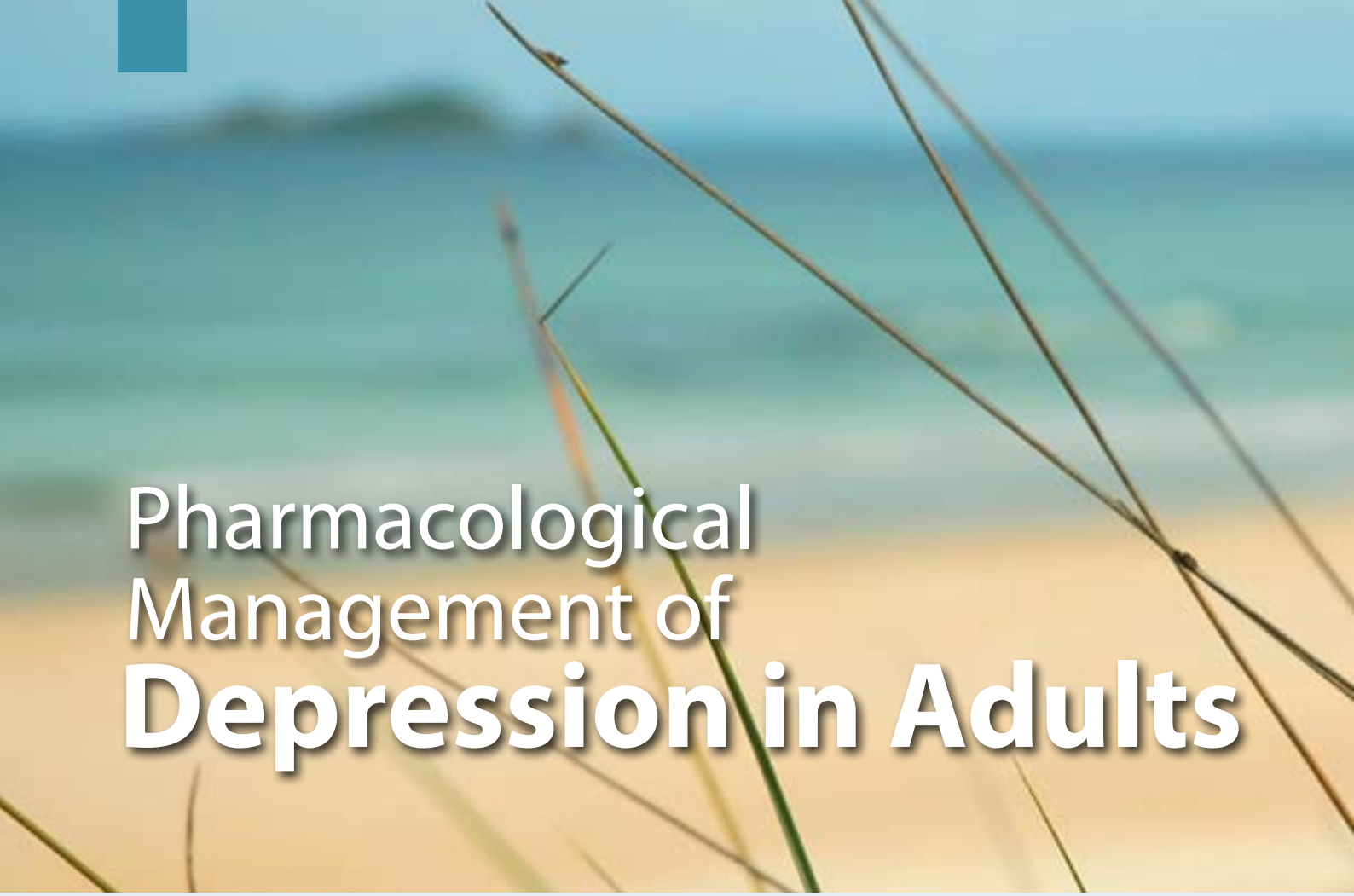


# Pharmacological Management of Depression in Adults

## Drug treatment in adults – general principles[1]

- First-line treatment for an adult with moderate depression is either a selective serotonin reuptake inhibitor (SSRI) or a psychological therapy (e.g., 6–8 sessions of problem-solving or cognitive behavioural therapy over 10–12 weeks)
- An adult starting antidepressant treatment who is not considered at increased risk of suicide should be reviewed by the health practitioner within 1–2 weeks and monitored at least 2 weekly until there is clear improvement
- An adult considered at risk of suicide should be followed up more frequently based on assessment of risk and the likelihood of this changing
- Practitioners should consider the use of a tool such as the Patient Health Questionnaire for Depression (PHQ-9) to assist monitoring treatment response in depressed adults
- If an adult on antidepressant medication has had only a partial response after 3–4 weeks, consider increasing the dose
- If an adult on antidepressant medication has not responded to treatment by 4–6 weeks, review the diagnosis and the treatment plan and, if the diagnosis is unchanged, consider either increasing the dose, changing the antidepressant, or changing or adding a psychological therapy
- An adult with depression who is responding to antidepressant treatment should normally continue to take the antidepressant for at least 6 months after remission in order to reduce the risk of relapse
- Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years
- Depressed adults who have not shown an adequate response to two full courses of treatment (psychological or pharmacological) should be referred for review by mental health services while continuing treatment

## Antidepressant Choice

All antidepressant drugs are approximately equal in effectiveness, although individual patient response may vary markedly.[10]

For most indications the SSRIs are considered first-line as they are better tolerated and have a wider safety margin than the tricyclic antidepressants (TCAs) and irreversible nonselective monoamine oxidase inhibitors (MAOIs).[11]

