Use of antidepressant medications in the general practice setting

A critical review

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BACKGROUND Antidepressants are commonly prescribed in general practice for depression, but also for a wide range of other psychiatric conditions and physical problems.
OBJECTIVE This review, although concentrating on the use of antidepressants in depression, also reviews their use in other conditions commonly seen in general practice.
DISCUSSION For most major depression, all antidepressant drugs have equal efficacy.[1] The choice of antidepressant drug needs to be tailored to the particular patient's medical condition and personal preferences. It is likely that adverse effects are the major determinant in the choice of antidepressant for a particular patient. However, in treating conditions other than depression, the efficacy of the antidepressant drug can be the primary issue of drug choice.

Glossary (DSM-IV)

Major depression
Clinical syndrome lasting two weeks with at least five of the following symptoms: depressed mood, loss of interest or pleasure, significant weight loss or gain or appetite disturbance, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, impaired thinking or concentration, indecisiveness, recurring thoughts of death, or suicidal thoughts.

Mild depression
Mild disability, functions normally with effort (Hamilton score 7–17)

Moderate depression
No psychotic features, midway between mild and severe (Hamilton score 18–24)

Severe
Most of the symptoms, observable disability with work or other areas of functioning (Hamilton score >25)

Dysthymia
Chronic mild depressive disorder present on most days for two years with at least two of the following symptoms: appetite disturbance, insomnia or hypersomnia, decreased energy or fatigue, low self esteem, decreased concentration or difficulty making decisions or feelings of hopelessness.

Minor depression or subsyndromal depression
Acute mood disorder that is less severe than major depression lasting two weeks of depressed mood or loss of interest with 1–3 of the major depression symptoms.

Figure 1. DSM-IV = American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn. Washington, DC: American Psychiatric Association Press, 1994.

Depression overview

To understand the use of antidepressants in general practice, clinicians need to know what evidence has been found for their use with the different types of depression. Depression is common in general practice, where it is usually treated with psychological strategies and/or antidepressant medication. Depression seen in general practice often coexists with physical conditions, and usually is of shorter duration and meets fewer of the diagnostic criteria for major depression than that seen in psychiatric clinics (Figure 1). As most studies have not been undertaken in general practice, findings are extrapolated from psychiatric outpatients.[2]

A thorough review of 315 randomised, controlled trials has demonstrated the effectiveness of all antidepressants when compared with placebo for major depression.[1] They were effective in older patients and primary care patients. In the 150 comparison studies involving more than 16 000 participants, 54% of patients randomly assigned to receive a 'newer antidepressant' (Table 1) and 54% of those assigned to receive an 'older antidepressant' experienced at least a 50% improvement in depressive symptoms.[1] In clinical practice, individual differences in response are seen within and across drug classes.

For mild and moderate major depression, antidepressant medications across all drug classes have similar efficacy to psychological strategies using cognitive behaviour therapy or problem solving techniques.[3,4] Good management should include discussion with the patient about the nature of depression, its course, treatment options and likelihood of response to treatment. Reassurance as to the effectiveness of treatment is important in combating the feelings of hopelessness and in maintaining treatment adherence.[5] Psychological strategies, eg. cognitive behaviour therapy, may be considered as first line treatment except when patients are presenting with either recurrent episodes of major depression or an initial episode with severe depression or with psychotic features.

For severe or psychotic depression there is some uncertainty that the 'newer antidepressants' are as effective as the tricylic antidepressants (TCAs).[6]

For dysthymia or chronic mild major depression sufficient current evidence of equal effectiveness with TCAs is available for two selective serotonin reuptake inhibitors (SSRIs), ie. fluoxetine and sertraline.

For minor depression, the data are insufficient for determining the efficacy of newer antidepressants and there is no good evidence that TCAs work in those patients with minor levels of depression.[7] In clinical practice psychological strategies are generally used.

The American College of Physicians recently released a position paper which states:

> 'For primary care patients with acute major depression or dysthymia, including elderly persons without significant comorbid conditions, physicians should consider either tricyclic antidepressants or newer antidepressants, such as SSRIs, as equally efficacious treatments'.[8]

Factors influencing drug choice

Table 1 details antidepressants currently available in Australia. Because efficacy of all agents is similar, the choice of antidepressant for major depression is influenced by three main factors:

- availability
- adverse effects including safety issues, and
- cost.

Each of these will be examined below. As with any therapeutic decision, the choice needs to be tailored to the individual patient.

