenergic selective serotonin antagonist. The speed of onset may be a little quicker than for SSRIs but there is no difference when compared to tricyclics. 22 [Level 1] It may be associated with sedation, weight gain and blood dyscrasias. Patients should be advised to report fevers, sore throats, stomatitis or other signs of infection during treatment. If any of these symptoms occur a full blood count should be checked and the drug stopped immediately if a blood dyscrasia is suspected. It may be best avoided in a patient who is immunocompromised e.g. having chemotherapy. 5, 17, 20 [Level 1-]

15.2.4 Stopping antidepressants

- If a patient has been taking antidepressants for 6 weeks or more the drug should not be stopped abruptly. Exceptions to this rule are:
  - If the drug has caused a serious adverse effect e.g. a cardiac arrhythmia in association with a tricyclic antidepressant, 6 or
  - The patient is entering the terminal phase. 19 [Level 4]

- Antidepressants should be withdrawn slowly, preferably over 4 weeks, by weekly reductions in dose. One exception to this rule is fluoxetine. At a dose of 20mg daily this may be stopped abruptly because of the long plasma half-life and active metabolite, but at higher doses gradual withdrawal is required. 6, 18, 19, 24 [Level 4]

- Symptoms may occur as a direct result of stopping the drug. This usually takes place within 5 days of stopping treatment. The symptoms may vary in form and intensity. They may also occur during the process of reducing a dose or, in the case of drugs with a short half-life, (e.g. paroxetine, venlafaxine) after missed doses. For SSRIs the commonest symptoms include a flu-like illness, dizziness exacerbated by movement, insomnia, excessive (vivid) dreaming and irritability. If these symptoms occur the rate of drug withdrawal should be slowed and the patient reassured. Symptoms usually do not last longer than 1–2 weeks. The drug should only be restarted if the symptoms are severe or prolonged. 6, 19, 24 [Level 4]

- Withdrawal of tricyclic antidepressants can cause cholinergic rebound with symptoms including headache, restlessness, diarrhoea, nausea and vomiting. 24 [Level 4]

15.2.5 Changing antidepressants

- The dose of the original drug should be slowly reduced and the new drug slowly introduced.
- The speed of the “cross-tapering” may need to be adjusted according to how well the patient tolerates the process. 19, 24 [Level 4]

- Some drugs should never be co-administered and in these cases cross-tapering should be avoided. Potential risks of administering two antidepressants together include pharmacokinetic interaction (e.g. the increase in tricyclic antidepressant level caused by some SSRIs) and pharmacodynamic interactions, such as the serotonin syndrome. 6, 25 [Level 4]

- If changing between two very similar anti-depressants e.g. different SSRIs, cross-tapering may not be required as administration of the second agent is likely to ameliorate the withdrawal effects of the first. 19 [Level 4] An exception to this is fluoxetine. Any switch from fluoxetine to another antidepressant should be done slowly and cautiously (see Table 15.4). This is due to the long half-life and active metabolites. 19, 24 [Level 4]

- Table 15.4 has been adapted from the guidelines of the South Maudsley NHS Foundation Trust, 19 UK Medicines Information 18 and Bazire 24 and gives further advice on how antidepressants should be switched or discontinued. This advice is derived from manufacturer’s information
and is partly theoretical. Caution is advised in all cases. The evidence is not specific to palliative care patients. In the palliative care setting it is important to remember that there may be limited time to achieve an improvement in the mood of the patient and hence in their quality of life. A more rapid switch under close medical supervision may be indicated. 19 [Level 4] 

- When switching between antidepressants it is important to be aware of gradual and modest incremental increases of dose, interactions and the risk of serotonin syndrome. 6 18, 19, 24 [Level 4]

<table>
<thead>
<tr>
<th>Table 15.3  Antidepressants in common use 17, 20, 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class of Antidepressant</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>SSRI</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Tricyclics</td>
</tr>
<tr>
<td>Lofepramine</td>
</tr>
<tr>
<td>NaSSA</td>
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<tr>
<td>From</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Tricyclics</td>
</tr>
<tr>
<td>Stopping antidepressants</td>
</tr>
</tbody>
</table>

*See stopping antidepressants - fluoxetine **According to clinical judgement

NB Unless otherwise specified, starting doses are as indicated in Table 15.3. Should not co-administer clomipramine and SSRIs or venlafaxine.

Clomipramine should be withdrawn before starting the other drugs.

Interactions with fluoxetine may occur as long as 5 weeks after it is stopped because of its long half-life.
15.3 STANDARDS

1. Screening for depression and anxiety should be part of every patient assessment. ⁶ [Grade D]
2. All patients who are depressed should be questioned about suicidal thoughts and intent. ⁶ [Grade D]
3. Treatment with antidepressants should be discussed with, and offered to, every patient where it is appropriate. ⁶ [Grade D]
4. The aim of treatment and possible side effects should be explained to the patient and documented in the case notes. ⁶ [Grade D]
5. Patients started on antidepressants who are not considered to be at increased risk of suicide, should be reviewed after 2 weeks and then regularly thereafter e.g. every 2 – 4 weeks to monitor clinical response. ⁶ [Grade D]
6. If a patient is assessed to be at increased risk of suicide they should be seen after a week and subsequently frequently as appropriate until they are no longer considered to be at significant risk. If a patient is considered to be a risk to themselves or others it may be necessary to consider urgent referral to Mental Health Care Services. ⁶ [Grade D]

15.4 REFERENCES


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