MAOIs (phenelzine, tranylcypromine) are now rarely used because of their severe, and potentially fatal, interactions with some foods and medications. They should only be initiated by psychiatrists familiar with their use.

Moclobemide may be useful, particularly in patients who are intolerant of the adverse effects of other antidepressants. The evidence suggests that it works at least in moderate depression but maybe less effective in severe depression. It provides an option when the patient is unable to tolerate anything else.

Choice of antidepressant is also based on individual patient factors. If a patient has responded well to an antidepressant in the past then that drug should be considered first choice. Concurrent medical and psychiatric illnesses e.g. epilepsy, cardiovascular disease and bipolar disorder will also influence choice.

Other factors to consider include:

- adverse effect profile of the drug or drug class e.g. activating effects of an SSRI may be useful when hypersomnia is a presenting symptom
- potential for drug interactions
- toxicity in overdose, as well as the likelihood that the patient will attempt a deliberate overdose

For more information see Table 3 over page.

## Dose titration and response

SSRIs can often be started with a 20 mg daily dose (for citalopram, fluoxetine and paroxetine) with no further dose increases. This will be sufficient for many adults.

When using TCAs, start with a low dose and increase slowly e.g. start with 25–50 mg of nortriptyline and increase by 25 mg every third night to 100 mg.

It is usual to take SSRIs in the morning due to the risk of insomnia and TCAs at night because they may be sedative.

Dose titration for both SSRIs and TCAs is usually slower for anxious patients as they appear more sensitive to side effects. It is not unusual for anxious patients to have more anxiety during the titration of SSRIs. Starting dose can be 10 mg of citalopram, fluoxetine or paroxetine. After a week, if the patient tolerates the medication, the dose can be increased.

Regular symptom review and monitoring of suicide risk are essential adjuncts to drug treatment. An assessment tool such as the Patient Health Questionnaire for Depression (PHQ-9) can be used to assist in the monitoring of treatment response in an adult with depression.[1]

