

Contents: The drug treatment of depression in primary care

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Depression is one of the most common reasons for consulting a GP. Antidepressant prescribing accounts for over £200 million of annual NHS spending.¹ Despite being a major cause of increased mortality, impaired quality of life and reduced productivity,² it is often unrecognised and many patients do not receive optimum treatment.³

In 1999, the government published the *National Service Framework for Mental Health (NSF)*³ which builds on their mental health strategy.⁴ Guidelines on depression in the community are also included in the work programme of the National Institute for Clinical Excellence (NICE).

The use of effective treatment, such as antidepressant drugs for depression, is an important part of the NSF. This *Bulletin* discusses the drug treatment of depression in primary care and considers a practical approach to prescribing.

Establishing a diagnosis

Depression is often difficult to diagnose in general practice, especially when it is associated with physical symptoms.⁵ Diagnostic tools are available and include the fourth revision of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV)⁶ and the tenth revision of the International Classification of Diseases (ICD-10)⁷ criteria.

Table 1 shows DSM-IV criteria for **major depression**. Patients who do not fit these criteria may have **dysthymia**, a chronic depressive state (>2 years duration), or **minor depression**.^{6,8}

SUMMARY

- * Although depression increases mortality, it is often unrecognised and many patients do not receive optimum treatment.
- * **The choice of antidepressant should be based on individual patient factors** such as likely tolerability, the risk of suicide and previous treatment response. Tricyclic antidepressants (TCAs), related drugs and selective serotonin-reuptake inhibitors (SSRIs) are suitable first-choice agents for most patients.
- * **Antidepressants should be continued for at least four to six months after recovery as there is good evidence that this reduces the risk of relapse.**
- * There are no clinically significant differences in efficacy between TCAs and SSRIs.
- * Although SSRIs are better tolerated than TCAs in terms of overall withdrawal rates from trials, the absolute difference is small. However, TCAs and SSRIs have different side-effect profiles, with TCAs having more anticholinergic and cardiotoxic effects.
- * When taken in overdose, older TCAs such as dothiepin and amitriptyline are more toxic and more likely to cause fatalities than SSRIs. Lofepramine seems to have a similar toxicity in overdose to that of SSRIs. It also has less anticholinergic and cardiotoxic effects than older TCAs, and is less sedating.
- * Newer drugs such as mirtazapine, nefazodone, reboxetine[▼] and venlafaxine may have a place in the treatment of patients in whom first-choice drugs are poorly tolerated or ineffective. However, further experience and studies are required to confirm their precise role in primary care.

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Who should be prescribed an antidepressant?

Systematic reviews have shown antidepressants to be effective in the acute treatment of all grades of depression,⁹ including patients with dysthymia¹⁰ and physical illness.¹¹ However, their benefit over placebo is less clear in milder cases.⁶ Many antidepressant studies are short and have been carried out in secondary care, making it difficult to generalise results to the primary care setting.¹ Studies often show a high (25 to 30%) placebo response,⁶ which reflects the difficulty in deciding who to treat.

Certain psychological treatments such as cognitive therapy, problem solving or interpersonal psychotherapy may be as effective as drugs in mild to moderate disease.⁹

A reasonable approach would be to start antidepressants as soon as possible in most patients with major depression (irrespective of stressful life events⁵), dysthymia or persistent minor depression.^{6,12} Psychological treatment may be tried first in mild cases, but this depends on its availability, the patient's history and their preference.^{6,12} All treatment should be coupled with supportive care, addressing social problems if present.⁷ Patients with psychotic symptoms or particularly at risk of suicide should be referred to a psychiatrist immediately. A history of bipolar affective disorder also warrants early referral.⁶

Which drug should be used?

The choice of antidepressant should be based upon the individual patient. In particular, the following factors should be considered:^{6,13}

- previous response to, or side-effects from, a particular drug
- concomitant psychiatric or medical conditions
- existing drug treatment (i.e. potential for drug interactions)
- suicide risk
- desirability of sedation or other effects associated with a particular drug
- patient's choice and likely compliance
- prescribing costs of drug or proven cost-effectiveness.

At least five of the following symptoms (including either 1 or 2) have been present over the last two weeks most of the day, or nearly every day, and cause clinically significant distress or impairment in functioning. The symptoms are not due to a physical/organic factor (e.g. substance abuse) or illness and are not better explained by bereavement (but this can be complicated by major depression).

1. Depressed mood.
2. Loss of interest or pleasure in almost all activities.
3. Significant weight loss or gain, or change in appetite nearly every day.
4. Insomnia or hypersomnia.
5. Psychomotor agitation or retardation (observable by others).
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive or inappropriate guilt.
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death or suicide.

Table 1. Diagnosis of major depression by DSM-IV⁶

If the patient has responded well to, and tolerated, a particular drug in the past, it is best to try the same drug again (provided there are no new contraindications).⁷ Tricyclic antidepressants (TCAs), related drugs and selective serotonin-reuptake inhibitors (SSRIs) are suitable first-choice agents for patients who have not previously taken antidepressants.

TCAs versus SSRIs

Which are the most effective?

