

Targeting depression in primary care

Most people with depression are managed in primary care with minimal input from secondary services. Since antidepressants are frequently prescribed, it's not surprising that drug information services such as TAIS and Medicines Line often receive requests for information about adverse effects, interactions, washout periods and other prescribing issues from both health professionals and consumers. This *NPS News* covers both current controversies and common questions in prescribing for depression.

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SSRIs—contra-indicated for children and adolescents?

Controversy surrounding prescribing of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents with major depressive disorder has centred around the fundamental issues of efficacy and safety.

A systematic review found that when only published data (5 trials, n=911) were considered, SSRIs appeared effective, however adding unpublished data (6 trials, n=1234) to the analysis considerably altered the balance between benefit and harm. Suicidal thoughts and impulses were reported more often on treatment than on placebo, but numbers were small and the risk estimates were weak and inconclusive. However, the evidence of benefit was also weak and the small changes in depression scores achieved were unlikely to be clinically significant. The benefits were not considered great enough to outweigh potential for harm for paroxetine, sertraline, citalopram and venlafaxine. Only fluoxetine had modest evidence of benefit together with minimal risk of harm.¹

Based on their own examination of this data, the UK Committee on Safety of Medicines (CSM)* issued warnings stating that there was evidence of benefit in paediatric depression only for fluoxetine, and that use of other SSRIs was contra-indicated as the ratio of benefit to harm was poor (or trials had not been done). US and Australian regulators have been less directive (see Box 1).

The US Food and Drug Administration† and the CSM are reviewing all available data, and more definitive statements may soon be possible. Some manufacturers have since warned that their medicines should not be used in children.

Box 1: Summary of Adverse Drug Reactions Advisory Committee (ADRAC) advice on use of SSRI antidepressants in children and adolescents (17 June 2004)²

Current data are inconclusive regarding the efficacy and safety of SSRIs in major depressive disorder in children and adolescents. ADRAC recommends the following.

- 1) If used, SSRI treatment of children and adolescents with major depression should be undertaken within the context of comprehensive management guidelines outlined in the NHMRC Clinical Practice Guidelines for Depression in Young People (1997). **Management should include careful monitoring for the emergence of suicidal ideation and behaviour.**
- 2) The choice of an SSRI for children or adolescents with major depression should be made only after taking into account the recent evaluations of clinical trial data and the product information. **The current Australian Product Information for paroxetine, venlafaxine and sertraline recommend against their use in children and adolescents.**
- 3) Those currently being treated with an SSRI **should not have their medication ceased abruptly.**

ADRAC noted that:

- none of the SSRIs is approved for treatment of paediatric major depression but drugs are used for this purpose
- increased suicidal ideation and behaviour during initial antidepressant treatment are known clinical phenomena.

(Full statement available at www.tga.gov.au/adr/adrac_ssri.htm)

* medicines.mhra.gov.uk/aboutagency/regframework/csm/csmhome.htm

† www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html



Prescribing pointers

Starting, stopping and changing antidepressants

In major depression, effective pharmacotherapy depends on achieving a therapeutic response and ensuring adequate therapy (drug, dose, duration). Ceasing therapy too soon after response or remission increases the risk of relapse. Antidepressant therapy can be considered in three phases:^{3,4}

- response—initial treatment until a reduction in depressive symptoms is achieved
- continuation—continued treatment while symptoms are in remission
- maintenance—to prevent recurrence after a stable period of remission.

Since classes of antidepressants have similar efficacy, the choice of drug is usually made on the basis of side-effect profiles and likely interactions with other conditions or medicines. It is suggested that prescribers become familiar with one or two drugs from each class.⁵ Persistence with therapy to achieve remission and prevent relapse may be more important than initial treatment choice.³ Drugs usually reserved for second-line therapy include mianserin, and monoamine oxidase inhibitors (MAOIs). Some guidelines^{3,5} suggest that tricyclic antidepressants (TCAs) can be used first-line, but their use is often limited by their adverse effects.⁴

Response

Documenting the initial severity and characteristics of depression may help both patient and practitioner assess response to drug therapy. Start older patients on lower doses and allow more time to respond.

Around 50% of patients respond to the first antidepressant chosen.⁵ Reasons for lack of response include non-compliance with treatment, physical or psychiatric co-morbidity, incorrect diagnosis (other physical or psychiatric illness including the type of depression), psychosocial factors including substance abuse, as well as a lack of effect with the drug or dose chosen.