**Table 3:** Comparison of antidepressants most commonly used in general practice in New Zealand.

| Tolerability considerations | |
|---|---|
| **Sedation** | SSRIs tend to be less sedating than TCAs. However all antidepressants may impair ability to drive or operate machinery. |
| **Anticholinergic effects** | Common problem with TCAs and paroxetine |
| **Orthostatic hypotension** | Least likely with SSRIs, venlafaxine and moclobemide |
| **Toxicity** | TCAs and venlafaxine are more toxic in overdose than SSRIs. |
| **Sexual dysfunction** | Less common with moclobemide |
| **Weight gain** | TCAs and paroxetine are associated with weight gain |
| **Withdrawal** | Some people experience withdrawal effects after missing 1 or 2 doses, especially when using a drug with a short half-life (e.g. paroxetine, venlafaxine).<br><br>At the end of a treatment course, taper antidepressant over several weeks and monitor for withdrawal symptoms. |

| Class considerations | |
|---|---|
| **SSRIs** | SSRIs are generally considered first-line agents.<br><br>SSRIs are relatively activating and usually best given as a single daily dose each morning.<br><br>Routine use of doses above those recommended rarely increases antidepressant effect. Higher doses are necessary for treatment of obsessive compulsive disorder. |
| **TCAs** | Nortriptyline is less sedating, and less likely to cause hypotension or anticholinergic effects than amitriptyline, dothiepin, doxepin and trimipramine.<br><br>TCAs are very toxic in overdose – 700 mg can be lethal in adults. |
| **MAOIs** | Moclobemide, a reversible, selective MAOI (RIMA), has far less potential for interactions than irreversible MAOIs (phenelzine and tranylcypromine) |
| **SNRI**<br><br>**(Venlafaxine)** | Venlafaxine has efficacy and tolerability comparable to the other classes of antidepressants.<br><br>May increase blood pressure, particularly with high doses. Caution required with cardiovascular disease. |

An adult with depression who is responding to antidepressant treatment should normally continue to take the antidepressant for at least 6 months after remission (not just after the initial response) of an episode of depression in order to reduce the risk of relapse.[1]

Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years.

When withdrawing treatment on completion or otherwise, reduce the dose gradually over at least 4 weeks to avoid discontinuation symptoms.

## Treatment with SSRIs

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants.No single SSRI has a significantly better safety or effectiveness.

If the first SSRI tried is not tolerated or does not work it is reasonable to try another SSRI.

When selecting an SSRI factors that influence patient tolerability become important such as drug interaction potential, severity of withdrawal syndrome and side effects.

### Interaction potential

SSRIs are metabolised by different isoenzymes, hence their potential for interaction varies which may influence drug choice.[11] Citalopram is a relatively weak inhibitor of CYP2D6 compared with the other SSRIs, and thus it interacts with a more limited range of drugs than fluoxetine and paroxetine.

The most important interactions are those with other drugs that affect serotonergic neurotransmission as these can lead to serotonin toxicity and, in severe cases, serotonin syndrome

## Response to antidepressants[1]

Some improvement is usually seen within two weeks of starting antidepressant treatment at a therapeutic dose.

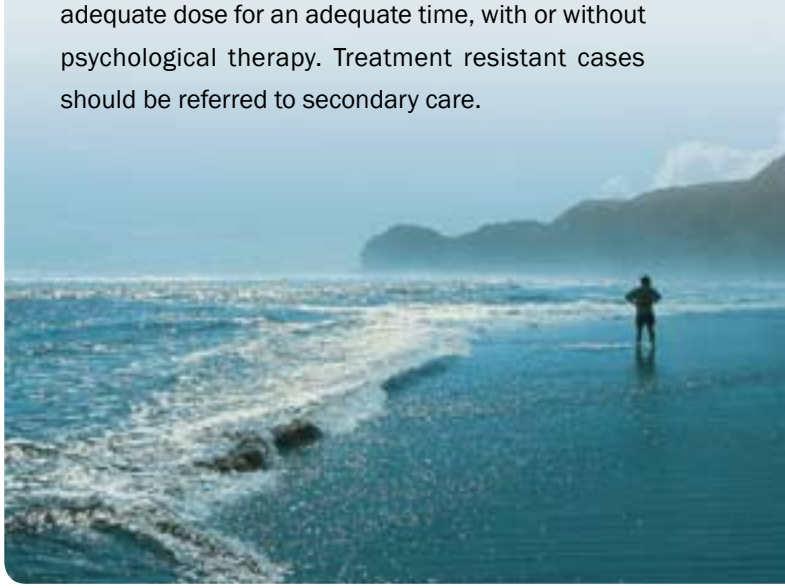
At 3–4 weeks, if there is no improvement or minimal response the practitioner should re-evaluate the treatment plan and consider changing to a different antidepressant, changing to a psychological therapy or adding a psychological therapy.

