Yorkshire Palliative Medicine Clinical Guidelines Group

Guidelines on the use of antidepressants in palliative care
October 2006

Authors: Dr Iain Lawrie and Dr Annette Edwards, on behalf of the Yorkshire Palliative Medicine Clinical Guidelines Group.

Overall objective: To provide evidence-based guidance for the use of antidepressants in specialist palliative care.

Search strategy: Medline, Embase, Cinahl and PsycINFO databases were searched using the words depression, depressive disorders, palliative care, terminal disease, advanced cancer and the individual drug name. Searches were limited to papers published in English relating to adult humans to October 2006. References obtained were hand searched for additional materials relevant to this review. Evidence for antidepressant use in palliative care was the primary search aim but, where such evidence was not available, evidence for their use in advanced cancer, chronic disease, the elderly and the general population was then sought.

Level of evidence: Evidence regarding medications included in this review has been graded according to criteria described by Keeley (2003) on behalf of the SIGN research group. (See Appendix 2).

Review date: October 2010

Competing interests: None declared

Disclaimer: These guidelines are the property of the Yorkshire Palliative Medicine Clinical Guidelines Group and are intended for qualified, specialist palliative medicine professionals as an information resource. They should be used in the clinical context of each individual patient’s needs and reference to appropriate prescribing texts / literature should also be made. The Clinical Guidelines Group takes no responsibility for any consequences of any actions taken as a result of using these guidelines.

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**INTRODUCTION**

Psychiatric disorders, especially mood disorders, are experienced more frequently by patients with cancer than the general population (Breitbart 1995 *Evidence=4*; Block 2000 *Evidence=4*). This can impact significantly on the quality of life of both patients and their carers. Depression is a significant symptom for approximately 25% of palliative care patients, but it is estimated that the majority of the psychological and psychiatric morbidity in cancer patients goes unrecognised and untreated (Maguire 1985 *Evidence=4*; Lloyd-Williams *et al* 1999 *Evidence=2++*).

In any guidelines on the use of antidepressants in palliative care, emphasis must be placed on the importance of identification of patients with depression. Unrecognised illness cannot be actively treated. However, it is recognised that there are no universally accepted criteria for diagnosing depression in the palliative care patient and its management can prove difficult, even among experienced clinicians (Lawrie *et al* 2004 *Evidence=3*).

Screening tools are widely used in all areas of medicine, and especially in the identification of psychological disorders and distress. Their use can be of value (Ward *et al* 2004 *Evidence=2-*), and some have been validated in palliative care populations (Lloyd-Williams *et al* 2003 *Evidence=1+*). Many of the signs and symptoms of depression may be present in these patients due to concomitant disease, making diagnosis more difficult.

The importance of non-drug treatments should not be underestimated. While pharmacological management of many symptoms is an integral part of palliative care provision, specialist psychology services’ involvement, where appropriate, should also be considered of importance in managing psychological distress. However, it should be recognised that palliative care specialists provide a significant amount of psychological support to patients as part of their routine work and that this practice should be both acknowledged and encouraged.

NICE has produced guidelines for the management of depression in primary and secondary care (NICE 2004) which are evidence-based and useful. The guidelines presented here are intended to complement those of NICE, but are tailored more specifically to use with palliative care populations.

The following drug treatments were reviewed to assess the strength of evidence for their use as antidepressants, with particular emphasis on their use in the palliative care population. As mentioned, other, non-pharmacological techniques are employed in the management of depression including specialist psychology support, counselling, relaxation and guided imagery, but these techniques have not been included in this review.
1. **Selective Serotonin Reuptake Inhibitors (SSRIs) & related antidepressants**
   - Citalopram
   - Escitalopram
   - Fluoxetine
   - Fluvoxamine
   - Paroxetine
   - Sertraline
   - Venlafaxine

2. **Tricyclic & related antidepressants**
   - Tricyclic antidepressants
     - Dosulepin
     - Lofepramine
     - Maprotiline
     - Mianserin
     - Trazodone

3. **Stimulants**
   - Dexamethasone & prednisolone
   - Dexamfetamine
   - Methylphenidate

4. **Monoamine Oxidase Inhibitors (MAOIs)**

5. **Other antidepressants**
   - Duloxetine
   - Flupentixol
   - Mirtazapine
   - Reboxetine
   - Tryptophan

6. **Herbal Preparations**
   - St John’s Wort

Drugs are presented in alphabetical order within their group. Guidelines’ recommendations are summarised in chart format (page 24) together with suggestions for antidepressant use in specific clinical scenarios (pages 25-27).

**Points to note**

**Hyponatraemia and Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH):** Hyponatraemia has been associated with all classes of antidepressants, more frequently in the elderly population, and possibly due to the inappropriate secretion of antidiuretic hormone. The clinical picture has been seen more often with SSRIs than with other types of antidepressants, but hyponatraemia should be considered in any patient taking an antidepressant who develops confusion, drowsiness or experiences convulsions. Other symptoms include lethargy, nausea and muscle cramps.

**Differences in response** to antidepressant preparations are to be expected among the population. While a great deal is known about drug half-lives and times taken to reach steady plasma states, these measurements can only be taken as a guide in actual clinical practice. The same can also be said for side
effect profiles and recommended doses for each preparation. All patients should be monitored regularly during the initial stages of antidepressant treatment and at appropriate intervals once a medication regime has been established.

**Drug interactions & adverse effects:** Only common or significant drug interactions and adverse effects for each medication reviewed have been included. Prescribers should refer to such sources as the current edition of the British National Formulary (BNF 2006 *Evidence=1++*) or the Electronic Medicines Compendium ([www.emcmedicines.org.uk](http://www.emcmedicines.org.uk)) for full and up-to-date guidance.
1. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) & RELATED ANTIDEPRESSANTS

Pharmacology: The Selective Serotonin Reuptake Inhibitors (SSRIs) work by preferentially increasing 5-hydroxytryptamine (5-HT / serotonin) transmission through inhibition of 5-HT uptake. They have little effect on noradrenaline and dopamine uptake. They are metabolised in the liver via the Cytochrome P450 (CYP 450) system to weakly active or inactive metabolites. The action of the SSRIs is unaffected by the presence of food in the stomach.

Licences: All SSRIs are licensed for the treatment of depressive illness. Individual drugs are also licensed for use in panic disorder, obsessive-compulsive disorder, bulimia nervosa, post-traumatic stress disorder and generalised anxiety disorder. Venlafaxine is licensed for management of major depression and general anxiety disorder (see also page 8).

Adverse Effects: Most side effects caused by SSRIs are usually mild to moderate and occur during the first few weeks of treatment, however certain specific side effects may persist with ongoing treatment.

- **common** (≥5%): nausea, vomiting, increased sweating, headache, dry mouth, tremor, sedation, insomnia, ejaculation disorder (Caballero & Nahata 2005 *Evidence=2++*), anxiety, anorexia, constipation, dizziness, asthenia.

Drug Interactions: See BNF (BNF 2006 *Evidence=1++*) and comments (page 6). Concomitant treatment with methylphenidate can inhibit the metabolism of some SSRIs.

SSRIs and bleeding: Platelet aggregation can be disrupted by SSRI antidepressants and venlafaxine due to inhibition of uptake of serotonin into platelets. This can lead to bleeding, particularly in the upper gastrointestinal tract. Consider prescribing gastroprotection alongside SSRIs for patients at high risk of bleeding (e.g. aspirin, NSAIDs, previous bleeds, elderly) (Paton & Ferrier 2005 *Evidence=1-*).

SSRIs and serotonin syndrome: Serotonin syndrome is a rare, but potentially life-threatening condition associated with an excess of 5-HT in the central nervous system (CNS). Diagnosis is clinical and the syndrome may go unrecognised, being mistaken for a viral illness, anxiety, neurological disorder or worsening psychiatric condition (Fennel & Hussain 2005 *Evidence=4*).

The syndrome is usually associated with high doses of serotonergic drugs, when combinations of serotonergic agents are used together, or when antidepressants are changed without an appropriate washout period between drugs. Less frequently, it can also be caused by moderate dosage of a single serotonergic drug (Tomaselli & Modestin 2004 *Evidence=3*) or in combination with non-serotonergic drugs such as oxycodone (Karunatilake & Buckley 2006 *Evidence=3*) or St John’s Wort (Dannawi 2002 *Evidence=3*). (See also Duloxetine, page 19).