If there is **no response** after 4–6 weeks, response to a longer trial is unlikely.^{4,7} **Switching** to a different drug class is recommended if there is no response after an adequate trial of a single medicine (4–6 weeks). Australian guidelines suggest changing to venlafaxine or a TCA if there is no response after an SSRI, or adding cognitive behavioural therapy (CBT) or interpersonal therapy (IPT) (see page 4).

- If there is a **partial response** after 4–6 weeks, then a longer trial or increased dose of the same drug may be reasonable but consider the following.
 - Initial placebo response in antidepressant trials is relatively high, and may account for early but unsustainable improvement.⁴

- The evidence for effectiveness of increased doses of SSRIs is inconclusive. Despite this, higher doses seem to be used. Higher doses may increase adverse effects without greatly increasing effectiveness.

In the UK, authorities have warned prescribers against prescribing paroxetine at higher than the recommended dose (20 mg daily) because of adverse effects and a lack of evidence for efficacy.⁸

If remission is not achieved after an adequate treatment duration (e.g. 3 months)³ consider psychiatric referral or consultation.^{3,5}

Switching to another drug

Switching to another antidepressant usually requires a 'washout period'. Gradual withdrawal from the drug being ceased minimises withdrawal symptoms, while a drug-free period before starting the new drug prevents drug interactions and possible serotonin syndrome. Durations of withdrawal and drug-free intervals differ between drugs (see Table 1 opposite).

Continuation and maintenance

Continuation of drug therapy for 6–12 months is recommended for all episodes of major depression.^{3–5} However, people with a history of recurrent depression and/or moderate to severe dysthymia⁸ have a higher risk of relapse than those with a single episode of major depression. Guidelines suggest that 2 recurrences of major depression within 5 years or 3 prior episodes may indicate a need for maintenance treatment of 3–5 years.^{5,9}

Although there are few studies assessing outcomes for treatment durations of more than 12 months, continuing antidepressant therapy for between 6–8 months and 2–3 years has been shown to reduce the absolute risk of relapse by about half in a meta-analysis which included mostly recurrent episodes. The risk of relapse for placebo was 41% compared to 19% for antidepressants.¹⁰

Scheduling routine follow-up may provide opportunity to detect and prevent relapse.

Cease therapy gradually to avoid withdrawal symptoms

When antidepressant therapy is to be **ceased** altogether, taper doses to avoid withdrawal symptoms (particularly with TCAs, SSRIs and venlafaxine). For SSRIs, reduce the daily dose by half no faster than weekly—withdrawal symptoms are least likely with fluoxetine, and most likely with paroxetine. Venlafaxine has a significant discontinuation syndrome similar to SSRIs.⁶



‡ See Therapeutic Guidelines: Psychotropic⁵, or Australian Medicines Handbook⁶ for more detailed information about choice of antidepressant.

§ Depressive symptoms that recur frequently over at least 2 years that do not meet criteria for major depression. Can be accompanied by episodes of major depression (sometimes this is called double depression).⁹

Talking points—improving treatment compliance

- Be aware that resistance to a ‘mental illness’ diagnosis may cause a patient to resist drug therapy (short- and long-term), and discussion may help.
- Describe likely adverse effects, and that these usually decrease with time. Unexpected adverse effects may limit compliance.¹¹
- Advise the person that
 - mood may not improve immediately
 - not all people respond to the first drug chosen, and there are other treatment options
- missing doses may reduce effectiveness
- drugs should not be ceased abruptly, but tapered gradually because of possible ‘rebound’ symptoms.
- Regular follow-up and monitoring in the early stages of treatment (even by phone, or by a practice nurse) may improve compliance.^{3,12}
- Provide a Consumer Medicine Information (CMI) leaflet or suggest the person obtain one from their pharmacist—a note on the script may remind them. Encourage the person to return with any questions that arise.

Table 1: Antidepressant changeover guide⁶

Note: Consider hospitalisation during washout/changeover if severely depressed

Drug	Recommendation	
	Withdrawal period when switching	Drug-free interval
Category A changeover (longest washout period)		
fluoxetine	fluoxetine —gradual withdrawal generally unnecessary; withdrawal symptoms very unlikely.	Wait for at least 2 weeks after stopping before starting next antidepressant.
phenelzine	phenelzine and tranylcypromine —withdraw gradually to minimise withdrawal effects. Maintain drug and diet restrictions for 2–3 weeks after stopping.	Wait 5 weeks after stopping fluoxetine before starting MAOI.
tranylcypromine		
Category B changeover (intermediate washout period)		
TCA SSRIs (except fluoxetine) mianserin mirtazapine	Withdraw gradually to prevent withdrawal symptoms (particularly if higher dose or long-term use). Of the SSRIs, withdrawal symptoms most likely with paroxetine. Usually reduce dose by 25% per day (when switching).	Wait for 2–4 days after stopping before starting next antidepressant.
Category C changeover (shortest washout period)		
moclobemide reboxetine venlafaxine	venlafaxine —withdraw gradually to prevent withdrawal symptoms (discontinuation syndrome is similar to SSRIs). moclobemide —withdrawal symptoms not reported.	Wait for 1–2 days after stopping before starting next antidepressant.
Serotonin syndrome can occur with: high doses of a single serotonergic agent; after adding a second serotonergic drug; or when drugs with different mechanisms of increasing serotonin are used together. Symptoms include: mental changes (confusion, agitation); hyperreflexia and clonus; flushing, shivering, sweating, hyperthermia. ¹³		