If there is insufficient response by 4–6 weeks review the diagnosis; if confirmed, review the treatment plan and consider either increasing the dose, changing the antidepressant, changing to a psychological therapy or adding a psychological therapy. A different medication often works even if the first option has been unsuccessful.

Up to a third of patients have a relatively slow response to antidepressants. Continuation of the same antidepressant can also be considered in patients who show a partial response at 6 weeks.

### Treatment resistance

This is defined as a lack of satisfactory response after a trial of two antidepressants given sequentially at an adequate dose for an adequate time, with or without psychological therapy. Treatment resistant cases should be referred to secondary care.



Features of serotonin toxicity (see Table 4) may be relatively mild, such as tremor and low grade restlessness. This may indicate the need to modify drug therapy. Serotonin syndrome is the most severe form of serotonin toxicity characterised by a recognised cluster of prominent and severe clinical features that usually require supportive management and stopping the causative agent(s). **If severe, refer immediately to an emergency department**

A number of drugs and herbal products (principally St John's Wort) have serotonergic activity and can cause serotonin toxicity or the syndrome if given alone, especially in high doses. The potential for toxicity is increased if these agents are given in combination (Table 5). For example there is the potential for a toxic interaction if St John's Wort is given with Fluoxetine, or if paroxetine is given with tramadol.

SSRIs can interfere with haemostasis, due to action on serotonin release from platelets, and may increase the risk of bleeding. Risk of upper gastrointestinal tract bleeding in patients taking SSRIs is significantly increased when an SSRI is combined with a nonsteroidal anti-inflammatory drug or low dose aspirin. Patients vulnerable to GI bleeding (e.g. those with a history of peptic ulcer disease, oesophageal varices or who are undergoing surgery) should be observed carefully, considered for an alternative class of antidepressant or given a protective drug.[11]

For further information on interactions refer: BPJ Special Edition, March 2007. Paroxetine Medication Brand change: Drug Interactions with Antidepressants.[12]

### Adverse Effects

The SSRIs have a similar adverse effect profile (Table 6).

Gastrointestinal effects and insomnia are generally mild and transient, and can often be minimised by taking the SSRI in the morning, with food. SSRIs are usually activating but if sedation is predominant they can be given at night instead of the morning.

**Table 4**: Features of Serotonin Toxicity[10]

| Clinical Features | Contributing factors |
|---|---|
| Abdominal cramps, agitation, diarrhoea, myoclonus, tremulousness, coma, tachycardia, hypotension, disorientation, profuse sweating, hyperpyrexia | Overdosage<br>Drug interaction, especially SSRI + MAOI or SSRI + serotonergic TCA (e.g. clomipramine, amitriptyline, imipramine)<br>Inadequate drug-free interval in changing medications<br>Idiosyncratic reaction |

**Table 5:** Drugs that may cause serotonin toxicity[10]

| Class | Drugs |
|---|---|
| antidepressants | TCAs (especially clomipramine), MAOIs (including moclobemide), SSRIs, mirtazapine, venlafaxine, St John's Wort |
| opioids | tramadol, pethidine, dextromethorphan |
| stimulants | amphetamines, sibutramine |
| 5HT1 agonists | sumatriptan, naratriptan, zolmitriptan |
| others | Ecstasy, LSD, cocaine. Selegiline, tryptophan, buspirone, lithium, linezolid |

**Table 6:** Relative frequency of common adverse effects.[10]

| SSRI or newer antidepressant | Agitation | Gastro-intestinal | Insomnia | Sedation | Sexual dysfunction | Weight gain |
|---|---|---|---|---|---|---|
| **Citalopram** | + | ++ | ++ | ++ | +++ | + |
| **Fluoxetine** | + | ++ | ++ | ++ | +++ | + |
| **Paroxetine** | + | ++ | ++ | ++ | +++ | + |
| **Venlafaxine** | ++ | +++ | ++ | ++ | +++ | + |

Approximate frequencies of adverse effects: +(>2%) = infrequent; ++(>10%) = moderately frequent; +++(>30%) = frequent.