Symptoms can be classed into four groups:
- **cognitive**: mental confusion, hypomania, agitation, headache, coma;
- **autonomic**: shivering, sweating, fever, hypertension, tachycardia, nausea, diarrhoea;
- **somatic**: myoclonus, clonus, hyperreflexia, tremor;
- **other**: insomnia, sleep disturbance, unrefreshing sleep.

Venlafaxine: is a Serotonin and Noradrenaline Reuptake Inhibitor (SNRI). While it is not an SSRI, it is included here because it shares some of the properties of this group. It is metabolised by the liver via CYP 450 system to an active metabolite. **Note**: The Medicines and Healthcare products Regulatory Agency (MHRA) recommends that, because of concerns about toxicity in overdose and adverse effects at therapeutic dose, treatment with venlafaxine should be initiated and maintained under specialist supervision in patients who are severely depressed, or who are hospitalised as a result, if they require doses of 300mg or above daily. The advice states that venlafaxine should not be used in patients with heart disease and uncontrolled hypertension, those at risk of developing cardiac arrhythmia, and those at high risk of suicide (MHRA 2006 Evidence=1++).

### Table 1: Properties of SSRIs/SNRIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>26-40 hours</td>
<td>Tablets (10/20/40mg) Oral Drops (40mg/ml)</td>
<td>20-40mg/day (max 60mg/day)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>27-32 hours</td>
<td>Tablets (5/10/20mg)</td>
<td>10-20mg/day (max 20mg/day)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1-6 days</td>
<td>Capsules (20/60mg) Liquid (20mg/5ml)</td>
<td>20-60mg/day (max 80mg/day)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>13-22 hours</td>
<td>Tablets (50/100mg)</td>
<td>50-100mg/day (max 300mg/day)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>21-24 hours</td>
<td>Tablets (20/30mg) Liquid (10mg/5ml)</td>
<td>20-40mg/day (max 60mg/day)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>24-36 hours</td>
<td>Tablets (50/100mg)</td>
<td>50mg/day (max 200mg/day)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5 hours</td>
<td>Tablets (37.5/75mg) MR Capsules (75/150mg)</td>
<td>75mg/day (max 375mg/day) MR: 75mg/day (max 225mg/day)</td>
</tr>
<tr>
<td></td>
<td>(active metab: 1-11 hours)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Citalopram Evidence:**

**Palliative Care / Advanced Cancer:**
- no specific evidence

**Chronic Disease:**
- **HIV / AIDS**: does not appear to affect CD4 counts (Caballero & Nahata 2005 Evidence=2++)
- **renal failure**: no efficacy studies; no change in the pharmacokinetics of citalopram in mild to moderate renal failure (Joffe et al 1998 Evidence=2+); no need to adjust dose in patients undergoing haemodialysis (Spigset et al 2000 Evidence=2-)
- **epilepsy**: low proconvulsive effect, but potential interactions of some SSRIs with anticonvulsant drugs. Seizure risk is dose related (Specchio et al 2004 Evidence=2-)

**Elderly:**
better side effect profile than TCAs (Baumann 1998 Evidence=4); start at lower dose and titrate (Parker & Brown 2000 Evidence=1++); dose reduction required (de Mendonça Lima et al 2005 Evidence=1+)

General Population:
more effective than placebo and equally as effective as TCAs, with a better side effect profile (Bezchlibnyk-Butler et al 2000 Evidence=1+; Keller 2000 Evidence=1++; Parker & Brown 2000 Evidence=1++)

Escitalopram Evidence:
Palliative Care / Advanced Cancer / Chronic Disease / Elderly:
no specific evidence
General Population:
proven efficacy in depression (Rush & Bose 2005 Evidence=1+)
better efficacy than placebo (Wade et al 2002 Evidence=1++)
similar efficacy to citalopram (Burke et al 2002 Evidence=1++; Auquier et al 2003 Evidence=1+)
similar efficacy to venlafaxine, but fewer side effects (Bielski et al 2004 Evidence=1++; Montgomery et al 2004 Evidence=1++)

Fluoxetine Evidence:
Palliative Care / Elderly:
no specific evidence
Advanced Cancer:
reduces psychological distress more than placebo (Razavi et al 1996 Evidence=1+)
equal efficacy to desimipramine (Holland et al 1998 Evidence=1-)
Chronic Disease:
renal failure: accumulation can possibly occur in chronic usage; no need to adjust dose in patients undergoing haemodialysis (Aronoff et al 1984 Evidence=2+), although manufacturers do recommend reduced dose in patients with impaired renal function (emc 2006 Evidence=1++)
General Population:
equal efficacy to paroxetine (Kroenke et al 2001 Evidence=1-); though slower onset of action (De Wilde et al 1993 Evidence=1++)
equal efficacy to sertraline (Kroenke et al 2001 Evidence=1-); though less well tolerated (Aguglia et al 1993 Evidence=1+)
similar efficacy to amitriptyline and better tolerated (Chouinard 1985 Evidence=1++; Feighner 1985 Evidence=1++; Young et al 1987 Evidence=2-)
equal efficacy to mirtazapine, but slower onset of action (Wheatley et al 1998 Evidence=1+)
uncertain efficacy in a comparison with venlafaxine (Costa e Silva 1998 Evidence=1+)

Fluvoxamine Evidence:
Palliative Care / Advanced Cancer / Elderly:
no specific evidence
Chronic Disease:
multiple sclerosis: response rate 79% (Benedetti et al 2004 Evidence=2+)
HIV / AIDS: significantly more effective than placebo, especially in early disease (Mauri et al 1994 Evidence=1+); 77% response (Perretta et al 1996 Evidence=2+)

General Population:
- equal efficacy to amitriptyline, possibly faster onset of action than fluoxetine, less well tolerated than other SSRIs (Wilde et al 1993 Evidence=3)

Paroxetine Evidence:
Palliative Care:
- no specific evidence
Advanced Cancer:
- no effect on fatigue (Morrow et al 2003 Evidence=1+; Roscoe et al 2005 Evidence=1+)
- equal efficacy to amitriptyline, but significantly fewer anticholinergic side effects (Pezzella et al 2001 Evidence=1+)
- proven efficacy in depression (Musselman et al 2001 Evidence=1+; Pae et al 2004 Evidence=2+)

Chronic Disease:
- HIV / AIDS: equal efficacy to fluoxetine (Singh & Catalán 1996 Evidence=2+); proven efficacy in depression (Grassi et al 1997 Evidence=2+); equal efficacy to fluoxetine and sertraline (Ferrando et al 1997 Evidence=2-); similar efficacy to imipramine, but better tolerability (Elliott et al 1998 Evidence=1+)
- COPD: improvement in emotion and coping with disease (Lacasse et al 2004 Evidence=1+)
- haemodialysis: proven efficacy in depression (Koo et al 2005 Evidence=2-)
- ischaemic heart disease: similar efficacy to nortriptyline but better tolerability (Nelson et al 1999 Evidence=1+)

Elderly:
- similar efficacy to amitriptyline, clomipramine, doxepin and mianserin (Bourin 2003 Evidence=1++)

General Population:
- as effective as placebo, similar efficacy to TCAs (but better tolerated) and other SSRIs (Wagstaff et al 2002 Evidence=1++)

Sertraline Evidence:
Palliative Care / Advanced Cancer:
- no specific evidence
Chronic Disease:
- post-stroke: reduction in risk of developing depression post-stroke (Rasmussen et al 2003 Evidence=1+)
- multiple sclerosis: significant benefit over supportive-expressive group therapy, but not over CBT in patients with MS (Mohr et al 2001 Evidence=2-)

Elderly:
- significantly more effective than placebo but no difference in outcome in patients with medical comorbidities (Sheikh et al 2004 Evidence=1++)
- significant discontinuation rate due to side effects (Schneider et al 2003 Evidence=1+; Wilson et al 2003 Evidence=1+)
- as effective as venlafaxine, but better tolerated (Oslin et al 2003 Evidence=1+)
General Population:
- no differences in efficacy, quality of life or side effects compared with paroxetine or fluoxetine (Åberg-Wistedt et al 2000 Evidence=1+; Kroenke et al 2001 Evidence=2-)
- equal efficacy, more side effects in early treatment, slower onset of action and less effect on anxiety than citalopram (Stahl 2000 Evidence=1++)
- lower efficacy than venlafaxine (Mehtonen et al 2000 Evidence=1-)

Venlafaxine Evidence:
Palliative Care / Advanced Cancer / Chronic Disease:
- no specific evidence

Elderly:
- response rate 78% (Zimmer 1999 Evidence=2-); equal efficacy to sertraline, but more side effects (Oslin et al 2003 Evidence=1+)