What's what

Selective serotonin reuptake inhibitors (SSRIs)	citalopram	Cipramil, Celapram, Talam, Talohexal	fluvoxamine	Faverin, Luvox, Movox
	escitalopram	Lexapro	paroxetine	Aropax, Oxetine, Paxtine
	fluoxetine	Auscap, Fluohexal, Lovan, Prozac, Zactin	sertraline	Zoloft
Tricyclic antidepressants (TCAs)	amitriptyline	Endep, Tryptanol	imipramine	Melipramine, Tofranil
	clomipramine	Anafranil, Placil (not PBS-listed for depression, restricted benefit for other disorders)	nortriptyline	Allegron
	dothiepin	Dothep, Prothiaden	trimipramine	Surmontil (not PBS-listed)
	doxepin	Deptran, Sinequan		
Monoamine oxidase inhibitors (MAOIs) (irreversible)	phenelzine	Nardil	tranylcypromine	Parnate
Other antidepressants	mianserin	Lumin, Tolvon	reboxetine	Edronax
	mirtazapine	Avanza, Axit 30, Mirtazon, Remeron	venlafaxine	Efexor
	moclobemide	Arima, Aurorix, Clobemix, Maosig, Mohexal		

The role of psychological and behavioural therapy

Non-drug therapies (CBT or IPT^{II}) feature prominently in recent Australian *beyondblue* depression guidelines³ and are recommended as:

- monotherapy for mild or moderate depression
- adjunctive second-line therapy if response is not achieved with a drug alone (in moderate to severe major depression)
- preventive therapy to prevent recurrence when a patient is in remission.

The guidelines state that therapy will be most effective in the context of a 'good' therapeutic relationship, which is important regardless of the type of therapeutic approach, and that CBT/IPT should not be used unless an experienced practitioner, competent in its use is available.

'The best outcomes are likely when a good therapeutic alliance is forged between the professional and the person, and an adequate treatment is provided over a long enough period. Co-ordination of the services provided by the different professionals will also enhance the outcomes.'

RANZCP Clinical Practice Guidelines for treatment of depression⁹

^{II} Cognitive behavioural therapy (includes structured problem-solving, identification, challenging and changing of maladaptive thoughts, feelings, perceptions and behaviours).¹⁴ Interpersonal therapy (short-term psychotherapy developed specifically for depression).

In the treatment of mild depression, antidepressants are no more effective than non-drug treatments such as CBT or supportive therapy.^{5,15}

In moderate to severe major depressive disorder, psychotherapy alone is less effective than a combination of drugs and psychotherapy.¹⁵ In severe depression, initial pharmacotherapy may be necessary before initiating psychotherapy.^{10,15}

In adolescents, CBT is more effective than a range of placebo interventions, but appears to be most effective in mild to moderate depression.¹⁶

The cognitive therapies (including problem-solving) have the best published evidence of effectiveness—nonetheless, guidelines do not preclude the use of other therapies.^{1,5} Specific counselling such as for relationship issues or substance abuse occurring with depression, may help if the person is motivated to make use of such interventions. Physical interventions such as exercise, relaxation training (for anxiety) and sleep hygiene also have a role.⁵

In practice, accessibility (cost and availability) and individual preferences can exclude the use of behavioural interventions. However, recent government funding (the Better Outcomes in Mental Health Care initiative) allows upskilling of GPs who wish to provide focused psychological services themselves, as well as providing access for patients of participating GPs to allied health services (free or small co-payment). Interested GPs should contact their local division of general practice.

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Declarations of interest have
been sought from all reviewers.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each patient.



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Choosing an antidepressant for special patient groups

The appropriateness of individual drugs in individual circumstances will vary. Consulting a specialised drug information service may be necessary. Carefully review all medications and consider potential interactions before prescribing.