Note: this is the frequency of occurrence of adverse effects, not the intensity with which they occur.

Sexual problems, such as decreased libido and difficulty achieving orgasm, occur in around 40% of people taking SSRIs, and in around 30% of cases the problem is likely to be drug-related, though estimates vary widely. A temporary dose reduction or a trial of specific phosphodiesterase inhibitors could be considered.[1]

All SSRIs can cause agitation, therefore in people in whom anxiety is a factor it is advisable to start with a low dose (about half the usual starting dose) and increase the dose slowly. Paroxetine appears to cause more anticholinergic effects (dry mouth, blurred vision, constipation) and for this reason it may be less suitable in elderly patients.

### Suicidal ideation

Early contact in the first week of treatment is important to enquire about suicidal ideation and about any increase in symptoms.[1]

In the first few days of treatment with an SSRI an increase in anxiety, restlessness or agitation may occur. This can be very distressing and may be associated with increased suicidality. Patients should be advised to contact the practitioner if this happens. A change of medication could be discussed in these circumstances if the cause appears to be related to medication rather than other stressors.

### Discontinuation syndrome

After cessation of an SSRI the most commonly reported discontinuation symptoms include dizziness, nausea, anxiety, vivid dreams and headache (Table 7). Occasionally, electric shock-like sensations are reported. Usually these symptoms are mild, last one to two weeks, and are rapidly reversed with reinstitution of the SSRI.[11]

SSRIs with shorter half-lives, such as paroxetine, have a higher incidence of withdrawal symptoms. Fluoxetine is the SSRI least likely to be associated with a discontinuation syndrome due to its long half-life.

Discontinuation symptoms usually begin within one to three days after abrupt cessation of the SSRI. To avoid discontinuation symptoms a continuous supply of medication and good compliance is necessary. When the decision is made to stop therapy, gradual withdrawal over at least four weeks is recommended. Generally, the higher the dose, the longer the withdrawal period.

### Cautions

**There are situations when an SSRI is not the first choice for clinical reasons or should be used with caution.**

Previous response to a drug is a good predictor of response to treatment of later episodes. Hence when a patient has responded well to an agent such as a TCA in the past it makes sense to consider that drug as first choice.

If the patient has experienced unacceptable side effects to an SSRI e.g. agitation, then it is best to avoid that agent. However it may be worth trying another SSRI before switching to another class.

Caution is recommended when using an SSRI with co-morbid conditions such as epilepsy or diabetes.

All psychotropics lower the seizure threshold, but if the person is well controlled on antiepileptic medication then SSRIs are very unlikely to affect seizure control. SSRIs are considered the antidepressants of choice in patients with concurrent cardiac disorders as TCAs have a greater risk of cardiotoxicity.

In patients with diabetes SSRIs may affect glycemic control. Hypoglycaemia has occurred during therapy and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when an SSRI is initiated or discontinued.

SSRIs are generally contraindicated if the patient enters a manic phase. Manic phase should lead to psychiatric review.

## Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are appropriate as a second-line treatment if there has been an unsatisfactory response to an SSRI. They can also be considered in those who have previously responded to a TCA.

All TCAs cause anticholinergic side effects (such as dry mouth, blurred vision, constipation, urinary retention and sweating), sedation and postural hypotension. Usual recommendations are to start with a low dose and titrate up to the full therapeutic dose as quickly as the patient can tolerate this.

TCAs can cause ventricular arrhythmias in the absence of adequate oxygenation of heart muscle (e.g., with ischaemic heart disease) and in overdose. TCAs are very toxic in overdose and seizures can occur.[1]

Nortriptyline is less sedating, and less likely to cause hypotension or anticholinergic effects, than amitriptyline, dothiepin, doxepin and imipramine.[10]

## Venlafaxine

Venlafaxine is a SNRI (serotonin and noradrenaline reuptake inhibitor) and is subsidised by PHARMAC for treating depression that has failed to respond to adequate trials of two other antidepressants.