Table 1. Antidepressants available in Australia 2002

Newer antidepressants (trade names)

Serotonin reuptake inhibitors (SSRIs)

Citalopram (Cipramil)

Fluoxetine (Auscap, DBL Fluoxetine, Erocap, Fluohexal, Fluoxetine-BC, GenRx Fluoxetine, Lovan, Prozac, SBPA Fluoxetine, Zactin)

Fluvoxamine (Faverin, Luvox)

Paroxetine (Aropax)

Sertraline (Zoloft)

Others

Nefazodone (Serzone)

Venlafaxine (Efexor, Efexor-XR)

Mirtazepine (Avanza, Remeron)

Reboxetine (Edronax)

Reversible monoamine oxidase inhibitors

Moclobemide (Arima, Aurorix, DBL Moclobemide, GenRx Moclobemide, Mohexal)

Older antidepressants (trade names)

Tricyclic antidepressants (TCAs)

First generation

Amitriptyline (Endep, Tryptanol)

Clomipramine (Anafranil, Clomipramine-BC, DBL Clomipramine, GenRx Clomipramine, Placil)

Doxepin (Deptran, Sinequan)

Imipramine (Melipramine, Tofranil)

Trimipramine (Surmontil)

Second generation

Dothiepin (Dothep, Prothiaden)

Nortriptyline (Allegron)

Nonselective monoamine oxidase inhibitors

Phenelzine (Nardil)

Tranylcypromine (Parnate)

Others

Mianserin (Lumin, Tolvon)

Table 2a. The 11 most common adverse effects of SSRIs and TCAs[8]

Adverse effects (%)	SSRIs	TCAs
Anxiety	11	9
Blurred vision	6	10*
Constipation	8	21*
Diarrhoea	12*	3
Dizziness	8	19*
Dry mouth	18	48*
Headache	15*	11
Insomnia	13*	6
Nausea	19*	9
Tremors	7	11*
Urinary disturbance	3	8

* Statistically significant difference

Table 2b. Uncommon adverse effects of SSRIs and TCAs[8]

SSRIs

- Extrapyramidal effects – acute dystonia, akathisia and Parkinsonism
- Neuropsychiatric syndromes – mania, frontal lobe syndrome
- Bradycardia
- Seizures
- Symptomatic hyponatremia
- Hepatotoxicity
- Prolonged bleeding time
- Granulocytopenia
- Serotonin syndrome

TCAs

- Orthostatic hypotension
- Neuroleptic malignant syndrome (similar to serotonin syndrome)
- Decreased seizure threshold
- Cardiac arrhythmias

Adverse effects

> 'Because older and newer antidepressants are equally efficacious, the physician and patient should jointly review the adverse effect profiles of both drug classes, so that an agent that fits the clinical needs of the patient can be chosen'.[8]

Patients will have preferences for avoiding the commonly encountered adverse effect profiles of the different drug classes. Adverse effects and tolerability of the newer antidepressants compared to TCAs can be examined by looking at comparative dropout rates in trials due to adverse effects. These appear to be slightly less with SSRIs (11%) compared with first generation TCAs (16%), and with reversible MAOIs (5%) compared with first generation TCAs (11%).[8] Dropouts did not significantly differ for SSRIs compared with second generation TCAs or tetracyclic antidepressants, which are the TCAs more commonly used by general practitioners. Total dropout rates due to any reason appear to be no different between SSRIs (31%) and TCAs (33%).[9] 'Newer and older antidepressants' do not differ for overall discontinuation rates in the trials that have been conducted, but adverse effect profiles vary significantly.

Common adverse effects

While the newer medications clearly have specific adverse effects, these may in general be less frequent or severe than those experienced with TCAs (Table 2a, b). Many of the common adverse effects of antidepressants, eg. nausea, insomnia with SSRIs, and dry mouth and constipation with TCAs, may settle within the first two weeks. SSRIs and venlafaxine induced insomnia and anxiety during the initial stages of therapy may settle or necessitate dose manipulation or changing to another agent. If a benzodiazepine is needed, it should only be prescribed short term.[5]

For other important adverse effects of both SSRIs and TCAs (eg. sexual dysfunction and suicide attempts) the data were insufficient to compare across the drug classes.[8] In 11% of the 315 antidepressant trials, varied sexual dysfunction was reported including nonspecific sexual problems, ejaculatory abnormality, decreased libido, male impotence, erectile dysfunction, and anorgasmia.

