How to choose an antidepressant
A guide for GPs

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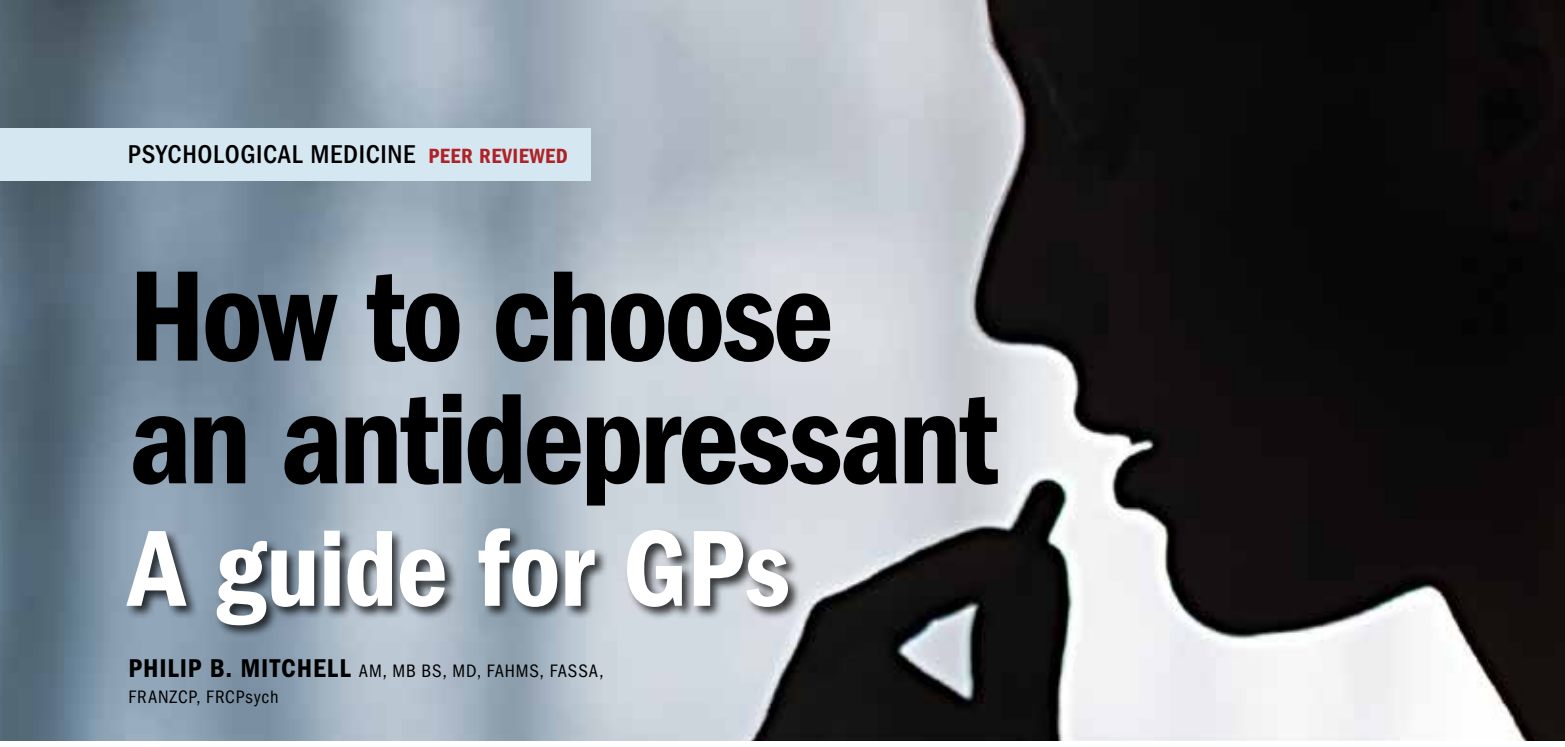

Depression and anxiety are among the most common health presentations to GPs in Australia. Since the 1990s, there has been an increasing range of antidepressants marketed in this country, making it difficult for GPs to decide on the appropriate choice for their patients. This article reviews the current landscape of antidepressants in Australia and details the pros and cons of the various options, drawing on both the published literature and the author's own clinical experience with mood disorders.

In Australia, mental health conditions such as depression and anxiety continue to be the most common issues managed by GPs.[1] GPs prescribe the majority (86%) of antidepressants in this country, with three-quarters of such prescribing initiated in the primary care setting.[2] Recent Australian primary care research from the diamond longitudinal study has reported high rates of both under-prescribing (41%) and overprescribing of antidepressants (i.e. for patients without formal depressive or anxiety disorders; 30%).[3] This finding of common undertreatment is consistent with an analysis of the 2007 Australian National Survey of Mental Health and Wellbeing.[4] According to the analysis, only 39% of those with mood and/or anxiety disorders sought professional help.[4] Of those who consulted a health professional, only two-thirds received an evidence-based treatment (such as an antidepressant or appropriate psychological treatment), with only 41% of those consulting receiving minimally adequate treatment (in terms of dose or duration).[4]