**Table 7:** Discontinuation symptoms[10]

| Class | Symptoms | Comments |
|---|---|---|
| **TCAs** | cholinergic rebound: hypersalivation, runny nose, abdominal cramping, diarrhoea, sleep disturbance | more common on stopping amitriptyline, doxepin, imipramine |
| **SSRIs** | dizziness, nausea, paraesthesia, anxiety, agitation, tremor, sweating, confusion, electric shock-like sensations | more common on stopping paroxetine and least likely with fluoxetine |
| **SNRI** | venlafaxine may cause a syndrome similar to that seen with SSRIs | particularly likely on stopping venlafaxine because of its short elimination half-life |

## Comparison of SSRIs and venlafaxine

| SSRI/SNRI | Advantages | Disadvantages |
|---|---|---|
| **Citalopram** | Interacts with fewer drugs compared with other SSRIs.<br>Short half-life allows minimal washout period when switching to another drug. | Moderate discontinuation symptoms on stopping. |
| **Fluoxetine** | Long half-life which may allow for less frequent administration in poorly compliant patients and less troublesome discontinuation effects. | Longer delay required before switching to other antidepressants.<br>Interacts with more drugs compared with citalopram. |
| **Paroxetine** | Short half-life allows minimal washout period when switching to another drug. | High incidence of discontinuation reactions.<br>Interacts with more drugs compared with citalopram. |
| **Venlafaxine** | May be a useful option for resistant depression. | May increase blood pressure, particularly with high doses.<br>Caution required with cardiovascular disease.<br>Higher withdrawal rates due to adverse effects. |

The reuptake effects of venlafaxine are dose dependent. At low doses (<150 mg/day), the drug acts like the SSRIs. At intermediate to high doses, the additional effects on noradrenaline reuptake become important.

Nausea, agitation, sexual dysfunction and insomnia at low doses of venlafaxine are probably mediated by effects on postsynaptic serotonergic receptors.

At intermediate to high doses, additional adverse effects such as raised blood pressure and headache are observed in some patients, these effects are probably due to an action on adrenergic receptors.

Venlafaxine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease and needs to be used with caution in these patients. Increase in blood pressure and serum cholesterol can occur with venlafaxine and monitoring is recommended. Like the SSRIs, venlafaxine has been associated with increased bleeding, including upper gastrointestinal bleeding.[13]

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

Refer: BPJ, Oct 2006. Venlafaxine: how and when to use.

## Other antidepressants are they still an option?

Mianserin and maprotiline should be avoided due to the significant risk of serious adverse effects and there are very limited indications for the use of the irreversible MAOIs.

### Mianserin

Mianserin use in New Zealand was associated with a series of deaths from agranulocytosis which led to its use being restricted under special authority to patients who also had cardiovascular disease or bladder neck obstruction. SSRIs were not available at that time and are suitable for most indications when mianserin would have been used.

### Maprotiline

Seizures have been reported in patients receiving maprotiline and have occurred principally in those with no previous history of seizures. It has generally been suggested that maprotiline may be associated with a higher incidence of seizures than the tricyclic antidepressants.

Maprotiline has been withdrawn in some countries, including Australia.

### Tranylcypromine/Phenelzine

There are limited indications for the use of these agents. If an irreversible MAOI is being considered then the patient probably requires specialist review. GPs need to remain aware of the major and potentially fatal interactions with other drugs, including some analgesics

## Changing from one antidepressant to another

Some patients do not respond to the first antidepressant prescribed and need to be changed 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.

When switching drugs, consider the need for washout periods, cross tapering and the management of discontinuation syndrome.An appropriate interval when changing from one antidepressant to another is recommended to avoid interactions. General recommendations are given in the Table 8, based on the pharmacokinetics of the parent drug and of active metabolites where appropriate. However, this is only a guide and strategies may vary according to individual factors.