General Population:
- more effective than SSRIs, but no evidence with other antidepressants (Smith et al 2002 Evidence=1++)
- significantly more effective than paroxetine in treatment resistant depression (Poirier & Boyer 1999 Evidence=1+)
- greater efficacy and faster onset of action than placebo, fluoxetine, fluvoxamine and paroxetine (Thase et al 2001 Evidence=1+)

Conclusion – SSRIs:
There is little evidence of significant differences in efficacy of available SSRIs. However, these guidelines would recommend the use of citalopram as a first line antidepressant in this class due to its favourable adverse effect profile and low risk for drug interactions. The availability of a liquid preparation makes it a suitable choice for palliative care patients. There is no reliable evidence that escitalopram may be more effective than citalopram. The availability of fluoxetine in liquid form is advantageous, but its relatively long half-life, slower onset of action and side effect profile must be taken into account when considering its use in the palliative care population. Fluvoxamine is possibly less well tolerated than other SSRIs and may lead to more drug interactions than other drugs in this class. Venlafaxine may also be useful in palliative care patients who also experience neuropathic pain (Ansari 2000 Evidence=1+), but caution is required in specific patient groups (see also MHRA recommendations, page 8).
2. TRICYCLIC & RELATED ANTIDEPRESSANTS

Pharmacology: Tricyclic antidepressants (TCAs) act by blocking synaptic reuptake of monoamines such as noradrenaline and 5-hydroxytryptamine. TCAs, and related antidepressants, are most effective in treating moderate to severe endogenous depression associated with psychomotor and physiological changes such as loss of appetite and sleep disturbance.

Licences: The tricyclic antidepressants dosulepin, maprotiline, mianserin and trazodone are all licensed for treatment of depression, especially where sedation is required. Amitriptyline, imipramine and nortriptyline are, in addition to being licensed for depression, also licensed for management of nocturnal enuresis in children, and trazodone for anxiety. Lofepramine is licensed for the treatment of depressive illness.

Adverse Effects: Dry mouth, dizziness, drowsiness, visual disturbance, constipation, urinary retention, postural hypotension, anxiety, confusion, ECG changes. Dosulepin is thought to be less safe in overdose.

Table 2: Properties of tricyclic & related antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclics (amitriptyline)</td>
<td>9-36 hours</td>
<td>Tablets (10/25/50mg)</td>
<td>75-200mg/day (max 200mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution (25mg/5ml &amp; 50mg/5ml)</td>
<td></td>
</tr>
<tr>
<td>Dosulepin</td>
<td>20-50 hours</td>
<td>Capsules (25mg)</td>
<td>25-50mg tds or od (max 225mg daily in hospitalised patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablets (75mg)</td>
<td></td>
</tr>
<tr>
<td>Lofepramine</td>
<td>2-6 hours</td>
<td>Tablets (70mg)</td>
<td>70mg bd / tds (max 210mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension (70mg/5ml)</td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td>60-90 hours</td>
<td>Tablets (25/50/75mg)</td>
<td>25-75mg/day (max 150mg/day)</td>
</tr>
<tr>
<td>Mianserin</td>
<td>6-40 hours</td>
<td>Tablets (10/20/30mg)</td>
<td>30-40mg/day (max 90mg/day)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>5-9 hours</td>
<td>Tablets (150mg)</td>
<td>100-150mg/day (max 300mg/day or 600mg/day in hospitalised patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsules (50/100mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liquid (50mg/5ml)</td>
<td></td>
</tr>
</tbody>
</table>

(‘Tricyclics’ has been used as an umbrella term to cover most of the available tricyclic antidepressants (e.g. amitriptyline, imipramine), as most behave in a similar manner. The majority of available evidence, however, does relate to amitriptyline. Lofepramine and dosulepin have been included separately due to their being regularly used in some areas of clinical practice.)

Tricyclics Evidence:

Palliative Care:
- no specific evidence

Advanced Cancer:
- equal efficacy to paroxetine (Pezzella et al 2001 Evidence=1+)

Chronic Disease:
- heart disease: effective in treatment of depression (Cohn et al 1993 Evidence=3; but more side effects (Nelson et al 1999 Evidence=1+); more cardiac adverse events seen than other antidepressants (Roose et al 1989 Evidence=3; Hartnett 1994 Evidence=4; Schmid et al 2004 Evidence=4))
Elderly:
- more effective than placebo (Wilson et al 2001 Evidence=1++)
- equal efficacy to paroxetine, but more autonomic side effects (Mulsant et al 1999 Evidence=1+)
- equal efficacy to citalopram, but better in severely depressed; increased autonomic side effects (Navarro et al 2001 Evidence=1-) 
- equal withdrawal rate to SSRIs (Wilson & Mottram 2004 Evidence=1+)

General Population:
- at least as efficacious as SSRIs (Guaiana et al 2003 Evidence=1++); but significantly higher withdrawal rate due to side effects (Guaiana et al 2003 Evidence=1++; Barbui et al 2000 Evidence=1++)

**Dosulepin Evidence:**
Palliative Care / Advanced Cancer:
- no specific evidence

Chronic Disease:
- **rheumatoid arthritis:** no significant difference compared to placebo; possible beneficial effect on pain and morning stiffness (Ash et al 1999 Evidence=1+)

Elderly:
- equal efficacy to fluvoxamine (Rahman et al 1991 Evidence=1+)

General Population:
- less effective than flupenthixol dihydrochloride (Dwivedi et al 1990 Evidence=2+)
- equal efficacy to fluoxetine (Corne & Hall 1989 Evidence=1+), imipramine (Eilenberg 1980 Evidence=2+), trazodone, mianserin (Blacker et al 1988 Evidence=1+) and amitriptyline (Mendlewicz et al 1980 Evidence=2+; Dahl et al 1981 Evidence=2+; Blacker et al 1988 Evidence=1+)

**Lofepramine Evidence:**
Palliative Care / Advanced Cancer / Chronic Disease / Elderly:
- no specific evidence

General Population:
- equal efficacy to amitriptyline (Marneros & Philipp 1979 Evidence=2+; McClelland et al 1979 Evidence=2+; Doonaji et al 1993 Evidence=1+), dosulepin (Lader et al 1998 Evidence=2+), fluoxetine (Robertson et al 1994 Evidence=1+) and paroxetine (Moon & Vince 1996 Evidence=1+)

**Maprotiline Evidence:**
Palliative Care / Advanced Cancer / Chronic Disease / Elderly:
- no specific evidence

General Population:
- similar efficacy to paroxetine (Schnyder & Koller-Leiser 1996 Evidence=1++; Szegedi et al 1997 Evidence=1++); more side effects than paroxetine (Schnyder & Koller-Leiser 1996 Evidence=1+)

**Mianserin Evidence:**
Palliative Care:
- significantly more effective, with no differences in side effects, compared to placebo (Costa et al 1985 Evidence=1+)

Cancer (not advanced):
- significantly more effective than placebo (Van Heeringen & Zivkov 1996 Evidence=1+)

**Chronic Disease / Elderly / General Population:**
- no specific evidence

**Trazodone Evidence:**
- **Palliative Care / Advanced Cancer / Elderly:**
  - no specific evidence
- **Chronic Disease:**
  - HIV / AIDS: pilot studies for treatment of adjustment disorder only
- **General Population:**
  - equal efficacy to paroxetine, but more side effects (Kasper et al 2005 Evidence=1++)

**Conclusion – tricyclic & related antidepressants:**
The tricyclic and related antidepressants have proven efficacy in the management of depression and, in many instances, have equal efficacy to SSRIs. They are particularly useful where sedation is required or where the patient may also have an element of neuropathic pain, although this group is not licensed for analgesic use in such circumstances. Lofepramine may be better tolerated than other drugs in this class. However, in general, the higher incidence of side effects with this group of antidepressants is an important limiting factor to their widespread use for the management of depression in palliative care.
3. STIMULANTS

Pharmacology: Dexamethasone and prednisolone are glucocorticoids, the former having insignificant mineralocorticoid activity. Dexamfetamine is a sympathomimetic amine with a central stimulant and anorectic activity. Methylphenidate is a mild CNS stimulant, predominantly affecting mental, rather than motor, activity.

Licenses: Dexamethasone, dexamfetamine, methylphenidate and prednisolone are not licensed for the treatment of depressive illness. The BNF states that amphetamines and related drugs (e.g., methylphenidate) should not be used for the management of depression (BNF 2006 Evidence=1++). However, in very specific circumstances in clinical practice, some clinicians use stimulants successfully outwith their product licences for management of depression (Sood et al 2006 Evidence=1-).