There are no clinically significant differences in efficacy between TCAs and SSRIs. This has been found in several systematic reviews,^{1,9,14} including a Cochrane Review,¹⁴ which analysed 98 randomised controlled trials (RCTs) in 9554 patients with depression. TCAs may be more effective in hospitalised patients with severe depression, but the evidence is inconsistent.⁶

Although most SSRIs are also licensed for anxiety, evidence that they are more effective than TCAs in treating depression with concomitant anxiety is lacking. Sedating drugs are not necessarily the most effective treatment for these patients.⁸ The depression should be treated first, as both conditions may then improve.⁸

Which are the safest in overdose?

Observational studies suggest that, when taken in overdose, older TCAs such as dothiepin and amitriptyline are more toxic and more likely to cause fatalities than SSRIs. Lofepramine seems to have a similar toxicity in overdose to that of SSRIs.^{15,16}

It is not currently clear whether certain drugs, particularly SSRIs such as fluoxetine, provoke suicidal behaviour. There is no consistent good quality evidence to support this. However, following anecdotal case reports with fluoxetine, the Committee on Safety of Medicines continue to monitor this issue. The suicide risk may increase in the early stages of treatment with any antidepressant and patients 'at-risk' should be closely monitored.¹⁷

Which are better tolerated?

Although SSRIs are significantly better tolerated than TCAs in terms of overall withdrawal rates from trials, the absolute difference is small. A meta-analysis of 123 RCTs in 9104 patients found that, compared with TCAs, SSRIs reduce the risk of withdrawal by about 4% during six weeks of treatment.¹³ Most comparisons used mainly older TCAs e.g. imipramine and amitriptyline, which are associated with more side-effects.¹⁸ However, it is unclear how withdrawal rates from RCTs relate to long-term treatment in primary care.

TCAs are commonly associated with anticholinergic side-effects ranging from constipation, dry mouth and blurred vision to potentially serious urinary retention, confusion and delirium in the ill or elderly. Cardiovascular effects such as arrhythmias and hypotension may also occur. TCAs can prolong the QT interval.¹⁹ Sedation and weight gain may also be a problem with some agents.²⁰

SSRIs are not without adverse effects. Gastrointestinal (GI) disturbances, such as nausea

(22%), diarrhoea (13%) and constipation (10%) are common.⁹ Central nervous system effects such as dizziness, agitation, insomnia and headache may also be problematic.⁹ Although SSRIs are less likely to cause apathy or lethargy than TCAs, sexual dysfunction and hyponatraemia may occur more frequently.²⁰ There is some evidence that SSRIs might alter platelet function, increasing the risk of GI bleeding, especially if used with non-steroidal anti-inflammatory drugs.²¹

Older or physically ill patients are more susceptible to adverse effects. For these people, it is best to select a drug with fewer anticholinergic and cardiovascular side-effects,⁷ such as an SSRI. Where possible, TCAs should be avoided in patients with ischaemic heart disease. SSRIs may be safer, but there have been few published studies in this area.²²

Amitriptyline and imipramine are well established and relatively inexpensive TCAs. However, newer TCAs, such as lofepramine, have less anticholinergic and cardiotoxic effects than the older agents.²³ Lofepramine is also safer in overdose (see earlier) and less sedating than older TCAs. Of the SSRIs, paroxetine has been associated with more extrapyramidal and withdrawal reactions.¹⁷

TCAs and SSRIs should be used cautiously in patients with epilepsy as they can lower the seizure threshold. Despite the lack of large studies in epilepsy, SSRIs are thought to be less of a problem than TCAs.²⁴ However, some antidepressants, such as fluoxetine and fluvoxamine, may increase plasma concentrations of phenytoin and carbamazepine.

All types of antidepressant have been associated with hyponatraemia, particularly in the elderly. The possibility of this should be considered in anyone who develops drowsiness, confusion or convulsions during treatment.

Monoamine-oxidase inhibitors

Monoamine-oxidase inhibitors (MAOIs) may be less effective than TCAs in severe depression,

but more effective in patients with atypical depression.⁹ In view of this, and their ability to interact with various drugs and foods, they are not first-choice agents.⁶ Patients on MAOIs must carry a warning card and avoid food and drink containing tyramine. Interactions are less likely with moclobemide, the reversible MAOI.

Newer antidepressants

In recent years, several newer antidepressants have been introduced.²⁵ These include **mirtazapine** (*Zispin*, Organon), **nefazodone** (*Dutonin*, Bristol-Myers Squibb), **reboxetine**[†] (*Edronax*, Pharmacia) and **venlafaxine** (*Efexor*, Wyeth). These drugs may have a place in the treatment of patients in whom first-choice drugs are poorly tolerated or ineffective. However, further experience and studies are required to confirm their precise role in primary care.

Prescribing considerations

It is advisable to initially limit the total amount of drug prescribed, in order to reduce the risk if taken in overdose.⁶ Low doses of TCAs should be prescribed at first and increased, according to tolerability, every three to seven days until the recognised minimum effective dose (125-150mg/day for most TCAs) is reached.^{6,23} Doses should be increased slowly in the elderly, who are more susceptible to side-effects such as sedation and hypotension.

