

Depression

Antidepressant Update

Key messages on the use of antidepressants

- Clinical response to antidepressants should be assessed by an adequate trial, i.e. appropriate dose for at least 4 – 6 weeks.
- It is often possible to manage adverse effects before switching treatment, e.g. dose reduction in anxiety.
- The basis for drug selection is multifactorial including the drug's adverse effect profile, potential for drug interactions, concurrent medical conditions, safety in overdose, and previous response to treatment (in the case of recurrent depression).
- SSRIs are usually the first choice antidepressant in older people but specific adverse effects and drug interactions require monitoring.
- Venlafaxine is a useful third line antidepressant which can be tried if there has been an unsatisfactory response to an adequate trial of two other antidepressants. Special authority is required.
- Venlafaxine can cause adverse cardiovascular effects. Patients should be assessed for cardiac risk before and during treatment.
- TCAs are considered relatively safe in pregnancy. There have been recent concerns over a possible link between congenital anomalies and first trimester exposure to paroxetine and perhaps other adverse outcomes of pregnancy with other SSRIs. Citalopram provides lower infant drug exposure than fluoxetine during breastfeeding.
- It is very important to identify and address key stressors and triggers for depression and to assess the risk of suicide and harm to others.

Effectiveness of antidepressants in treatment of depression in primary care

In mild depression the evidence for effectiveness of drug treatment is relatively weak and non-drug treatments should be considered first line. In moderate to severe depression, antidepressants have proven clinical effectiveness but individual response to antidepressants varies and only about 50% of patients respond to the first drug chosen. Most efficacy trials are based on response (i.e. improvement) not remission and residual symptoms are possible even after 6 weeks. In most patients residual symptoms (often reflecting continuation of underlying stressors) can be expected and should be actively managed.

Choice of antidepressant

There is no compelling evidence that one drug or drug group is more effective or better tolerated than another so choice of antidepressant is based on individual patient factors and includes:

- Previous response. If a patient has responded well to an antidepressant before, consider that drug as first choice.
- Adverse effects. Avoid drugs which have previously caused troublesome or unmanageable adverse effects. Consider the drug's adverse effect profile and its potential for aggravating any concurrent conditions. For example, avoid TCAs in cardiac conduction abnormalities.
- Assess the potential for drug interactions. For example, citalopram has a much lower potential for interactions than fluoxetine or venlafaxine.
- Individual tolerance to adverse effects. For some people the anticholinergic effects of TCAs will be unacceptable but others will not tolerate the stimulatory effects sometimes associated with SSRIs.
- Co-morbid psychiatric or medical conditions may influence drug choice.
- Compliance and concordance. If a person's drug taking is erratic and unreliable, fluoxetine may be a better choice than paroxetine as it has a long half-life and is less likely to cause discontinuation effects.
- Suicide risk. The potential for fatal overdose is much higher with TCAs than with SSRIs. Suicidal thinking has been linked to SSRIs but this can also occur with TCAs and any antidepressant drug treatment.

Optimising response

Optimising the response to antidepressant treatment involves initial drug choice as outlined above, use of an adequate dose for sufficient duration, management of adverse effects, review of diagnosis, management of patient expectations and the use of concurrent non-drug treatment. It is very important to explain to patients the possibility of non-drug options to augment antidepressants and the expectations of antidepressant therapy. A person's expectations and beliefs about their condition and treatments can influence compliance.

Appropriate dose and duration

Antidepressants should usually be started at the recommended initial dose and the response reviewed after 4 – 6 weeks. With TCAs, gradual titration every 3 – 7 days is generally recommended to assess tolerance of dose related side effects. A smaller initial dose should be considered in some situations, e.g. if there is associated panic disorder or anxiety or if the person has previously found drug treatment intolerable.

If response to an antidepressant is poor, partial or not sustained after 4 – 6 weeks, check the compliance and review the diagnosis before considering a change. Some patients may respond to an increase in dose according to the manufacturer's recommendations.

Temporary dose reduction to manage adverse effects may be warranted. For example, if an SSRI causes initial mild restlessness (not associated with severe anxiety or suicidal ideation), reducing the dose or short term use of a benzodiazepine may be effective instead of switching to an alternative drug.

Switching drug therapy

If there is a partial response, or an initial response that has become attenuated, a further increase in dose may be effective. If there is no response at all to the usual maximum dose then a response may be obtained by changing to another drug.