Adverse Effects: All stimulants should be used with caution in patients with hypertensive disease, symptomatic cardiovascular disease, renal impairment, thyroid disease, hyperexcitability, glaucoma, Tourette’s syndrome and porphyria. Stimulants should be withdrawn gradually in all patients other than those on very short courses.

dexamethasone and prednisolone:
- include: diabetes, paranoia, euphoria, gastric irritation, osteoporosis, proximal myopathy, Cushing’s syndrome.

dexamfetamine:
- include: insomnia, restlessness, irritability, euphoria, tremor, dizziness, headache, dry mouth, anorexia and other gastro-intestinal symptoms, sweating, convulsions, tachycardia, palpitations, rhabdomyolysis, renal damage.

methylphenidate:
- very common (≥10%): nervousness, insomnia;
- common (>1-<10%): headache, drowsiness, dizziness, dyskinesia, abdominal pain, nausea, vomiting, tachycardia, palpitations, arrhythmia, hypertension, rash, pruritus, urticaria, fever, arthralgia, scalp hair loss.

Dexamethasone metabolism can be influenced by co-administration of a number of drugs including some antibiotics and antiepileptic drugs. The drug itself can alter metabolism of, for example, hypoglycaemic agents, antihypertensives, diuretics, antivirals, aspirin and warfarin.

Dexamfetamine should be used with caution in patients taking beta blockers, as it can cause severe hypertension, and in patients taking haloperidol, due to the risk of acute dystonia. Its effects may be antagonised by adrenoreceptor blocking drugs or phenothiazines. It can affect the metabolism of some anticonvulsant drugs, and the analgesic effect (though not the respiratory depressant effect) of morphine can be increased.

Methylphenidate interferes with the metabolism of warfarin, some anticonvulsants and tricyclic antidepressants.
### Table 3: Properties of stimulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>2-6 hours</td>
<td>Tablets (500mcg/2mg) Oral solution (2mg/5ml) Injection (4/24mg/ml)</td>
<td>500mcg-10mg/day (can be higher)</td>
</tr>
<tr>
<td>Dexamfetamine</td>
<td>10-28 hours</td>
<td>Tablets (5mg)</td>
<td>No recommendation</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>2-4 hours</td>
<td>Tablets (5/10/20mg) (also available as MR capsules)</td>
<td>Start: 5-10mg/day Usual: 5-30mg/day (max 60mg/day)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1-4 hours</td>
<td>Tablets (1/2.5/5/25mg) Soluble Tablets (5mg)</td>
<td>10-20mg/day (max 60mg/day)</td>
</tr>
</tbody>
</table>

**Dexamethasone / Prednisolone Evidence:**

**Palliative Care / Advanced Cancer:**
- positive effect of dexamethasone on depression (Bruera et al 1985 Evidence=2+)

**Chronic Disease:**
- physical illness: elevated mood in 62% of 80 patients given ACTH and cortisone, but lowered in 16% and led to psychoses in 11% (Goolker & Schein 1953 Evidence=2+)
- multiple sclerosis / skin disease: positive effect of prednisolone on mood (Cameron et al 1985 Evidence=3)
- COPD: higher levels of depression in patients taking long term, low dose prednisolone (Gift et al 1989 Evidence=3)
- psychiatric illness: beneficial effect of oral and intravenous dexamethasone on mood (Bazire 2000 Evidence=3)

**Elderly / General Population:**
- no specific evidence

**Dexamfetamine Evidence:**

**Palliative Care / Elderly / General Population:**
- no specific evidence

**Advanced Cancer:**
- marked response in hospitalised cancer patients (Olin & Masand 1996 Evidence=3)

**Chronic Disease:**
- medically ill: moderate or marked response in medically ill patients (Masand et al 1991 Evidence=3)

**Methylphenidate Evidence:**

**Palliative Care:**
- antidepressant effect observed, but less marked as disease progressed (Macleod 1998 Evidence=2-)
- rapid effect on depressive symptoms (Homsi et al 2000 Evidence=3; Homsi et al 2001 Evidence=2+)

**Advanced Cancer:**
- marked response in hospitalised cancer patients (Fernandez et al 1987 Evidence=3; Olin & Masand 1996 Evidence=3)

**Chronic Disease:**
- no specific evidence

**Elderly:**
- safe, effective and rapidly acting in medically ill, older patients compared to placebo (Wallace *et al* 1995 *Evidence*=2)
- marked improvement in depressive symptoms (Katon & Raskind 1980 *Evidence*=3)

**General Population:**
- moderate or marked response in medically ill patients (Masand *et al* 1991 *Evidence*=3)

**Conclusion – stimulants:**
While there is some, low-grade evidence that stimulants are possibly effective in the management of depression, these drugs are not licensed for this purpose. They may, however, have a role in the management of patients with an extremely limited prognosis and severe depression associated with psychomotor retardation. Anecdotal, and other, reports appear to suggest that stimulants used in this situation have a rapid onset of action (Rozans *et al* 2002 *Evidence*=1), being stopped after five days if no obvious clinical improvement has been noted. They should be used under close supervision and with caution.
4. MONOAMINE OXIDASE INHIBITORS (MAOIs)

Pharmacology: The Monoamine Oxidase Inhibitor (MAOI) group includes phenelzine, isocarboxazid and tranylcypromine which irreversibly inhibit monoamine oxidase types A and B; and the reversible MAOI moclobemide, which inhibits monoamine oxidase type A, resulting in fewer side effects. Both types of MAOI variably affect metabolism of serotonin, noradrenaline, adrenaline and dopamine, among others.

Licence: MAOIs are licensed for use in depressive illness, with moclobemide also licensed for use in managing social phobia.

Adverse Effects:
- common: postural hypotension (especially in elderly) and dizziness;
- less common: sleep disturbance, dizziness, gastrointestinal disorders, headache, restlessness, agitation, paraesthesia, dry mouth, visual disturbance, oedema, skin reactions, confusional states;
- other: tranylcypromine has stimulant properties and is considered the most hazardous of the MAOIs.

Safety: MAOIs inhibit monamine oxidase, the enzyme that breaks down tyramine and tryptophan, found in a variety of food and beverages. The accumulation of these two substances triggers the release of norepinephrine, which can precipitate a hypertensive crisis, and causes sweating, headache, dilated pupils, palpitations, arrhythmias and even intracerebral haemorrhage. Patients prescribed MAOIs should avoid tyramine- and tryptophan-containing foods and beverages.

Drug Interactions: MAOIs interact with many other medications. Of note are opioid analgesics, which should be avoided while taking and for two weeks after stopping MAOIs (BNF 2006 Evidence=1++); antimuscarinics, due to an increased risk of antimuscarinic side effects when used concomitantly; and anxiolytics and hypnotics. Prescribers should refer to the current edition of the BNF or other reference source if considering use of MAOIs, or other antidepressants when patients have been taking an MAOI. The interactions and side effects of the reversible MAOI moclobemide are thought to possibly be less than that of the other, ‘standard’ MAOIs.

Conclusion – MAOIs:
MAOIs are used much less frequently than other classes of antidepressant due to the dangers of dietary and drug interactions, and the fact that it is less complicated to prescribe MAOIs after having tried other drugs than vice versa. In view of the fact that most patients seen in palliative care are prescribed multiple medications, many common ones having significant interactions with MAOIs, it is sensible to conclude that MAOIs would feature very rarely in the pharmacopoeia of the palliative medicine physician.

For these reasons, no further details regarding MAOIs have been included in these guidelines.
5. OTHER ANTIDEPRESSANTS

DULOXETINE
Pharmacology: Duloxetine is a combined Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) that also weakly inhibits dopamine reuptake. (Duloxetine has been included in this section as it is a more recent addition to the drugs available of the management of depression.)

License: Duloxetine is licensed for use in major depressive disorder and stress urinary incontinence.

Adverse Effects:
- **very common** (≥10%): insomnia, nausea, dry mouth, constipation, fatigue;
- **common** (≥1%): anorexia, thirst, sleep disorder, anxiety, decreased libido, headache, dizziness, tremor, blurred vision, diarrhoea, vomiting, dyspepsia, sweating, lethargy, pruritis, weakness.

Drug Interactions: Duloxetine can interact to cause serotonin syndrome (see page 7) if taken with serotonergic products. It also interacts with a wide range of other prescribed medications. Clinicians should refer to the current edition of the BNF or other reference source.