Patient group	General issues and concerns	Selective serotonin reuptake inhibitors (SSRIs)	Tricyclic antidepressants (TCAs)	Other antidepressants										
Suicidal patient	<p>Refer patients with high or immediate suicide risk. If risk is difficult to assess, consider consequences of overdose.</p> <p>Prescribing points</p> <p>Consider toxicity in overdose (and the availability of other prescribed drugs) when choosing the antidepressant. Limit quantities and repeats.</p> <p>Combinations of antidepressants are more lethal in overdose and are not recommended.¹</p>	<p>Relatively safe in overdose, but limit the quantity dispensed.</p>	<p>Most toxic in overdose—avoid use in people with high suicide risk.</p>	<p>MAOIs are toxic in overdose—avoid use.</p> <p>Reboxetine, mirtazapine, mianserin and moclobemide are relatively safe in overdose—venlafaxine is relatively more toxic than these in overdose.²</p>										
Adolescents and children <small>(See ADRAC 2004 statement, Box 1, page 1, NPS News 35.)</small>	<p>Regardless of therapy chosen, monitor suicidal ideation—suicide risk is high in this age group.</p> <p>Prescribing points</p> <p>Psychological therapy is first-line.³ CBT has evidence of benefit for mild or moderate depressive disorder.⁴</p> <p>If SSRIs are considered necessary, the patient should be monitored closely and supervision by a child psychiatrist is suggested.²</p>	<p>In Australia none of the SSRIs is approved for paediatric major depression, but off-label use occurs. If used, start with lower doses.</p> <p>Paroxetine manufacturer warns against its use in children.</p> <p>Evidence for efficacy of SSRIs is poor—only fluoxetine has modest evidence of benefit.⁵</p>	<p>TCAs are no more effective than placebo in children and adolescents and toxicity in overdose is a concern due to suicide risk in this age group.⁶</p>	<p>Reboxetine, moclobemide and mianserin—safety and efficacy not established.</p> <p>Venlafaxine manufacturer warns against use in children and adolescents.</p> <p>Mirtazapine trials do not support efficacy in paediatric depression according to the UK's Committee on Safety of Medicines.⁷</p>										
Pregnancy	<p>Assess the potential for benefit and harm in both mother and foetus, of both treatment and non-treatment. Discuss clearly and document these discussions.</p> <p>For milder depression, consider psychological therapy.</p> <p>Prescribing points</p> <p>Withdrawal symptoms in infants are similar in all antidepressant classes. Their onset and severity depend on the drug's half-life (shorter half-life means slower onset and more intense symptoms).</p> <p>Review medication needs in women taking antidepressants who conceive, but change of medication not necessarily required.¹ Consider risk of recurrence if antidepressant ceased.</p> <ul style="list-style-type: none"> — Use the lowest effective dose. — Consider reducing dose closer to delivery to minimise infant withdrawal effects.^{1,2} 	<p>Considered generally safe in pregnancy. No evidence of malformation or growth retardation, but data are limited.</p> <p>Serotonergic effects such as agitation, jitteriness, diarrhoea, poor feeding, and sleep disturbances have been reported in neonates—thought to be withdrawal effects.^{1,8} Most resolved within 2 weeks.¹</p> <p>One study (n=997) suggested SSRI or TCA use in late pregnancy increased risk of some neonatal adverse effects (e.g. respiratory distress), but overall risk remained low.⁹</p> <p>Little data exists on longer-term infant development.² A small study noted developmental differences in fine motor skills in infants aged 6–40 months¹⁰, but more data are needed.</p> <p>ADEC category C</p>	<p>Considered generally safe in pregnancy. No evidence of increased risk of malformation.</p> <p>Longer experience than with SSRIs, but consider adverse effects and toxicity in overdose.</p> <p>Anticholinergic adverse effects and withdrawal reactions have been observed in infants (irritability, insomnia, fever and colic).^{1,2}</p> <p>One study (n=997) suggested SSRI or TCA use in late pregnancy increased risk of some neonatal adverse effects (e.g. respiratory distress), but overall risk remained low.⁹</p> <p>ADEC category C</p>	<p>Mirtazapine, moclobemide and reboxetine have not been studied adequately.</p> <p>Longer experience with mianserin than SSRIs, and considered generally safe in pregnancy.</p> <p>Venlafaxine does not appear to be associated with increased risk of congenital abnormality.¹¹ Data on neonatal adverse effects are limited and safety is uncertain.¹</p> <p>Tranylcypromine and other MAOIs have been suspected of decreasing uterine blood flow and increasing the risk of adverse pregnancy outcome.</p> <p>ADEC categories</p> <table border="0"> <tr> <td>Mianserin</td> <td>B2</td> </tr> <tr> <td>Mirtazapine</td> <td>B3</td> </tr> <tr> <td>Moclobemide</td> <td>B3</td> </tr> <tr> <td>Reboxetine</td> <td>not categorised by ADEC/manufacturer: B1</td> </tr> <tr> <td>Venlafaxine</td> <td>B2</td> </tr> </table>	Mianserin	B2	Mirtazapine	B3	Moclobemide	B3	Reboxetine	not categorised by ADEC/manufacturer: B1	Venlafaxine	B2