Safety issues

In a recent review, less than 10% of the 315 trials using antidepressants (N=35 000 patients) reported on suicides.[1] In all, 19 suicide attempts and 15 suicides were described. There is a trend toward lower risk for suicide in patients treated with SSRIs, presumably due to treatment of the underlying depression. Despite widespread use of TCAs, which have potentially higher lethality in overdose, drug over dosage of any kind is responsible for only a small minority of completed suicides.[10] Overdoses with any of the agents can be fatal, although one of the advantages of the newer drugs is their theoretical lower toxicity in overdose than the TCAs, mainly due to reduced cardiotoxicity. There has been only one death reported to be due to fluoxetine alone, in a patient who was thought to have taken up to 6000 mg.[11] Venlafaxine may be more toxic than SSRIs in an overdose.

Uncommon adverse effects

Less than 1% of patients had serious adverse effects in the trials.[1] Doctors need to be aware of the more rare but serious side effects, (eg. orthostatic hypotension and cardiac arrhythmias) when choosing an agent for elderly persons and patients with comorbid conditions.

Doctors need to ensure that every instance of a serious adverse effect is accurately reported to the Adverse Drug Reaction Advisory Committee, PO Box 100, Woden, ACT 2606.

Cost

One primary care based study that had no rigid treatment guidelines has shown that there was no difference in overall depression outcomes or health care costs when volunteer patients, randomly assigned to TCAs or SSRIs are given usual care by their regular doctors.[12] Despite slightly more participants being changed from TCAs to the more expensive SSRIs, the cost equivalence was attributed to more doctor visits being required to titrate the dosage of TCAs, whereas the therapeutic dose for SSRIs is usually the initial dosage.

In practice, GPs appear less likely to discontinue using SSRIs than TCAs, even after adjusting for patient age, sex and severity of depression.[13] Similarly, in a long term follow up study, patients assigned to fluoxetine therapy were significantly more likely to continue taking the initial SSRI antidepressant than the TCA group.[14] Despite evidence being strong that TCAs are as efficacious for depressed

Table 3. Doses for antidepressant drug therapy

Drug according to class	Start dose (mg/day)	Rate of dose	Usual therapeutic dose (mg/day)	Maximum dose (mg/day)	Half life (in days)	Cost ($) per usual therapeutic daily dose
SSRIs						
Citalopram	20	2–4 weeks	20	60	1.5	1.22
Fluoxetine	20	Several weeks	20	80*	5 + metab	1.20
Paroxetine	20	2–4 weeks	20	50	1	1.27
Sertraline	50	2–4 weeks	50	200	1	1.30
Fluvoxamine	50***	Initially every 5–7 days, then 2–4 weeks	100	300**	1	1.21
MAOIs						
Phenelzine	30*	Initially every 3–4 days, then 2–3 weeks	45–60*	90*	1 hour	0.80–1.06
Tranylcypromine	20*		20–30*	30*	2 hours	0.53–0.80
Moclobemide	300**	2–3 weeks	300–450**	600**	1.5 hours	1.03–1.55
TCAs						
Amitriptyline	General range of 50–75	Initially every 2–3 days, then 2–3 weeks	General range of 75–150	250	2	0.36–0.43
Imipramine					2	0.40–0.80
Clomipramine					2.5	1.11–2.22
Dothiepin					2.5	0.25–0.49
Doxepin					2.25	0.39–0.46
Trimipramine					1 + metab	1.03–2.06
Nortriptyline	"	"	75–100	100	1 + metab	0.40–0.53
Others						
Mianserin	30–60	Initially every 2–3 days, then weekly	30–90	120	1.5 + metab	0.78–2.28
Nefazodone	100–200**	Weekly	300–600**	600**	3 hours + metab	1.06–2.11
Venlafaxine	75**(controlled release XR single dose available	1–2 weeks	150**	375**	5 hours + metab	1.85

* Daily dose to be administered in 2-3 divided doses in the daytime (not in the evening or at night)
** Daily dose to be administered in 2-3 divided doses
*** Single dose at night
Costs are based on the Schedule of Pharmaceutical Benefits February 2001 and Mims No 3 2001.

patients who are able to reach and maintain a therapeutic dose, SSRIs seem to have some advantages over TCAs with their adverse effect profile and ease of dosing that outweigh their initial costs.[15]

Other issues in the treatment of depression

Dosage

To replicate the benefits of antidepressants in clinical trials, doctors need to work with their patients to achieve therapeutic doses and may have to go to maximum doses to achieve a response (Table 3). Education about the following factors may help in achieving such doses:

- the need to take medication daily for at least 2–4 weeks for an effect
- the need to continue treatment even when they feel better
- not to stop treatment without consulting a doctor
- what to do if questions arise
- how to titrate the dose, and
- the need to discuss the consequences of specific adverse effects for individual patients.