FLUPENTIXOL
Pharmacology: Flupentixol is a neuroleptic drug used in the treatment of schizophrenic psychoses. Its action is through blockade of dopamine receptors in the meso-limbic area of the brain.

License: Flupentixol is licensed for use in depressive illness and psychoses.

Adverse Effects:
- **common**: restlessness, insomnia, hypomania. Use with caution in patients with cardiovascular disease, renal impairment and porphyria.

Drug Interactions: Flupentixol interacts with a wide range of prescribed medications. Drowsiness has been noted when taken with codeine and anxiolytics. Clinicians should refer to the current edition of the BNF or other reference source.

MIRTAZAPINE
Pharmacology: Mirtazapine is a presynaptic α-2 antagonist that increases the release of noradrenaline and 5-HT. It has a low affinity for acetylcholine and dopamine receptors and is metabolised by the liver via CYP 450 system to a less active metabolite.

License: Mirtazapine is licensed for use in depressive illness.

Adverse Effects: Most side effects are usually mild to moderate and occur during the first few weeks of treatment. They include increased appetite, weight gain, drowsiness and sedation. Mirtazapine carries a rare risk of causing neutropenia and agranulocytosis.
**Drug Interactions:** Mirtazapine can increase plasma levels of warfarin, and plasma levels of mirtazapine can be altered if given in conjunction with ketoconazole, cimetidine, carbamazepine or phenytoin, for example.

**REBOXETINE**

*Pharmacology:* Reboxetine is a highly selective and potent inhibitor of noradrenaline reuptake, with a weak effect on 5-HT reuptake and no effect on dopamine. (Reboxetine has been included in this section as it is a more recent addition to the drugs available of the management of depression.)

*License:* Reboxetine is licensed for use in depressive illness.

*Adverse Effects:*
- **common:** vertigo, tachycardia, postural hypotension, vasodilation, constipation, anorexia, chills, erectile dysfunction, pain;
- **caution:** severe renal or hepatic failure, cardiovascular disease, epilepsy, bipolar disorders, urinary retention, prostatic hypertrophy, glaucoma.

*Drug Interactions:* Reboxetine can interact with macrolide antibiotics, antifungals and SSRIs, among others. There is an increased risk of hypokalaemia with diuretics.

**TRYPTOPHAN**

*Pharmacology:* Tryptophan is an essential dietary amino acid that is the body's main source of 5-HT. Therapeutic administration of tryptophan is thought to re-establish the inhibitory action of 5-HT, thereby reducing feelings of anxiety and depression.

*License:* The use of tryptophan is limited to hospital specialists for patients with severe and disabling depressive illness of more than two years’ duration, only after an adequate trial of standard antidepressant drug treatment, and only as an adjunct to other antidepressant medication.

*Adverse Effects:* Headache, light-headedness. Transient nausea can occur in the first few days of treatment.

*Drug Interactions:* Sexual disinhibition has been reported when tryptophan has been used with phenothiazines or benzodiazepines.

**Table 4: Properties of other antidepressants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>8-17 hours</td>
<td>Capsules (30/60mg)</td>
<td>60mg/day (max 60mg/day)</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>3 weeks-3 months</td>
<td>Tablets (500mcg/1mg)</td>
<td>500mcg-3mg/day (max 3mg/day)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>20-40 hours</td>
<td>Tablets (30mg) Orodispersible Tablets(15/30/45mg) Oral Solution (15mg/ml)</td>
<td>15-45mg/day (max 45mg/day)</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>13 hours</td>
<td>Tablets (4mg)</td>
<td>8-10mg/day (max 12mg/day)</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>1-3 hours</td>
<td>Tablets (500mg)</td>
<td>1g tds (max 6g/day)</td>
</tr>
</tbody>
</table>

**Duloxetine Evidence:**
Palliative Care / Advanced Cancer / Chronic Disease:
- no specific evidence

**Elderly:**
- more effective than placebo, with a beneficial effect on pain symptoms (Nelson *et al* 2005 *Evidence=1+*)

**General Population:**
- more effective than placebo, similar efficacy to paroxetine (Detke *et al* 2004 *Evidence=1-*)
- more effective than placebo, with a beneficial effect on pain symptoms (Detke *et al* 2002 *Evidence=1++*)
- more effective than placebo; possibly greater efficacy than paroxetine and fluoxetine (Dunner *et al* 2003 *Evidence=1-*)
- effective in women of all age groups (Burt *et al* 2005 *Evidence=1+*)

**Flupentixol Evidence:**

**Palliative Care / Chronic Disease:**
- effect seen in depression (Lloyd-Williams 1994 *Evidence=3*)

**General Population:**
- more effective than amitriptyline, with faster onset of action and fewer side effects (Høstmælingen *et al* 1989 *Evidence=1+*); depot preparation effective, but time to onset of action may be longer than other preparations (Budde 1992 *Evidence=2-*)

**Mirtazapine Evidence:**

**Palliative Care / Chronic Disease:**
- no specific evidence

**Advanced Cancer:**
- effective, independent of dose (Theobald *et al* 2002 *Evidence=2-*)

**Elderly:**
- safe and effective, better than placebo and significantly more effective than trazodone (Halikas 1995 *Evidence level=1++*); similar efficacy, but fewer withdrawals due to side effects, than paroxetine (Schatzberg *et al* 2001 *Evidence=1++*)

**General Population:**
- equally as effective as amitriptyline (Smith *et al* 1990 *Evidence=1++*; Bremner 1995 *Evidence=1++*; Zivkov & de Jongh 1995 *Evidence=1++*; Zivkov *et al* 1995 *Evidence=1++*), citalopram and venlafaxine (Guelfi *et al* 2001 *Evidence=1++*); significantly more effective than fluoxetine (Wheatley *et al* 1998 *Evidence=1+*) and paroxetine (Benkert *et al* 2002 *Evidence=1-*)
- more rapid onset of action than citalopram (Leinonen *et al* 1999 *Evidence=1+*) and paroxetine (Benkert *et al* 2002 *Evidence=1-*)

**Reboxetine Evidence:**

**Palliative Care:**
- no specific evidence

**Advanced Cancer:**
- effective in major depressive disorder (Grassi *et al* 2004 *Evidence=2-*)

**Chronic Disease:**
- HIV / AIDS: effective in major depressive disorder (Carvalhal *et al* 2003 *Evidence=2-*)
General Population:
- improves cognitive functioning in depressed patients compared to paroxetine and placebo (Ferguson et al 2003 Evidence=1+)
- as effective as imipramine in treating depression, but fewer side effects (Berzeweski et al 1997 Evidence=1++; Katona et al 1999 Evidence=1++)
- as effective as fluoxetine, with similar side effect occurrence, compared to placebo (Andreoli et al 2002 Evidence=1+)
- effective in patients showing no response to fluoxetine (Fava et al 2003 Evidence=1-)
- greater and faster-onset response than desipramine and placebo (Scates & Doraiswamy 2000 Evidence=1-)

Tryptophan Evidence:
Palliative Care / Advanced Cancer / Chronic Disease / Elderly:
- no specific evidence

General Population:
- evidence of effect over placebo (Shaw et al 2006 Evidence=2++)

Conclusion – other antidepressants:
While, as with many other medications, efficacy evidence for this group of antidepressants in palliative care populations is lacking, there is evidence of antidepressant effect for all drugs, to varying degrees. Mirtazapine is a safe and effective antidepressant with a favourable side effect profile and some evidence of more rapid onset of action. It has a low incidence of interaction with other drugs. It is safe and effective in the elderly, and in patients with a history of seizures, cardiac failure or diabetes. For these reasons, it is a suitable preparation for use in the management of depression in palliative care populations. Duloxetine has proven efficacy, with possible beneficial effects on pain, and reboxetine also has antidepressant efficacy, but both drugs are relatively new in this field and probably require further investigation. Reboxetine may be useful in serotonin syndrome due to its very weak effect on 5-HT and also in HIV, as its lack of effect on CYP 2D6 means it does not interfere with protease inhibitor metabolism. Flupentixol, while used in individuals with severe depression, has a longer onset of action and its pharmacokinetic properties make it less suitable for palliative care patients. The evidence for tryptophan is scarce at present.
6. HERBAL PREPARATIONS (St John’s Wort)

Pharmacology: The action of St John’s Wort (*Hypericum perforatum*) is thought to include multiple mechanisms including serotonin uptake and MAOI inhibition, GABA-ergic activity, monoamine reuptake and regulation of some 5-HT receptors. Approximately seven groups of pharmacologically active compounds have been identified from extracts of *Hypericum perforatum* to date.