There are no hard and fast rules to guide which drug to switch to. Similar factors that governed the initial drug choice may be relevant and there may be some logic in trying a drug from a different class. However, a response or better tolerability is often seen by changing to another drug from the same class, (e.g. switching from fluoxetine to citalopram). This may be explained by subtle differences in pharmacology or differences in drug metabolism and genetic polymorphism. (See article on pharmacogenetics on page 32). When switching drugs, consider the need for washout periods and cross tapering and the management of discontinuation syndrome. (bpac^{nz}, 2004).

Venlafaxine: how and when to use

Venlafaxine may be a useful option for resistant depression

Venlafaxine is a third-line option for the treatment of depression, which has failed to respond to adequate trials of two other antidepressants (NICE, 2004). It is chemically distinct from SSRIs and TCAs and inhibits re-uptake of both serotonin and nor-adrenaline. Remission rates of depression with venlafaxine may be slightly better than with SSRIs as a group (Han, 2005) but on the other hand withdrawal rates due to adverse drug reactions may be higher than with some other antidepressants (NICE, 2004).

Vocationally trained GPs can now prescribe extended release venlafaxine (Efexor-XR) under special authority for people who have trialled and failed to respond to two antidepressants for an adequate time (usually at least 4 weeks).

Venlafaxine is reserved for the treatment of depression resistant to other drugs. It is not a first line option as it is not significantly more effective than other drugs in primary care, it has higher withdrawal rates due to adverse effects and is more expensive.

Venlafaxine has different adverse effects to other antidepressants

Venlafaxine shares some adverse reactions and prescribing precautions with other antidepressants but also has some different ones.

Both venlafaxine and SSRIs can cause hyponatraemia, serotonergic effects and discontinuation syndrome. Cardiotoxicity is more problematic with venlafaxine than with SSRIs, but it usually causes less anticholinergic effects than TCAs.

Venlafaxine can increase heart rate, blood pressure and prolong QTc interval. Clinically significant increases in serum cholesterol have been noted, especially after prolonged administration of high doses.

In overdose there is some evidence that venlafaxine is more toxic than SSRIs (Buckley, 2002) but it is unclear if this is due to higher drug toxicity *per se* or its use by people at higher risk of suicide.

Venlafaxine and cardiovascular risk

The safety of venlafaxine for people with a history of cardiovascular disease has been the subject of recent debate. In the UK the Medical and Healthcare products Regulatory Agency (MHRA) has recently updated its prescribing advice for venlafaxine as follows:

“Venlafaxine is contraindicated in patients with an identified high risk of a serious cardiac ventricular arrhythmia and uncontrolled hypertension.

It should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent MI).

Regular measurement of BP is recommended for patients receiving venlafaxine. For patients who experience a sustained increase in BP while receiving venlafaxine, either dose reduction or discontinuation should be considered.” (MHRA, 2006)

The wording in the current New Zealand prescribing information is different but the message is similar emphasising extreme caution in patients with a history of, or at risk of, cardiovascular disease.

Drug interactions with venlafaxine differ from other antidepressants

The profile of clinically significant drug interactions with venlafaxine is different to that of SSRIs and TCAs.

Venlafaxine is metabolised by CYP2D6 to an active metabolite which is subsequently metabolised by CYP3A4. Potent inhibitors of CYP2D6 such as amiodarone or cimetidine will slow conversion to the active metabolite and increase plasma concentrations of venlafaxine. It is possible that poor metabolisers or those taking concurrent CYP2D6 inhibitors may be less likely to tolerate venlafaxine (de Leon, 2006).

A potent inhibitor of CYP3A4 (e.g. erythromycin or ketoconazole) will tend to increase the availability of the active metabolite and the potential for dose related adverse effects (MHRA, 2006).

Further information on drug interactions and precautions is available from the drug's datasheet available from Medsafe (<http://snipurl.com/y1kz>).

For more information on the CYP enzyme system and its effect on antidepressant medications see page 32.

Switching from other antidepressants to venlafaxine

Venlafaxine is usually started at a dose of 75 mg daily after a suggested washout period as in Table 1. For panic disorder 37.5 mg daily for 4 - 7 days is recommended as the starting dose.

When switching from venlafaxine to another antidepressant allow a 7 day washout period for moclobemide or MAOIs and 3 days for other antidepressants.

Table 1. Recommended minimum washout periods when switching from other antidepressants to venlafaxine.

Switching to venlafaxine from...	Suggested washout time	Comments
MAOIs or Fluoxetine	2 weeks	
Paroxetine or Citalopram	3 days	Some SSRI withdrawal effects may still be observed. Consider cross tapering especially with high doses of SSRI.
TCAs	4 days	Some specific TCA withdrawal effects may still be observed. Consider cross tapering especially with high doses of TCAs.
Moclobemide	1 day	

If there has been no response to treatment, it is important to ensure that the drug has been taken regularly, at a suitable dose and for an adequate period before considering a switch to another drug.