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Patient group	General issues and concerns	Selective serotonin reuptake inhibitors (SSRIs)	Tricyclic antidepressants (TCAs)	Other antidepressants
Breastfeeding	<p>Untreated postnatal depression carries potential harm for both mother and child.</p> <p>Prescribing points</p> <p>Most antidepressants transfer to breast milk in very low quantities and are considered probably compatible with breastfeeding.^{12,13}</p> <ul style="list-style-type: none"> — Avoid sustained-release or controlled-release formulations—a simple oral dose form is preferred. — For non-sustained-release doses, to minimise infant exposure, feed just before or at time of dose. Generally avoid feeding for 2–3 hours after dose when drug concentration is usually highest.¹² Alternatively express and discard this feed (unnecessary for most drugs). — Use the lowest effective dose. — Monitor the infant response. 	<p>Minimal quantities in breast milk. Sertraline, citalopram, fluvoxamine and paroxetine show acceptably low infant doses and no short-term adverse effects.^{2,13}</p> <p>Because of fluoxetine's longer half-life, there is potential for accumulation in the infant.^{1,2} While significant adverse effects have not been reported, monitor infant for excessive crying, irritability, sleep disturbance, gastrointestinal upset.¹³</p>	<p>Transfer to breast milk is low. There is a long history of use without significant reports of adverse effects.¹³ Therefore TCAs are considered compatible with breastfeeding.</p> <p>However there is a higher adverse effect profile for the mother and greater toxicity in overdose.¹ Nortriptyline is preferred due to fewer anticholinergic effects and less likelihood of orthostatic hypotension.¹</p> <p>There have been case reports of respiratory depression with doxepin.¹</p>	<p>Mianserin, irreversible nonselective MAOIs, mirtazapine and reboxetine have not been adequately studied.</p> <p>Infant plasma concentrations higher with venlafaxine than most SSRIs but considered probably compatible.¹</p> <p>Moclobemide has low concentrations in breast milk but little is known about safety.²</p>
Late-life depression	<p>Dominant features of depression may differ. Psychosocial interventions may help—under-recognition may hamper treatment.¹⁴</p> <p>Consider referral for assessment of underlying cerebrovascular disease.¹⁴</p> <p>Can be difficult to distinguish dementia and depression. Cognitive impairment or decline should be objectively assessed where dementia is suspected.</p> <p>Prescribing points</p> <p>Start low and go slow—response may be more gradual in the elderly who may have slower drug clearance.</p>	<p>SSRIs appear to be safe in the elderly¹⁴, and have fewer adverse effects. Be aware of drug interactions due to the number and types of other medicines.</p> <p>Start with lower than usual doses and increase gradually.</p> <p>There is a greater risk of hyponatraemia in the elderly.</p>	<p>TCAs generally not recommended in the elderly because of anticholinergic and alpha₁-adrenergic blocking effects. If a TCA is chosen, nortriptyline has the least potential for adverse effects.²</p> <p>Use of TCAs for sedation increases the risk of falls.</p>	
Cardiovascular disease	<p>Co-existence of depression and cardiovascular disease appears to be relatively common.¹⁵</p>	<p>SSRIs are preferred, but note that paroxetine and fluoxetine potentially interact with some cardiovascular drugs (e.g. simvastatin, amlodipine, diltiazem, propranolol, metoprolol). Sertraline and citalopram have less potential for these interactions.¹⁵</p> <p>Trials of SSRIs in people with cardiovascular disease and depression suggest these drugs did not increase cardiovascular adverse effects on cardiovascular outcomes including left ventricular ejection fraction.¹⁵</p>	<p>TCAs not first preference because of concerns about cardiotoxic effects (e.g. arrhythmia, hypotension).</p>	<p>Venlafaxine may be used but can increase blood pressure, especially at high doses.</p> <p>Reboxetine may alter control of treated hypertension and can increase heart rate.²</p> <p>MAOIs may induce orthostatic hypotension.</p>
Depression with anxiety	<p>Anxiety symptoms often resolve with effective antidepressant therapy—additional drugs (e.g. benzodiazepines) are not usually required. Consider behavioural treatments for specific anxious behaviours.¹⁶</p>			

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