Although TCAs have been the most commonly prescribed antidepressant in general practice, surveys show inadequate dosage in 50% of patients treated for major depression in general practice.[16] General practitioners need to use higher doses of antidepressants in patients with major depression to achieve positive therapeutic outcomes. Although lower doses of antidepressants are often used by GPs on patients with minor depression, there are no studies available of their effectiveness.

Duration of therapy

A delay in onset of antidepressant response of at least 1–2 weeks after therapeutic dosage is reached occurs with all antidepressants. The drug should be trialled for at least 4–6 weeks after the therapeutic dose is reached before treatment is changed. There is some evidence that up to one-third of patients with no improvement at two weeks respond to treatment at eight weeks.[17] Adverse effects may also subside over this period.

Antidepressants should be continued for at least four months beyond initial recovery or improvement after a single episode of major depression to prevent a relapse within this period. About 35% of patients who discontinue antidepressant medication will experience relapse within six months.[8] The greatest risk seems to be in the first 2–4 months after recovery. Maintenance treatment with TCAs and SSRIs (citalopram, fluoxetine, paroxetine, fluvoxamine and sertraline) has been shown to decrease the relapse rate for up to six months. A strategy that has been shown to help patients adhere to medication is frequent in person or telephone follow up visits to titrate medication, monitor symptoms and address adverse effects.[1]

For recurrent depression, continuing the treatment at therapeutic doses for recovery is better than reduced maintenance doses. Long term therapy (3–5 years) should be considered for those patients who have had two or more depressive episodes, one severe episode or a strong family history of recurrent depression. Maintenance therapy, with TCAs and SSRIs, has been shown to decrease relapse rates.[8]

Ceasing antidepressants

Withdrawal syndromes lasting a few weeks have been described with TCAs, SSRIs and venlafaxine, usually when the drugs have been taken for several months. Patients describe abdominal pain, nausea, vomiting, diarrhoea, insomnia, rhinorrhoea, light headedness and flu-like symptoms.[2] Patients receiving higher doses, those with a previous history of discontinuation symptoms and those who develop withdrawal symptoms when the antidepressant is ceased, may require tapering over 4–7 days, or longer, if discontinuation symptoms are severe. It may be difficult to distinguish between antidepressant discontinuation effects, clinical features of depression, adverse effects of SSRIs, and the potentially life threatening serotonin syndrome. Patients with the serotonin syndrome show features of hypomania, confusion, myoclonus, hypertension, tremor, and diarrhoea. This condition is sometimes fatal.

Failure to respond to first choice of therapy

Doctors need to ask themselves:

- is the patient compliant and is the diagnosis correct?
- have relevant psychosocial factors been addressed?
- has drug or alcohol abuse been addressed?
- have the dosage and duration of the drug been adequate?

Other options for treatment

For mild to moderate major depression consider psychological strategies or St John's wort. Psychological strategies (eg. interpersonal therapy, cognitive behavioural therapy and problem solving therapy) have all been shown to be equivalent to TCAs in the treatment of mild to moderate major depression.[3,4] For short term treatment of mild depression, St John's wort (300–1800 mg/day) has been compared in 14 trials (N=1417) against placebo or first generation TCAs and shown to be significantly more effective than placebo but similar to first generation TCAs given in low doses. Although this agent might be considered, patients should be warned that there is variability in the standardised dosages in preparations and limited evidence on the adverse effects (particularly in view of the recent findings that it effects the cytochrome P450 system) or long term effects. More severe and refractory depression might necessitate referral to a psychiatrist for the use of lithium or ECT.

Changing from one drug to another

There is some data[18] to suggest that changing within a particular class of drugs (eg. SSRIs) is useful and intolerable adverse effects from one SSRI do not

Table 4. Antidepressant free intervals recommended when changing from one antidepressant to another*

(The risk of adverse effects needs to be weighed against the risk of undue delay in each individual case)

Changing to	citalopram, fluvoxamine, paroxetine, sertraline	fluoxetine	moclobemide	nefazodone	venlafaxine	TCA	mianserin	irreversible non-selective MAOI†
Changing from								
citalopram fluvoxamine paroxetine sertraline	nil	nil	nil‡	3–4 days	nil	nil§	nil	2 weeks
fluoxetine	1 week	–	1 week	1 week	1 week	1 week	1 week	5 weeks‖
moclobemide	nil¶	nil¶	–	nil¶	nil¶	nil¶	nil¶	nil
nefazodone	3 days	3 days	nil	–	3 days	nil	nil	1 week
venlafaxine	3 days	3 days	nil	3 days	–	nil	nil	1 week
TCA	1 week changeover required**	1 week changeover required**	nil††	3–4 days	3–4 days	nil	nil	1 week
mianserin	nil	nil	nil	nil	nil	nil	–	1 week
irreversible non-selective MAOI	2 weeks	2 weeks	nil‡‡	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks

Nil = start the new drug on the next day

* Always start the new drug at low dosage

† Irreversible nonselective MAOIs (phenelzine, tranylcypromine) should be commenced with caution after all other antidepressants because of the risk of severe hypertension, stroke and serotonin syndrome. Allowance should be made for the washout period (5 half-lives) and individual patient differences in kinetics

‡ Moclobemide dosage should be held at 300 mg/day for the first week. Dosage 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 before ceasing to commence moclobemide.

§ Note that TCA concentrations may be elevated for at least several weeks due to persisting SSRI induced cytochrome P450 inhibition.

‖ Five weeks is necessary because of the long half lives of fluoxetine and its active metabolite

¶ If moderate doses of both drugs are involved

** This includes period of tapering of the TCA dose

†† Moclobemide dosage should be held at 300 mg/day for the first week. Dosage may be subsequently increased if necessary. This recommendation is only for changing from low or moderate doses of TCAs. Changing from clomipramine is an exception (1 week antidepressant free interval required)

‡‡ If moderate doses of both drugs are involved, but irreversible nonselective MAOI dietary guidelines, see Table 4, p.18, Therapeutic Guidelines: Psychotropic Version 4, 2000, should be continued for two weeks

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necessarily predict intolerable adverse effects from a similar medication. Although, in one study most patients who could not tolerate fluoxetine were able to tolerate sertraline,[18] there is more likelihood that changing to a different class will produce a response, (eg. SSRI to TCA or venlafaxine).

Combinations of antidepressants have not been shown to be more effective than monotherapy and there is a greater risk of adverse effects and lethality in the event of overdose.[5] When changing antidepressants doctors need to allow enough time:

- to avoid the serotonergic syndrome when switching between irreversible MAOIs and other antidepressants, and
- because SSRIs inhibit the metabolism of many other antidepressants when switching between SSRIs and other antidepressants.

Recommendations for changing from one antidepressant to another are represented in Table 4.

Contraindications and significant clinical interactions of drugs

When starting a patient with a physical illness on an antidepressant drug, doctors need to be aware of drug interactions between medications (Table 5). Patients with cardiac disease, prostatism or acute angle glaucoma should not receive TCAs.

What drugs are safe for pregnant and breastfeeding women?

TCAs have been widely used during the first trimester of pregnancy and have not shown any teratogenic effects.[20] Similarly, SSRIs appear to have a low teratogenic risk, although some perinatal complications (eg. premature delivery) have been reported with third trimester exposure. Infants whose mothers take high doses in the third trimester could have some withdrawal symptoms.[21] Fluoxetine is the most studied and there have been no reports of increased short term risk to infants. Data on the long term developmental outcomes of children exposed to SSRIs during pregnancy and breastfeeding are limited. Almost all antidepressants cross into breast milk but this may not predict infant drug exposure.[22] There are case reports of no adverse effects for TCAs, SSRIs, MAOIs. However, there are often small numbers of babies included in studies and a lack of long term follow up.[23] Children of mothers with untreated postpartum depression are delayed in motor development, have lower IQs and have slower rates of growth when compared with children of mothers whose depression has been successfully treated.[21] Therefore prescription of an

Table 5. Drug interactions[19]

Medications whose levels may be increased by selective serotonin reuptake inhibitors due to cytochrome P450 inhibition

- TCAs, eg. amitriptyline, dothiepin
- beta-blockers, eg. propranolol, metoprolol
- codeine
- antipsychotics, eg. haloperidol
- anticonvulsants, eg. carbamazepine, valproic acid, phenytoin
- benzodiazepines, eg. diazepam, triazolam, alprazolam, midazolam
- warfarin
- cyclosporin
- calcium channel antagonists, eg. nifedipine, diltiazem
- antiarrhythmics, eg. quinidine, lignocaine, flecainide, digoxin
- terfenadine
- barbiturates

Other significant interactions with selective serotonin reuptake inhibitors

Drug class	Clinical features of interaction	Comments
Irreversible MAOIs	'Serotonergic syndrome' (hypomania, confusion, myoclonus, hypertension, tremor, diarrhoea, death)	For guidelines on changing from MAOIs to SSRIs (or vice versa) see Table 4
Lithium	Increased lithium levels, neurotoxicity	Usually a safe combination