Although older TCAs are often prescribed in low doses, it is not clear whether this relates to large reductions in effectiveness. **Where possible, treatment should be titrated to dosages at which efficacy is proven, especially in severe depression.**⁶

Patients may need to be reviewed every week or two initially to assess side-effects, response, compliance and suicidal risk. However, a response is not expected within the first two weeks and decisions to alter treatment should be made after at least four to six weeks. If there is no sign of improvement after four weeks, a response is

unlikely (elderly patients may take longer to respond).⁶

If there has been no response to treatment, it is important to ensure the drug has been **taken regularly**, at a **suitable dose** and for an **adequate period**. The diagnosis may need to be confirmed and the patient assessed for other physical or psychiatric conditions, as well as social factors. Although evidence supporting the best approach to initial non-response is limited, it may be worth switching to a different drug class. Referral to a psychiatrist is appropriate when at least two treatment attempts have failed or resulted in only partial response.⁶

When switching antidepressants, a cross-tapering approach may be preferred (i.e. slowly reducing one drug, while the other is slowly introduced). However, this may not always be necessary and can be dangerous in certain cases where clinically significant interactions occur (such as a serotonin syndrome when using drugs with serotonergic activity). A washout period is sometimes needed. The specific advice should be checked for each situation.²³

About 37% of patients in primary care relapse within a year of remission from depression.⁶ **Antidepressants should, therefore, be continued for at least four to six months after recovery as there is good evidence that this will reduce the risk of relapse.**⁹ Elderly patients may benefit from at least twelve months treatment.⁶

Maintenance treatment may need to be considered for patients who have recurrent depression, as this has been found to reduce the risk of recurrence.⁹ The optimum duration is not confirmed, but some people may need treatment at a full therapeutic dose indefinitely.¹² It is advisable to start long-term maintenance treatment only under the supervision of a psychiatrist.²⁶

Antidepressants that have been taken regularly for at least six weeks must not be discontinued abruptly, unless a serious adverse effect has occurred.²³ Stopping treatment

Comparative costs of some antidepressants

Prices taken from the Drug Tariff and Chemist and Druggist, March 2001.
Based on 28 days treatment at usual BNF dose range. Dose titration may be necessary.

TCAs

Amitriptyline

Generic tabs 75-200mg £2.00-£4.80

Dothiepin (Dosulepin)

Generic tabs 75-150mg* £2.78-£5.56
Prothiaden tabs 75-150mg* £4.20-£8.40

Lofepramine

Generic tabs 140-210mg £10.13-£15.20
Gamanil tabs 140-210mg £9.84-£14.76

SSRIs

Citalopram

Generic tabs 20-60mg £16.03-£43.13

Cipramil tabs

20-60mg £7.07

Fluoxetine

Generic caps 20mg £7.07
Prozac caps 20mg £18.52

Paroxetine

Generic tabs 20-50mg £16.58-£45.66

Sertraline

Generic tabs 50-200mg £16.20-£53.02

Newer antidepressants

Mirtazapine

Generic tabs 15-45mg £11.46-£34.38

Nefazodone

Generic tabs 100-600mg £8.40-£25.20

Reboxetine

Generic tabs 8-12mg £17.65-£26.47

Venlafaxine

Generic tabs 75-150mg† £23.97-£39.97

Efexor XL m/r caps 75-225mg £23.97-£63.94



Notes: Doses given as total daily dose * up to 225mg/day in severe depression
Elderly patients may require lower doses † up to 375mg/day in severe depression

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Date of preparation: March 2001

quickly can sometimes cause a withdrawal reaction. It is best to reduce the dose gradually over at least two to four weeks,²³ but slower withdrawal may be necessary after longer periods (e.g. over six weeks after a six month course).²⁶ Fluoxetine, which has a long half-life, is less likely to cause a withdrawal reaction.^{6,26}

It is important to encourage compliance by ensuring patients understand their treatment (table 2). Primary care pharmacists are well placed to provide advice. A recent guide discusses the role of pharmacists in mental health.²⁸

Conclusion

The choice of antidepressant should be based on individual patient factors such as likely tolerability, risk of suicide and previous response to treatment. Adequate treatment duration is important to help prevent relapse.

It would be useful for local policies to be developed where GPs and psychiatrists agree on the use of a few antidepressants from different classes in primary care. However, further studies are still required to determine the best approach in this setting.

Adapted with permission from work produced by the Welsh Medicines Resource Centre and originally published as a WeMeReC Bulletin.

Table 2. Information for patients

A response is unlikely within the first two weeks (full effect may take up to six weeks).

Treatment should be continued for at least four to six months after recovery.

Most side-effects are minor and often improve with time.

Treatment should not be stopped abruptly.

The unlicensed herbal remedy, St John's Wort (*Hypericum perforatum*) must not be taken as well as antidepressants because it interacts with many drugs e.g. SSRIs.²⁷

The DVLA suggest a cautious approach to driving when taking all antidepressants.