Although antidepressants are indicated for both depressive and anxiety disorders, this article will focus on their use for patients with depression. Most national guidelines concerning the management of depression have recommended that antidepressants are indicated for those with moderate or severe levels of depression.[5-7] Psychological treatments are mainly indicated for those with mild levels of depression but may also be useful in conjunction with antidepressants for moderate or severe depression.[8]

A recent network meta-analysis of all controlled trials of antidepressants has confirmed that all marketed antidepressants are more effective than placebo, while identifying some differences in efficacy and tolerability.[9] Regarding efficacy in the primary care setting, the recent UK PANDA trial reported on a pragmatic placebo-controlled trial of the selective serotonin reuptake inhibitor (SSRI) antidepressant sertraline in primary care patients.[10] Participants were included if they had depressive symptoms of any severity or duration, and where there was clinical uncertainty about the benefit of an antidepressant. The study found that sertraline did not reduce depressive symptoms within six weeks, but over that time there were significant improvements in anxiety, quality of life and self-rated mental health. There was some evidence of antidepressant efficacy by 12 weeks. The findings of this study supported the prescription of SSRIs in a wider group of primary care patients than previously recommended, including those with mild to moderate symptoms who did not meet formal diagnostic criteria for depression or generalised anxiety disorder.

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Figure. In contemporary practice it is most common to first use a selective serotonin reuptake inhibitor (SSRI) antidepressant. If the SSRI is not effective, or poorly tolerated, other antidepressant classes or a different SSRI should then be considered.

This article will not provide an overview of the management of depression nor focus on the patient with treatment-resistant depression as these topics have been covered recently.[11,12] More detailed management guidelines are also available elsewhere.[7,13] Rather, the focus here will be specifically on the choice of antidepressants for depression, drawing on both the relevant literature and the author's clinical experience.

Which antidepressant class should be used first? And if no success, what then?

In Australia (as in most developed nations), the most commonly prescribed antidepressant classes are (in order): SSRIs, serotonin–noradrenaline reuptake inhibitors (SNRIs), mirtazapine, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Figure). Other antidepressants marketed here include agomelatine, vortioxetine and reboxetine.[14]

In contemporary practice, it is most common to first use an SSRI antidepressant. If the SSRI is not effective, or poorly tolerated, other antidepressant classes or a different SSRI should then be considered.

Selective serotonin reuptake inhibitors (SSRIs)

In the author's experience, SSRIs are frequently effective and usually well tolerated by antidepressant-naive patients. Despite contemporary community and professional scepticism about the benefit of antidepressants, many patients are pleasantly surprised by the benefit they gain from these drugs, and the major improvements in day-to-day functioning they experience. Practitioners need to be aware, however, of the limitations of antidepressants, as only about one-third of patients with depression experience full remission after the first exposure to an SSRI.[15]

There are six SSRIs marketed in Australia, these being (in alphabetical order, all being available now as generics): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

All SSRIs have similar efficacy; however, a given patient may respond to, or tolerate, one SSRI but not another. In general, side effects differ minimally within this antidepressant class. Many patients initially experience nausea, which usually settles within a few days. Other common adverse effects are headache, insomnia and dizziness – again, these often settle with time. Some patients experience gastrointestinal effects such as diarrhoea, particularly with sertraline (otherwise a very useful SSRI). Some, paradoxically, develop somnolence and/or fatigue, more commonly with fluvoxamine and paroxetine. Agitation and heightened anxiety can also occur and need to be distinguished from the symptoms of the depression itself.

Although there has been concern that some patients become more suicidal on SSRIs, there is no convincing evidence for this in adults, though this may occur in children and adolescents. Some patients (about 10%) develop a 'blunting' of emotions, describing this as an attenuated ability to experience the normal (nonpathological) emotional range. Sexual dysfunction occurs in 20 to 30% of patients, male and female, with effects on libido and capacity to achieve orgasm. For males, erectile difficulties (sometimes responsive to agents such as sildenafil) and inhibited ejaculation are not uncommon. Other, less common complications are an increased tendency for bleeding and inappropriate antidiuretic hormone secretion (typically presenting in older patients, with confusion and hallucinations). SSRIs also increase risk of falls and reduced bone density. All serotonergic antidepressants can interact with the analgesic tramadol and should not be coprescribed.

Poxetine is the most likely SSRI to cause significant discontinuation symptoms, probably because of its relatively shorter half-life. Common antidepressant discontinuation symptoms include anxiety, irritability, thinking difficulties and 'head spinning' or dizziness. These symptoms usually last only one to two weeks. Discontinuation symptoms are more likely if patients have taken large doses of antidepressants for a long duration, necessitating slow dose reduction if they are to be ceased.

SSRIs, like all other antidepressants, may also induce manic symptoms. Although there is debate whether this indicates an underlying bipolar disorder, in the author's experience most patients with this adverse effect never go on to develop elevated episodes unrelated to antidepressants.