Significant interactions with moclobemide

Drug class	Clinical features of interaction	Comments
Pethidine	Uncertain, but serious interaction between pethidine and older MAOIs	Avoid
Cimetidine	Reduces moclobemide metabolism	Halve moclobemide dose
TCAs, SSRIs	Deaths reported with moclobemide and clomipramine	Avoid combination

Further Reading: Martin J, Fay M. Cytochrome P450 drug interactions: Are they clinically relevant? Australian Prescriber 2001; 24:10-12.

antidepressant for a breastfeeding woman is a case specific harm-benefit decision.

Using antidepressants for other conditions

The preceding section has concentrated on the use of antidepressants for the treatment of depression. However, there are many other conditions for which GPs prescribe antidepressants. Their efficacy in these psychiatric and chronic conditions is examined below.

Insomnia, sleep disorders

The more sedating antidepressants are often prescribed for patients presenting with anxiety or insomnia. Additionally, TCAs (eg. low dose amitriptyline) are commonly used in general practice for their sedating properties in people who are not experiencing major depression. There have been no clinical trials directly assessing the TCAs as simple hypnotics, but one study has demonstrated improvement of various markers of sleep disturbance in patients with chronic primary insomnia treated with doxepin.[24] There have also been no placebo controlled trials of the use of TCAs specifically to treat insomnia in depressed patients. However, there is some evidence from a small trial that imipramine might be slightly superior to doxepin in improving markers of sleep disturbance in depressed patients with insomnia.[25] For SSRIs, there is some evidence that fluoxetine treatment of depressed patients with sleep disturbance improves the symptoms of insomnia.[26] In another study, when patients treated with fluoxetine or imipramine were compared, there was no difference in the rate of improvement in insomnia in the patients treated with the two drugs.[27] Nefazodone and fluoxetine have been compared in a randomised trial in patients with depression and insomnia, and nefazodone had significantly better effects on various different markers of sleep disturbance.[28] It can be concluded that the use of TCAs to treat insomnia has no strong evidence base, but may be reasonable, based on clinical experience. In depressed patients, TCAs (particularly imipramine) and fluoxetine both improve symptoms of insomnia; and nefazodone might be slightly superior to fluoxetine in improving symptoms of insomnia in depressed patients.

Post-traumatic stress disorder

TCAs have been shown to have some beneficial effects in patients with post-traumatic stress disorder (PTSD), although most treated patients still met the diagnostic criteria for the disorder at the end of treatment. Depressive symptoms probably respond better than other symptoms.[29,30] SSRIs have also been shown to have significant benefits in PTSD, and there is some evidence that the effect is independent from the antidepressant effect. The evidence for a beneficial effect of phenelzine is conflicting, with some studies showing a clinically significant benefit, and others no benefit. The evidence for a mild beneficial effect of moclobemide is weak.[31–33]

Social phobia

In small trials (RCTs), the SSRIs fluvoxamine and paroxetine have been shown to be effective in alleviating symptoms and avoidance behaviour.[34–36] Sertraline was also shown to be effective in a crossover study.[37] Phenelzine although shown to be effective has concerns about the risk of hypertensive crises, which has reduced its acceptability.[38] The reversible MOAI, moclobemide, in a large RCT with dosages of 300 mg twice daily showed a reduction of the symptoms and impairment associated with the disorder. There have not been any RCTs with nefadozone or venlafaxine in social phobia nor any comparisons between the newer drugs. There is no evidence that TCAs are effective in patients with phobias.

Panic disorder

Evidence that tricyclic antidepressants are effective in treating panic disorder dates back to work from the 1960s with imipramine.[39] Subsequent meta-analyses of treatment with SSRIs, including paroxetine, fluvoxamine and the serotonergic tricyclic clomipramine have shown all three treatments to be significantly superior to placebo in alleviating panic.[39,40] In general, the doses of SSRIs required to treat panic are higher than the doses of SSRIs required to treat depression. In one study moclobemide was as effective as clomipramine in treating panic when used in a dose of 450 mg per day.[41] When treating panic disorder both TCAs (especially imipramine and clomipramine) and SSRIs may be considered as first line antidepressant therapy.