Licence: St John’s Wort is not licensed for the treatment of depression. It is a popular herbal ‘over the counter’ remedy for mild to moderate depression.

Adverse Effects:
- common (>1-<5%): dyspepsia, diarrhoea, anorexia, nausea, constipation, rash, pruritis, photosensitisation, fatigue, sedation, restlessness, anxiety, dizziness, headache, dry mouth.

Drug Interactions: St John’s Wort can induce a number of drug metabolising enzymes and interacts with a wide range of prescribed medications. Few of these interactions are clearly identified or understood at this time. Reference should be made to the current edition of the BNF or other reference source whenever its use is being considered. St John’s Wort should not be used in conjunction with other antidepressants.

**St John’s Wort Evidence:**

Palliative Care / Advanced Cancer / Chronic Disease / Elderly:
- no specific evidence

General Population:
- greater efficacy than placebo and equal efficacy to standard antidepressants in mild to moderate depression; only minimal benefit over placebo in severe depression; fewer side effects than older antidepressants and possibly SSRIs (Linde *et al* 2005 *Evidence*=1++)
- as effective as standard antidepressants in mild to moderate depression and significantly more effective than placebo (Whiskey *et al* 2001 *Evidence*=1+)
- no evidence of benefit in severe depression (Hypericum Depression Trial Study Group 2002 *Evidence*=1++; Shelton *et al* 2001 *Evidence*=1++)

**Conclusion – St John’s Wort:**

There is some evidence of benefit of St John’s Wort in the treatment of mild to moderate depression, but not severe depression. The uncertain drug interaction profile of the preparation and lack of clear pharmacokinetic and pharmacodynamic data mean that it cannot be recommended for use in palliative care patients at this time.
Yorkshire Regional Palliative Medicine Clinical Guidelines Group: Antidepressants
October 2006

Table 5: Summary of recommendations

<table>
<thead>
<tr>
<th>1st Line Drug</th>
<th>Starting Dose</th>
<th>Dose Range</th>
<th>Dose Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20mg once daily</td>
<td>20-60mg daily</td>
<td>Elderly: start at a lower dose and titrate. Caution in severe renal impairment</td>
</tr>
<tr>
<td>or Mirtazapine</td>
<td>15mg once daily (nocte)</td>
<td>15-45mg daily (one or two doses)</td>
<td>Caution in severe hepatic &amp; renal impairment</td>
</tr>
</tbody>
</table>

| 2nd Line Trial | 75mg daily in 2-3 doses | 75-375mg daily in 2-3 doses. MR preparation for once daily dosing | Avoid in severe hepatic or renal impairment; halve dose in moderate renal impairment |

| 3rd Line Venlafaxine and Consider Psychiatry referral |

N.B. Non-pharmacological approaches to the management of depression in palliative care patients should be considered at all stages.
Special Considerations

Where nausea is a problem
Nausea is a common side effect of many antidepressants and, in patients who are depressed but also troubled by pre-existing nausea, choice of antidepressant treatment becomes clinically more important.

It has been suggested that controlled-release formulations of certain antidepressants (e.g., paroxetine, venlafaxine, but not fluoxetine) may be less likely to produce additional nausea, possibly due to reduced fluctuation between peak and trough plasma drug concentrations (De Vane 2003 Evidence=4), although the evidence for this is weak at present. Citalopram has been shown to result in lower levels of nausea than sertraline (Stahl 2000 Evidence=1++; Greist et al 2004 Evidence=1+); and mirtazapine appears better than paroxetine (Wade et al 2003 Evidence=1+) and venlafaxine (Fawcett & Barkin 1998 Evidence=1++; Nutt 2002 Evidence=4).

However, only mirtazapine has been suggested as being suitable for the treatment of nausea (Teixeira et al 2005 Evidence=3; Kast 2001 Evidence=4). Insufficient evidence for this claim is available at present.

At this time, it would appear reasonable to continue to recommend both citalopram (where the decision has been made to use a SSRI) and mirtazapine as first line antidepressants for palliative care patients experiencing nausea.

Where the patient has a short prognosis
Consideration needs to be given to the use of antidepressants in palliative care, where patients’ prognoses may be short. In such situations, antidepressant therapy may still be worthwhile. There is evidence that onset of action of mirtazapine may be earlier than that of other preparations (Leinonen et al 1999 Evidence=1++; Stahl et al 2001 Evidence=1-; Benkert et al 2002 Evidence=1-).

In patients whose prognoses are estimated at less than six weeks and where psychomotor retardation is a major feature, a stimulant drug, such as methylphenidate, may be more appropriate. Methylphenidate has been shown to effect a response in a short number of days (Katon & Raskind 1980 Evidence=3; Fernandez et al 1987 Evidence=3; Masand et al 1991 Evidence=3; Bukberg et al 1984 Evidence=2-; Olin & Masand 1996 Evidence=3; Homsi et al 2000 Evidence=3; Homsi et al 2001 Evidence=2+). A reduced response to methylphenidate in the last six weeks of life, possibly due to the relative impenetrability of the CNS to dopamine as part of the dying process, has been suggested (Macleod 1998 Evidence=2-), but has not been reported by other researchers.
In patients with neuropathic pain

Certain antidepressants appear to have a role in the management of both somatic and neuropathic pain, independent of their effect on mood, and at doses sub-therapeutic for the treatment of depression (Onghena & Van Houdenhove 1992 Evidence=1+; Ansari 2000 Evidence=2+). Tricyclic antidepressants have traditionally been used to manage neuropathic pain in clinical practice (an unlicensed indication), the majority of studies involving patients with diabetic painful neuropathy (Theesen & Marsh 1989 Evidence=3; Max et al 1992 Evidence=1+). However, analgesic effects have also been noticed with SSRIIs (paroxetine – Sindrup et al 1990 Evidence=1+; Sindrup et al 1991 Evidence=2+; citalopram – Sindrup et al 1992 Evidence=1+) and SNRIs (venlafaxine – Taylor & Rowbotham 1996 Evidence=4; duloxetine – Detke et al 2002 Evidence=1++; Nelson et al 2005 Evidence=1++; Raskin et al 2006 Evidence=2+). Preparations with mixed serotonergic and noradrenergic action may be more effective in bringing about analgesia (Jung et al 1997 Evidence=1+), possibly due to their role in the inhibition of pain signal transmission.

However, newer antidepressant preparations are generally better tolerated than tricyclic antidepressants, especially at doses required to achieve an antidepressant effect (Ansari 2000 Evidence=2+). Hence it would seem appropriate to continue to recommend citalopram first line for the management of depression in palliative care patients also experiencing neuropathic pain. Other co-analgesics may subsequently be required. Duloxetine may be an appropriate second line choice, but further evidence for its use in such situations is still required.

Where anxiety is a problem

Anxiety can be a problem in palliative care patients and is often present in patients who are depressed. Management of acute anxiety generally involves the use of a benzodiazepine (BNF 2006 Evidence=1++) but may mask a diagnosis of depression. In depressed patients where anxiety is a chronic feature (i.e., four weeks’ duration or more) an antidepressant which is also effective in managing anxiety may be required.

Several antidepressant product licences mention their use where sedation is required, although it should be noted that sedation does not necessarily equate with reducing anxiety. Trazodone is licensed for the management of anxiety, and both paroxetine and venlafaxine are licensed for general anxiety disorder. Citalopram, escitalopram and paroxetine hold licences for use in panic disorder.

Citalopram has been found to reduce anxiety in the general population (Stahl 2000 Evidence=1++) and reboxetine may also have an anxiolytic effect in depressed patients (Ferguson et al 2003 Evidence=1+; Versiani et al 2002 Evidence=1++). Trazodone may be associated with more side effects than SSRI preparations (Kasper et al 2005 Evidence=1++), and concerns exists regarding venlafaxine (MHRA 2006 Evidence=1++)(see also page 8). Hence, given its proven effectiveness and low rate of adverse effects, citalopram would be an appropriate choice in palliative care patients.
Where suicidal ideation is a feature
Patients displaying active suicidal ideation present particular difficulties for clinicians, when consideration of the choice of drug is important and involvement of a specialist mental health professional may be advisable.