Antidepressants for elderly people

The prevalence of major depression in people over the age of 60 years is approximately 5% to 15% but is considerably higher in those with serious health problems. About half of elderly people with major depression will benefit significantly from antidepressant medication. However elderly people, especially those who are frail, have serious comorbidities or are on multiple medications, are particularly susceptible to adverse effects from antidepressants.

In the elderly, doses should be increased more gradually as they are more susceptible to side-effects such as sedation and hypotension.

SSRIs and TCAs have similar efficacy in elderly people

A Cochrane review of trials of antidepressants for people over 55 years concluded that there is no significant difference in efficacy across antidepressant classes (Mottram, 2006).

Elderly people are susceptible to the adverse effects of antidepressants

Clinical trials have shown lower rates of withdrawal from treatment for any reason with SSRIs compared to TCAs. However the profile of adverse effects is different between these drug classes.

Elderly people who take TCAs have high rates of anticholinergic adverse effects, for example, approximately one-quarter will experience dry mouth and one-tenth constipation. Hypotension and sedation are also relatively common. Elderly people are at increased risk of memory impairment, confusion and hallucinations related to TCA use.

Although there is a low prevalence of adverse effects with SSRIs a number of elderly people may experience nausea, vomiting, dizziness or drowsiness and find the drug intolerable (Wilson, 2004). Less common, but serious adverse effects include hyponatraemia, especially early in treatment, and increased bleeding risk. The increased risk of bleeding is exacerbated by concomitant use of an NSAID.

Elderly people are at increased risk of drug interactions

Elderly people taking antidepressants along side other medications are at particular risk of interactions. Fluoxetine and paroxetine are potent inhibitors of various hepatic cytochrome metabolising enzymes which may precipitate significant drug interactions. Citalopram has a relatively low risk of interactions in comparison.

(For more information on the CYP enzyme system and its effect on antidepressant medications see page 32).

SSRIs have the potential to interact with many drugs acting on the nervous system. Significant drug interactions with TCAs include additive anticholinergic, sedative and hypotensive effects.

Other important interactions are increased risk of hyponatraemia with diuretics and increased bleeding risk with warfarin or NSAIDs.

Antidepressants and comorbidities

Depression with a mental or physical comorbidity is common in elderly people. Serious ill health is a risk factor for the development of a major depressive illness and depressed elderly people frequently have unrelated comorbidities. Suicide is more common in people with comorbid physical and mental illness.

People with depression plus comorbid physical or mental health problems are likely to benefit from antidepressant treatment but prescribers often have concerns about the interaction of these treatments with the comorbid condition. These are discussed in Table 2.

Selecting an antidepressant for an elderly person

Studies on the use of antidepressants by elderly people can only provide a general guide to treatment of individual patients.

Antidepressants are not recommended for the initial treatment of mild depression because the risk benefit ratio is poor. However if the patient does not respond to non-pharmacological interventions or has a past history of moderate or severe depression, antidepressants may be indicated.

When antidepressants are indicated, the choice for individual patients is determined by the past response to antidepressant medication, adverse effect profile of antidepressants, comorbidities and other medications the patient is using.

Most guidelines now recommend an SSRI as first choice. In New Zealand it is often reasonable to choose citalopram as it is fully funded and has a narrower range of drug interactions than fluoxetine or paroxetine. In view of the vulnerability of older people to adverse effects of antidepressant medication it is wise to start any antidepressant with a low dose and increase gradually as required and tolerated. Six weeks is often required before the effect of an antidepressant can be assessed. If the response is only partial at six weeks, the same dose should be continued for a further six weeks.

For people who develop SSRI specific adverse effects it may be worth considering changing to a TCA. As with all antidepressants for older people it is sensible to start with a low dose and increase the dose gradually allowing plenty of time for a response. There is evidence that low doses of TCAs may be just as effective as the full standard doses and are less likely to result in adverse effects (Furukawa, 2003).

Elderly people with treatment resistant depression can use venlafaxine but special consideration should be given to the potential for adverse cardiovascular effects.

Table 2. Antidepressant medication for people with physical illness

People with physical illness and a moderate to severe major depressive illness are likely to benefit from the use of antidepressants. However there are some specific issues that need to be considered.

Cardiac disease

Most antidepressants have some contraindications in cardiac disease. TCAs may induce arrhythmia and can cause hypotension. Caution is required with venlafaxine. SSRIs appear to be generally safer but this has not yet been subject to large-scale trials.

Dementia

Depression can be treated in people with dementia the same way that it is treated in other older people.