Higher doses of medication should be tapered before commencing a change of drug and the new drug should be started at a low dose.

## Stopping drug therapy

Antidepressants that have been taken regularly for at least six weeks must not be discontinued abruptly, unless a serious adverse effect has occurred. Stopping treatment quickly can sometimes cause discontinuation symptoms. It is best to reduce the dose gradually over at least four weeks, but slower withdrawal may be necessary after longer periods, for example, over six weeks after a six month course.

**Table 8:** Antidepressant-free intervals recommended when changing from one antidepressant to another.[11]

| | | Changing to | | | | | |
|---|---|---|---|---|---|---|---|
| | | **citalopram paroxetine** | **fluoxetine** | **moclobemide** | **venlafaxine** | **TCAs** | **tranylcypromine phenelzine** |
| **Changing from** | **citalopram paroxetine** | nil | nil | 2 to 4 days[a] | 2 to 4 days | 2 to 4 days[c] | 1 week |
| | **fluoxetine[d]** | 1 week | - | 1 week | 1 week | 2 weeks[c] | 5 weeks |
| | **Moclobemide[a] (if moderate or lower doses of both drugs)** | 1 to 2 days | 1 to 2 days | - | 1 to 2 days | 1 to 2 days | nil |
| | **venlafaxine** | 1 to 2 days | 1 to 2 days | 1 to 2 days | - | 1 to 2 days | 1 week |
| | **TCAs** | 2 to 4 days | 2 to 4 days | 2 to 4 days[e] (1 week for clomipramine) | 2 to 4 days | nil | 1 week |
| | **tranylcypromine[b] phenelzine[b]** | 2 weeks | 2 weeks | Nil (for moderate or low doses of both drugs) | 2 weeks | 2 weeks | 2 weeks |

## Notes

- The risk of adverse effects needs to be weighed against the risk of undue delay in response to treatment.
- Monitor closely to detect adverse effects, particularly serotonin toxicity
- Nil = start the new drug on the next day

a. If changing from the short acting SSRIs (citalopram, paroxetine) moclobemide dose should be held at 300 mg/day for the first week. Dose may be subsequently increased if necessary. This recommendation is only for changing from low or moderate doses of SSRIs. High doses of SSRIs should be gradually reduced and then stopped before starting moclobemide.

b. Irreversible nonselective MAOIs (phenelzine, tranylcypromine) should be commenced with caution after all other antidepressants because of the risk of severe hypertension, stroke and serotonin toxicity. Allowance should be made for the washout period.

c. When changing from an SSRI to a TCA, the TCA concentration may be elevated for at least several weeks due to persisting SSRI-induced cytochrome P450 inhibition.

d. Care is required when changing from fluoxetine to another antidepressant as it has a longer half-life than other SSRIs, leading to meaningful concentrations of fluoxetine or its active metabolite being present for about 5 weeks after cessation.

e. When changing from a TCA to moclobemide, the moclobemide dose should be held at 300 mg/day for the first week. Dose may be subsequently increased if necessary. This recommendation is only for changing from low or moderate doses of TCA (e.g. up to 150 mg imipramine).

## Pregnancy

**Note: The treatment of depression in pregnancy, breastfeeding and postnatal depression will be covered in detail in a subsequent publication.**

Decisions about management must be individualised and should be guided by life history of depression (number and severity of episodes), prior occurrence of depression during pregnancy or postpartum, and severity of symptoms at the time of conception and throughout the pregnancy.

Close monitoring by a psychiatrist may be required.

When antidepressants are the treatment of choice, SSRIs, except paroxetine, are recommended as an appropriate first-line therapy for most women.

Paroxetine should be avoided in pregnancy due to teratogenic risk, in accordance with Medsafe advice.[14] Some practitioners may recommend shorter-acting SSRIs such as citalopram, but the longer half-life of fluoxetine means that any neonatal withdrawal effects are likely to be more gradual. For women at risk of preterm birth, the practitioner may wish to consider the use of a TCA in preference to an SSRI, as there is some evidence that SSRIs may increase the risk of premature labour.[1]