Certain classes of antidepressant and specific preparations have been identified as having increased risk of toxicity in overdose. This is true for TCAs (Kapur et al 1992 Evidence=1--; BNF 2006 Evidence=1++) due to their propensity to cause cardiac side effects such as arrhythmia and heart block. Newer, tricyclic-related antidepressants, such as trazodone, may be associated with a lower rate of cardiotoxicity in overdose, but may result in additional side effects (BNF 2006 Evidence=1++). Evidence for the risks of SSRI antidepressants in overdose has been contentious. No increased risk of suicide or non-fatal self harm comparing adult users of SSRIs and TCAs has been reported (Fergusson et al 2005 Evidence=1+), although this differs from other advice given by regulatory bodies (MHRA 2006 Evidence=1++). The reduced cardiotoxicity of SSRIs has led to their use being recommended where there is a significant risk of deliberate self harm (BNF 2006 Evidence=1++). Specific recommendations have been made regarding the avoidance of venlafaxine in patients at risk of deliberate self harm, possibly due to increased cardiotoxicity in overdose (MHRA 2006 Evidence=1++) (See also page 8).

In palliative care patients who are depressed and thought to be at risk of self harm, the recommendations made for first line antidepressant prescription in these guidelines appear appropriate (i.e., citalopram or mirtazapine). General measures such as frequent review of the patient, involvement of experienced mental health professionals and provision of limited supplies of medication on initial prescribing should also be considered.

In patients with renal impairment
It may be necessary to adjust doses of antidepressant therapy where patients have impaired renal function. Citalopram and mirtazapine can be used with caution in severe renal failure (see Appendix 1). Sertraline can be used at normal dose. Consider liaison with a renal pharmacist / physician and the use of other sources of information.
CONCLUSIONS

Clinical guidelines have become an important component of clinical medical practice over recent years both as a result of the expansion of evidence based medicine and concerns regarding clinical governance. Difficulties exist, however, in the application of evidence based medicine to palliative care (Keeley 1999 Evidence=4), including problems in measuring quality of care and in applying rigorous research methodology in such a vulnerable group of patients (Higginson 1999 Evidence=4).

Such problems were evident in developing these guidelines on the use of antidepressants in palliative care. Data regarding this patient group was often unavailable or studies were small. Hence information regarding safety, efficacy and side effect profiles was also obtained from studies of patients with advanced malignant disease or with concomitant medical pathologies. These guidelines represent a thorough review of the available evidence and, in the absence of large, randomised, double-blind, placebo-controlled studies in palliative care, are a guide to treatment of depression in this population.

**Citalopram** has been chosen as a first line agent for management of depression in palliative care due to strong evidence regarding its efficacy, as well as its favourable adverse effect profile, availability in liquid form and low propensity for interaction with other drugs. **Mirtazapine** has also been included as a first line choice, being a safe, effective antidepressant with a more favourable adverse effect profile, and useful in patients who are nauseated or when a sedative effect would not be detrimental. Reasonable evidence also exists that it may act more quickly than other preparations. **Venlafaxine**, another effective, well-tolerated preparation, has been included for depression not responsive to first or second line agents, but recent cautions and recommendations regarding its use should be noted (see page 8).

The importance of non-pharmacological interventions when managing depression in palliative care practice, either independently or in conjunction with drug treatment cannot be emphasised more strongly. Depression is a disabling, multifactorial condition which requires a broad, multifaceted approach to management, and use of antidepressants is only one component of such management.
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolites (A=active, I=inactive)</th>
<th>Main Route of Elimination (D=drug, M=metabolites)</th>
<th>Dose/interval in renal failure (Sweetman 2004 Evidence=1++)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Nortriptyline (A) 10-Hydroxyamitriptyline (A) 10-Hydroxynortriptyline (A)</td>
<td>Urine &lt;10% (D) 90% (M)</td>
<td>Normal dose</td>
<td>Introduce / withdraw treatment gradually in renal impairment</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Dimethylcitalopram (A)</td>
<td>Urine (M)</td>
<td>Reduced or alternate day dosing may be necessary if GFR &lt;53ml/min</td>
<td>Use with caution in severe renal failure</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Dimethylcitalopram (A) Citalopram-N-oxide (A) Deaminated propionic acid derivative (I)</td>
<td>Hepatic 85% Urine 12% (D)</td>
<td>20-50</td>
<td>Normal dose or alternate days Normal dose or alternate days</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Various metabolites (I)</td>
<td>Renal (D, M)</td>
<td>Limited / no data available</td>
<td>Elderly may require reduced dose</td>
</tr>
<tr>
<td>Dexamfetamine</td>
<td>Hydroxylated metabolites (A)</td>
<td>Urine 45% (D, M)</td>
<td>Limited / no data available</td>
<td>Start low &amp; titrate slowly in elderly</td>
</tr>
<tr>
<td>Dosulepin</td>
<td>Desmethyllothiepin (A)</td>
<td>Urine (M)</td>
<td>Limited / no data available</td>
<td>As for amitriptyline</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>4-Hydroxy duloxetine (I) 5-Hydroxy, 6-methoxy duloxetine (I)</td>
<td>Urine 70% (M) Faeces 20% (M)</td>
<td>Limited / no data available</td>
<td>Manufacturers do not recommend use in severe renal impairment</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Norfluoxetine (A) (and other unidentified M)</td>
<td>Urine &lt;12% (D) 7% (M) Faeces 15% (D)</td>
<td>Normal dose or alternate days Normal dose or alternate days</td>
<td>Accumulation can occur in severe renal failure during chronic treatment</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>Limited / no data available</td>
<td>Urine (M) Faeces (M)</td>
<td>Limited / no data available</td>
<td>Elderly may require reduced dose</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Various metabolites (I)</td>
<td>Urine (I, D)</td>
<td>Limited / no data available</td>
<td>Elderly may require reduced dose</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>Desipramine (A)</td>
<td>Urine (M)</td>
<td>Limited / no data available</td>
<td>Elderly may require reduced dose</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Desmethylmaprotiline (A) Maprotiline-N-oxide (A)</td>
<td>Urine 57% (M) 3-4% (D) Hepatic 30% (M)</td>
<td>Reduced or alternate day dosing may be necessary in moderate to severely impaired renal function</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Ritalinic acid (PPAA) (I) Hydroxymethylphenidate (I) Hydroxyritalinic acid (I)</td>
<td>Urine 80% (M) 1% (D)</td>
<td>Normal dose</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Desmethylmianserin (A) 8-Hydroxyethylmianserin (A)</td>
<td>Urine (M)</td>
<td>Limited / no data available</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>8-Hydroxymirtazapine (I) N-Demethylmirtazapine (A) N-Oxide mirtazapine (I)</td>
<td>Urine &gt;75% (D) Faeces 15% (D)</td>
<td>20-50</td>
<td>Normal dose or alternate days Normal dose or alternate days</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Oxidation (I) &amp; methylation (I)</td>
<td>Urine 2% (D) Faeces 36% (D)</td>
<td>Limited / no data available</td>
<td>Elderly may require reduced dose</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Prednisolone glucuronide (I) Prednisolone sulphate (I) Conjugated prednisolone (I)</td>
<td>Renal (D, M)</td>
<td>Limited / no data available</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>O-desethytreboxetine</td>
<td>Urine 68% (M) 10% (D)</td>
<td>Reduced or alternate day dosing may be necessary in impaired renal function</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>N-Desmethylsertraline (I)</td>
<td>Urine (M); Faeces (M)</td>
<td>Normal dose</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>St John's wort</td>
<td>Limited / no data available – amount &amp; concentration of metabolites can vary between products</td>
<td>Limited / no data available</td>
<td>Limited / no data available</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Trazodone</td>
<td>m-Chlorophenylpiperazine</td>
<td>Urine (M); Faeces (M)</td>
<td>Normal dose</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Limited / no data available</td>
<td>Hepatic</td>
<td>Limited / no data available</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>O-Desmethylvenlafaxine (A) N-Desmethylvenlafaxine (A) NO-Didesmethylvenlafaxine (A)</td>
<td>Hepatic (D) Renal 1% (D) 37-50% (M)</td>
<td>Normal dose</td>
<td>Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite</td>
</tr>
</tbody>
</table>
Appendix 2

**Grading of evidence**

Evidence identified as relevant to this review was graded according to published criteria identified for the purpose of creating clinical guidelines. A summary of these criteria is included below.