Serotonin–noradrenaline reuptake inhibitors (SNRIs)

There are three SNRIs marketed in Australia: desvenlafaxine, duloxetine and venlafaxine. The author's experience has been that although desvenlafaxine tends to have fewer adverse effects, it is somewhat less effective than the other two. SNRIs are usually used when SSRIs do not work. SNRIs are probably more effective than SSRIs but also more prone to causing adverse effects. At lower doses the serotonergic action is predominant, while at higher doses (225 mg and above) there is an additional noradrenergic effect. Many side effects are shared with the SSRIs, but at higher doses of SNRIs the noradrenergic effects of excessive sweating (particularly

MANAGING DEPRESSION DURING THE COVID-19 PANDEMIC

Presentations of both anxiety and depression have certainly become more prevalent during the current pandemic. In the author's experience, the general apprehension and fear related to COVID-19 in the general community has been amplified and compounded in many of those with a history of prior anxiety or depressive disorders.

The author has seen patients presenting with depressive relapses where the COVID-19 restrictions have impacted on income, career, education and relationships. For example, one patient's partner was overseas and was unable to return home after sudden cessation of flights from that country. Another patient needed to precipitately return to the family home soon after moving interstate to start tertiary studies, because of the COVID-19 university lockdown. Although general management of depression in these circumstances does not differ substantially from routine practice, GPs need to be alert to the specific pandemic-related circumstances relevant to their particular patient.

General resources for managing anxiety and depression related to COVID-19 are available at the Black Dog Institute website: https://www.blackdoginstitute.org.au

during sleep), constipation and hypertension become apparent. SNRIs need to be avoided or used cautiously in patients with a history of hypertension.

Although SSRIs are usually nonlethal on overdose, SNRIs are more concerning, with overdose lethality comparable with that of some TCAs. Also, the SNRIs (particularly venlafaxine) are highly prone to causing discontinuation symptoms, with venlafaxine commonly associated with this, probably because of its short half-life.

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)

Over the 30 years since the advent of SSRIs and SNRIs, TCAs and MAOIs have been much less frequently prescribed in primary care. This has been largely related to the greater tolerability and fewer safety concerns with the newer antidepressants. The main safety issues with TCAs are their effect on cardiac conduction pathways and high lethality in overdose, while the older ('irreversible') MAOIs necessitate significant dietary restrictions (avoiding food containing tyramine) and involve risk of significant drug interactions (e.g. with pethidine). Nonetheless, specialists familiar with less treatment-responsive presentations of depression are aware that both TCAs and MAOIs are, in general, more effective than SSRIs and SNRIs. In current practice, TCAs and MAOIs are now regarded as best initiated by psychiatrists. Unfortunately, there are some practitioners who regard use of these antidepressants as 'dangerous and old fashioned', leading to considerable patient distress. The reality, however, is that some patients with severe depression only respond to these older antidepressants, and invariably deteriorate when transferred to one of the newly marketed agents.

Of the TCAs, nortriptyline is one of the best tolerated, with minimal anticholinergic effects, and is reliably commonly effective. Although the newer ('reversible') MAOI moclobemide was marketed in the 1990s, it has turned out to be a weak antidepressant and is now uncommonly used.

Other new antidepressants

Mirtazapine is pharmacologically distinct from other antidepressants, acting on several noradrenergic and serotonergic receptors. As it has anxiolytic properties in addition to being antidepressant, it is often used for depressed patients with comorbid anxiety. In terms of adverse effects, appetite stimulation and weight gain are often substantial, and it may affect sleep – more commonly causing somnolence, but sometimes insomnia.

Agomelatine is both an agonist of the melatonin receptor and a blocker of one of the serotonin receptors (5-HT2C), though it is not clear which of these actions is mainly responsible for the antidepressant effect. Routine monitoring of liver function is recommended in view of its common (1 to 2% of prescribed patients) elevation of liver enzymes. Side effects are similar to those of the SSRIs, though it may be less prone to sexual side effects. In clinical practice, it has been viewed as a relatively weak antidepressant.

Vortioxetine is the most recently marketed antidepressant in Australia. It inhibits serotonin uptake like the SSRIs, and acts on several serotonin receptors. Its side effect profile is like that of the SSRIs.

Reboxetine is the only 'newer' antidepressant that is a selective noradrenaline reuptake inhibitor. Although this distinct mechanism suggested a useful clinical therapeutic niche, it has turned out to be one of the weakest and most poorly tolerated antidepressants.[9] It frequently causes severe insomnia and anxiety, with one of the author's patients describing the effect as similar to 'taking an overdose of caffeine'. It may also lead to hypertension.

Conclusion

Depression is a highly common presentation in Australian primary care, with GPs being the major initiators and prescribers of antidepressants. This article gives an overview of the advantages and disadvantages of the various antidepressants available in this country. Use of these medications should be viewed as only one of the options for managing depression, with many patients benefiting from evidence-based psychological treatments alone, or in conjunction with antidepressants. As depression is associated with marked disability, effective treatment can make a profound difference to the lives of your patients. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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