Epilepsy

Standard treatments for depression (including ECT) are safe and effective for people with seizure disorders.

Glaucoma

TCAs may precipitate acute narrow-angle glaucoma in susceptible individuals because of their anticholinergic effects. Fluoxetine appears safe but intra-ocular pressure needs to be carefully monitored in those at risk.

Prostatism

TCAs may lead to urinary obstruction for men with prostatism. Fluoxetine and citalopram are unlikely to cause this.

Anticoagulation

SSRIs interact with warfarin. Citalopram has a relatively low interaction potential and fluoxetine a relatively high one.

Migraine

SSRIs and sumatriptan may interact and should be combined with caution.

(Adapted from Ellis, 2004)

Antidepressants in pregnancy and breastfeeding

Depression during pregnancy or in the postnatal period significantly impacts on a mother's ability to care for herself and her baby. Appropriate management is essential. When non-pharmacological interventions are unlikely to be effective, selection of an appropriate antidepressant requires consideration of several important factors:

- Risk of teratogenicity from *in utero* exposure,
- Withdrawal effects at delivery,
- Long term effects on childhood development from drug exposure, and
- Suitability of the drug for post-natal treatment and in breastfeeding.

Recent concerns about SSRIs in pregnancy

The teratogenic potential of most antidepressants apart from mood stabilisers appears to be low (Ellis, 2004). However, recent studies have indicated possible problems with SSRIs.

Paroxetine has been linked to increased rates of congenital malformations in the infants of mothers who took paroxetine in the first trimester. This has prompted the UK Medical and Healthcare products Regulatory Agency (MHRA) to ask prescribers to consider if the use of paroxetine is appropriate for their patients who are pregnant or are planning pregnancy (MHRA, 2005).

In addition SSRIs as a group have been recently linked to adverse pregnancy outcomes (Wen, 2006; Oberlander, 2006) and increased risk of newborn persistent pulmonary hypertension (Chambers, 2006). The absolute risk increase of adverse events appears to be small but the data are being currently reviewed by ADRAC in Australia and MARC in New Zealand. We hope to report any advice in the next edition of 'best practice'.

Other SSRIs, such as citalopram and fluoxetine, are currently considered suitable as first line pharmacotherapy for depression in pregnancy (Huntington, 2004). TCAs are also considered to be relatively safe.

There is no evidence that venlafaxine is teratogenic but there is much less experience of using this drug in pregnancy than SSRIs or TCAs.

SSRI withdrawal effects in the infant at delivery

There is a risk of withdrawal effects in neonates if maternal use of SSRIs continues into the third trimester. These effects are more likely with paroxetine because of its shorter duration of action. Withdrawal signs in the neonate include respiratory distress, cyanosis, apnoea, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and sleeping problems. In the majority of cases the complications begin immediately or soon (<24 hours) after delivery.

Few studies on long term effects on child development

There are few studies on the effects of antidepressant use during pregnancy on long-term child development.

Premature or sick infants may be more at risk from antidepressants in breast milk

Most studies of antidepressants and breastfeeding find transmission to breast milk to be limited. However immaturity of the infant hepatic metabolic systems should be considered, particularly in premature or ill infants.

In breastfeeding, drug safety is assessed by estimating the weight adjusted infant dose compared with the maternal dose. In this regard fluoxetine provides the greatest infant dose, paroxetine the least and citalopram somewhere in between. The level of infant drug exposure provided by fluoxetine and its active metabolite does not preclude its use in breastfeeding but citalopram and paroxetine may be considered potentially safer options.

Suicide and antidepressants

The majority of people with depression have some thoughts of suicide, often linked to general negativity and hopelessness. Suicide is the main cause of the increased mortality related to depression. Suicidal behaviour can occur even in people with mild depression.

Increased suicidality at start of treatment

There may be a small but significant increase in suicidal thoughts in the early stages of treatment with all antidepressants. This may be related to increased levels of energy and motivation whilst mood remains low in the early stages of treatment. Similarly, increases in suicidal ideation reported soon after starting some SSRIs may be related to increased levels of anxiety which may occur in the early stages of treatment with these drugs.

There appears to be an increased risk of suicidal behaviour in young adults started on SSRIs and although the evidence for this is not strong, it is wise to monitor people less than 30 years of age more closely when starting antidepressants.

NICE (2004) recommends that all people under 30 years should be seen one week after commencing antidepressant medication and frequently thereafter.

Antidepressants in overdose

Antidepressants are implicated in approximately 20% of deaths from drug poisoning in the UK. The majority of these (approximately 90%) are TCAs, which are cardiotoxic in overdose. This is an important consideration when choosing an antidepressant medication.

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