Obsessive compulsive disorder

Clomipramine was the first antidepressant to show evidence of efficacy in the treatment of obsessive compulsive disorder (OCD).[42] SSRIs have also been shown to be effective and in a meta-analysis, clomipramine was shown to be more effective than fluoxetine.[43] Most studies have randomised small numbers of patients and few placebo controlled studies have been carried out.[44] Clomipramine and SSRIs should be considered first line treatment when treating OCD with an antidepressant. Comorbid depressive symptoms tend to improve before obsessive compulsive symptoms in these patients.[44]

Dementia and comorbid depression, dementia with disruptive vocalisation

Reported rates of depressive disorders among individuals with dementia vary widely with quoted prevalence rates from 0–87%. Most studies find rates for significant depression vary between 5–30%.[45] In small studies, mild beneficial effects have been reported for clomipramine,[46] nortriptyline[47] and in studies against SSRIs, imipramine.[48] There is some evidence that TCAs worsen cognition in demented patients in a subtle manner. In regard to SSRIs, small studies of fluoxetine versus

amitriptyline,[49] citalopram versus placebo[50] and sertraline versus placebo[51] have tended to show mild beneficial effects for SSRIs where cognitive impairment is found with tricyclic antidepressants. One larger study on a diffuse group of patients with depression and cognitive impairment indicated beneficial effects for moclobemide over placebo.[52] Results should be interpreted with caution as patient numbers are small and depression in this group is notoriously difficult to diagnose. Practitioners planning to treat depression in demented individuals should be aware of the fact that many symptoms of depression can overlap with those of dementia. The tricyclic antidepressants are likely to exacerbate cholinergic deficits causing cognitive impairment in patients with Alzheimer disease.[53] Frail elderly patients on multiple medications are often prone to drug interactions. Where an antidepressant is indicated because of persisting depression beyond two weeks, the best available evidence favours moclobemide, and there is reasonable evidence that SSRIs are better tolerated than TCAs in this population. No quality evidence on the usefulness or otherwise of antidepressants in the treatment of disruptive vocalisation in those with dementia could be traced for this review.

Chronic fatigue syndrome

There is good evidence that the SSRIs are not effective in the treatment of chronic fatigue syndrome (CFS). A double blind, placebo controlled study of fluoxetine at a dose of 20 mg daily for eight weeks showed no improvement in any of the features of CFS.[54] Importantly, there were also no benefits in the subgroup of patients with coexistent depression, which is, of course, common in this condition. The only studies suggesting that TCAs might be effective in the treatment of CFS have studied patients with predominantly fibromyalgia, and have not shown major benefits.[55] Phenelzine (15 mg daily) has been shown to have a mild, but clinically and statistically significant, beneficial effect on self reported symptoms of CFS.[56] Moclobemide (up to 600 mg daily) has also been shown to have a mild beneficial effect in patients with CFS who also have coexistent major depression, but not in those without depression.[57] It can be concluded that neither SSRIs nor TCAs have a beneficial effect in CFS, including patients with coexistent depression, although TCAs might have minor benefits in fibromyalgia. MAOIs (both phenelzine and moclobemide) probably have significant benefits in patients with CFS with coexistent depression, but not in patients without depression.

Chronic pain

It is accepted that TCAs have a role in the management of chronic nonmalignant pain,[58] but a review of the efficacy of SSRIs in the management of chronic pain concludes that this group of drugs was only seen to be consistently helpful for mixed-chronic pain. The evidence is conflicting for migraine headache, tension headache, diabetic neuropathy and fibromyalgia.[59] Some studies have supported the benefit of moclobemide in fibromyalgia,[60,61] but others have questioned its usefulness because of the poor success of the drug with regard to sleep.[62] There is still insufficient evidence to recommend the use of nefazodone and venlafaxine for chronic pain in the general practice setting.

Urinary incontinence, enuresis

While TCAs such as imipramine have been used for the management of nocturnal enuresis in children and urinary incontinence in adults, a review of the literature does not strongly support their use for either of these situations. In the management of nocturnal enuresis in children, there is evidence of benefit while taking a TCA,[63] but other reviews have noted that the quick response to TCA is not sustained and that the side effects are potentially serious. The review of available literature did not find strong evidence to support the use of imipramine for incontinence due to bladder instability.[64]

Anorexia nervosa and bulimia nervosa

The results of studies of psychological strategies and drugs have overall been more favourable for patients with bulimia nervosa than for patients with anorexia nervosa.[65] There is no evidence that amitriptyline has any effect in anorexic patients[66] while fluoxetine and venlafaxine have shown a small effect in a few studies.[67,68] Statistically significant effects concerning the reduction of bulimic or depressive symptoms have been demonstrated for TCAs, SSRIs and nonselective MAOIs. The antibulimic effect appears not to be associated with the antidepressant effect.[65,69,70]