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, OR RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, OR RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews of RCTs, OR RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case-control or cohort studies OR high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Nonanalytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

*From: Keeley PW. Clinical guidelines. *Palliat Med* 2003; **17**: 368-74*
Appendix 3

Abbreviations

5-HT  5-hydroxytryptamine / serotonin
ACTH  adreno-cortico trophic hormone
AIDS  acquired immunodeficiency syndrome
BDI  Beck Depression Inventory
BNF  British National Formulary
BPRS  Brief Psychiatry Rating Scale
BSI  Brief Symptom Inventory
CBT  cognitive behavioural therapy
CDS-R  Carroll Depression Scales (Revised)
CGI  Clinical Global Impression Scale
CNS  central nervous system
COPD  chronic obstructive pulmonary disease
CrCl  creatinine clearance (ml/minute)
CYP  cytochrome P
DSM-IV Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG  electrocardiogram
emc  electronic medicines compendium
EPDS  Edinburgh Postnatal Depression Scale
g  gram
GABA  gamma-aminobutyric acid
GDS  Geriatric Depression Scale
HADS  Hospital Anxiety and Depression Scale
HAM-A  Hamilton Anxiety Rating Scale
HAM-D  Hamilton Depression Rating Scale
HIV  human immunodeficiency virus
MADRS  Montgomery-Åsberg Depression Rating Scale
MAOI  monoamine oxidase inhibitor
max  maximum
mcg  microgram(s)
metab  metabolites
mg  milligram(s)
MHRA  Medicines and Healthcare products Regulatory Agency
ml  millilitre(s)
MR  modified-release
MS  multiple sclerosis
NSAID  non-steroidal anti-inflammatory drug
RCT  randomised controlled trial
SIADH  syndrome of inappropriate antidiuretic hormone secretion
SIGN  Scottish Intercollegiate Guidelines Network
SNRI  serotonin and noradrenaline reuptake inhibitor
SSRI  selective serotonin reuptake inhibitor
TCA  tricyclic antidepressant
tds  three times daily
Appendix 4

Depression rating scales

Below are brief summaries of a range of depression rating scales used in clinical practice and in research studies. This list is by no means exhaustive.

**Beck Depression Inventory (BDI)**
A 21-question multiple choice inventory administered by a health professional about how the individual has been feeling over the preceding week. Questions range in scope from feelings of sadness to loss of libido (Beck *et al* 1961).

**Brief Psychiatry Rating Scale (BPRS)**
Sixteen items rated from 0 (not present) to 6 (extremely severe), including somatic concern, anxiety, depressed mood, hostility and hallucinations. This quantitative scale was developed for schizophrenia states but also includes depression symptoms and rates the current clinical picture only. It is not a diagnostic tool (Overall & Gorham 1962).

**Brief Symptom Inventory (BSI)**
This tool measures current psychological symptom status and is orientated toward psychiatric diagnoses. A self-administered 53-item scale yields scores that dictate psychological distress. It takes 7-10 minutes to complete and is easily scored. It does not have a specific suicide subscale and is expensive to purchase (Derogatis & Melisaratos 1983).

**Carroll Depression Scale – Revised (CDS-R)**
Derived from the HAM-D, this 61-item, self report inventory includes all the symptoms of depressive disorders included in the DSM-IV. It also includes a screening instrument. Both the CDS-R and Brief CDS use a simple yes / no format and display good levels of both sensitivity (87%) and specificity (58%) for depression (Carroll *et al* 1981).

**Clinical Global Impression (CGI) Scale**
The CGI scale refers to the global impression of the patient and requires clinical experience with the syndrome under assessment. The scale can only be completed following or during treatment. The concept of improvement refers to the clinical ‘distance’ between an individual’s current condition and that prior to the start of treatment. The scale has a single item measured on a 7 point scale from 1 (‘normal’, not ill) to 7 (extremely ill) (Guy 1976).

**Edinburgh Postnatal Depression Scale (EPDS)**
The EPDS consists of ten short statements and the patient rates which of four possible responses to each statement is closest to how they have been feeling over the preceding week. The scale takes 5 minutes or less to complete. Items are scored and, of those who score above the threshold for diagnosis of probable depression, 92.3% are likely to be suffering from a depressive disorder of varying severity (Cox *et al* 1987).
Geriatric Depression Scale (GDS)
This scale has been tested and used extensively in the older population and can be used in healthy, medically ill and mild to moderately cognitively impaired older adults. By means of a brief questionnaire, participants are asked to answer 30 questions by responding either yes or no in reference to how they feel on the day of administration. The GDS was found to have 92% sensitivity and 89% specificity when evaluated against diagnostic criteria (Yesavage et al 1983).

Hamilton Anxiety Rating (HAM-A) Scale
This 14-item scale was developed to assess and quantify symptom severity in individuals with anxiety. It measures the severity of symptoms (on a scale of 0 to 4) such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness and other physical symptoms (Hamilton 1959).

Hamilton Depression Rating (HAM-D) Scale
This scale is used to assess the severity of depression in patients already diagnosed with an affective disorder. There are two versions of the scale using either 21 or 17 items. Scoring is from 0 to 4, higher scores indicating more severe the depression. Questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss (Hamilton 1960).

Hospital Anxiety and Depression Scale (HADS)
The HADS scale was developed to identify anxiety and depression in patients in non-psychiatric hospital clinics. It is divided into anxiety and depression subscales, both containing seven intermingled items. All symptoms relating to somatic disorders (e.g., dizziness, headaches, insomnia, fatigue) are excluded. The tool displays acceptable internal consistency, sensitivity and specificity (Zigmond & Snaith 1983).

Montgomery-Åsberg Depression Rating Scale (MADRS)
The MADRS measures the effect of treatment on depression severity and, as such, requires a baseline assessment (before treatment) with subsequent assessments during the course of treatment. It measures the severity of a number of symptoms (scale from 0 to 6), including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation and restlessness (Montgomery & Åsberg 1979).

Zung Depression Scale
This 20-item self-report questionnaire is used as a screening tool, covering affective, psychological and somatic symptoms associated with depression. Items are framed in terms of positive and negative statements. It can be effectively used in a variety of clinical settings. The scale has 87% sensitivity and 76% specificity for depression (Zung 1965).
Appendix 5

Reviewing efficacy of, withdrawing and swapping antidepressants

Reviewing efficacy of antidepressant medication
Similar to good practice in other areas of medicine, the use of medications in the management of depressive illness requires appropriate clinical supervision and regular review. Many antidepressant medications have the potential to cause side effects, albeit often early in treatment, mild and self-limiting, but patients should be made aware of this prior to commencing treatment.

As a general rule, patients should be reviewed within four weeks of starting antidepressant treatment in order to assess continuing side effects and to determine any clinical effect. Initial review may be earlier in specific circumstances (e.g., suicidal ideation, other troublesome symptoms, clinical deterioration of mood). It should be remembered, however, that many antidepressant preparations may take longer than four weeks to display any identifiable effect on mood.

If a decision to continue treatment after four weeks is taken, patients should then be reviewed monthly for at least two months. After this, it may be appropriate to extend periods between reviews to two months or longer.

In clinical practice, if treatment with antidepressant medication is effective, it should generally be continued for a maintenance period of four to six months following the return of mood to normal.

Withdrawing antidepressant medication
As with many other drugs, all antidepressants have the potential to cause withdrawal phenomena and should not be stopped abruptly (after six weeks of treatment) unless a serious adverse effect has occurred (Taylor et al. 2001).

Antidepressant medication should be withdrawn gradually over a period of four weeks in decremental doses. An exception to this general rule is fluoxetine which, due to its long half life, can be stopped abruptly from its usual dose of 20mg per day.

Withdrawal symptoms, should they occur, include dizziness, electric shock sensations, anxiety and agitation, insomnia, flu-like symptoms, diarrhoea and abdominal spasms, paraesthesia, mood swings, nausea and low mood. If such symptoms are experienced, it may be useful to slow the rate of drug withdrawal. Most symptoms last for 1-2 weeks at most.

Swapping antidepressant medication
Abrupt withdrawal of an antidepressant should be avoided when swapping from one preparation to another. The Maudsley Prescribing Guidelines recommend cross tapering of drugs where possible (Taylor et al. 2001), where the dose of the drug being stopped is gradually reduced while the new drug is
slowly introduced. The speed of cross tapering will be determined by the patient’s clinical response.

Some drugs, due to interactions, cannot be cross tapered. Prescribers should consult either the Maudsley Prescribing Guidelines or the current edition of the BNF for further guidance. In some cases, however, no cross tapering is necessary, e.g., when swapping between SSRI preparations.

The Maudsley Prescribing Guidelines include a set of useful reference tables regarding swapping between antidepressants.
Appendix 6

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