Premenstrual syndrome

Several studies have supported the use of SSRIs for the treatment of premenstrual disorder and premenstrual dysphoric disorder. While the majority of these studies are small, they consistently show benefits from the SSRI used in the trial, including sertraline[71–73] and fluoxetine.[74–77] Some studies have also supported the use of SSRIs in the late luteal phase only, including clomipramine[78] and sertraline.[79,80] A few studies have found imipramine[81] or desipramine to also be useful in treating premenstrual syndrome, but usually with increased side effects, compared to SSRIs.[82] Other studies found TCAs less effective than SSRIs.[71]

Conclusion

There is good evidence that TCAs are as efficacious as SSRIs in the treatment of major depression. A more important question however, is how effective they are when prescribed by GPs in the primary care setting. As a result of their equal efficacy, choice of the different antidepressants largely depends on cost and the anticipated adverse effects. The

adverse effect profiles of the different classes of agents are different, and this allows patient preferences and comorbidities to be important factors in drug choice.

Doctors would be better able to advise patients about the best use of antidepressants if there was more information available on functional status and quality of life when patients are taking antidepressants, as most information currently available involves depression or anxiety scales and the incidence of specific adverse effects. More information is also required on the use of antidepressants in general practice settings in patients with comorbid conditions, and in special patient groups such as adolescents. As the prevalence of minor depression and dysthymia is high in general practice, more information on the use of pharmacotherapy in conjunction with psychotherapy, for treatment of these two important conditions is needed.

Antidepressant drugs are also used for a variety of indications other than depression. The strength of evidence about the use of the different classes of drugs for these indications is variable. In order to use these drugs wisely, practitioners need to know the evidence for their efficacy when used for indications other than depression.

Acknowledgments

This review was written by a committee appointed by the Victorian Drug Usage Advisory Committee (VDUAC). An initial full literature search for the effectiveness of antidepressants for all known indications was undertaken by the Centre for Clinical Effectiveness at Monash University. For each of the indications for antidepressant drugs, one committee member reviewed the relevant papers and summarised the evidence. Dr Hegarty wrote the final manuscript which was approved by the full committee.

A PDF summary of the guidelines is available from the VDUAC's website: http://www.vduac.org.au/antidgdl.pdf

SUMMARY OF IMPORTANT POINTS

Depression

- All antidepressant drugs have similar efficacy to psychological strategies for mild to moderate major depression.
- Most patients do best with a combination of antidepressant medication and psychological strategies.
- All antidepressants have equal efficacy in the treatment of major depression.
- Because of their equal efficacy, it is the adverse effect profile which largely determines the choice of antidepressant in the treatment of major depression.
- In acute depression patients should trial an antidepressant for at least 4–6 weeks and if it is suitable, stay on the drug for at least four months at the same dose.
- For recurrent depression, continuing the treatment at therapeutic doses for recovery is better than reduced maintenance doses. Long term therapy (3–5 years) should be considered for those patients who have had two or more depressive episodes, one severe episode, or a strong family history of recurrent depression.
- Changing from one antidepressant to another is complex and blood levels of many medications are raised by the use of SSRIs.

Other psychiatric conditions

There is **good evidence of the effectiveness** of:

- TCAs (especially imipramine and clomipramine) and SSRIs for panic disorder
- TCAs and SSRIs for obsessive compulsive disorder
- SSRIs for post-traumatic stress disorder
- TCAs, SSRIs and nonselective MAOIs for bulimia nervosa
- SSRIs (fluvoxamine, paroxetine) and moclobemide for social phobia.

There is **good evidence of the ineffectiveness** of:

- SSRIs for anorexia nervosa.

There is **reasonable evidence of the effectiveness** of:

- moclobemide for dementia and comorbid depression.

Other current uses

There is **good evidence of the effectiveness** of:

- TCAs for chronic pain
- MAOIs for chronic fatigue syndrome with coexistent depression
- SSRIs for premenstrual syndrome.

There is **good evidence of the ineffectiveness** of:

- TCAs and SSRIs for chronic fatigue syndrome.

There is **not enough good evidence for the effectiveness** of:

- TCAs for enuresis or urinary incontinence
- SSRIs for chronic pain.

There is **no good evidence for the effectiveness** of

- TCAs or SSRIs for insomnia in patients who are not depressed
- any antidepressant for disruptive vocalisation with dementia.

Conflict of interest: none declared.

References are available for this article. Email afp@racgp.org.au or phone 03 8699 0546.