

# Drug treatment for anxiety

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**SUMMARY**

Antidepressants are recommended as first-line when pharmacotherapy is required for anxiety disorders.

Selective serotonin reuptake inhibitors are effective in all anxiety disorders, and selective and noradrenaline reuptake inhibitors in most anxiety disorders. They are the drugs of first choice.

With the exception of obsessive compulsive disorder, there is little evidence of a dose-response relationship with antidepressants and many patients will respond to standard doses.

Anxiety is generally slower to respond to treatment than depression and clinicians should avoid rapid dose escalation.

The outcomes are likely to be enhanced if patients receive cognitive behavioural therapy in addition to pharmacotherapy.

Benzodiazepines are not the first-line treatment for anxiety disorders.

**Introduction**

Anxiety is a universal experience. When it becomes persistent, or persists after a triggering stressor has resolved, or is out of proportion to what would be expected and interferes with functioning, it may have reached the level of a disorder.

Both psychological and pharmacological treatment strategies for anxiety disorder have a good evidence base. Established drug treatments for anxiety target serotonin, noradrenaline and gamma-aminobutyric acid (GABA) neurotransmitter systems. They include virtually all classes of antidepressants, as well as benzodiazepines (Table). However, there is more evidence for certain classes of antidepressants over others, and benzodiazepines have a number of disadvantages that preclude their first-line use.

**An overview of practice**

A stepped-care model for the management of anxiety is recommended. Australian<sup>2</sup> and UK<sup>3</sup> guidelines list non-drug approaches as initial interventions. They include individual non-guided or guided self-help, and psychoeducational groups. For patients who

present with marked functional impairment and those who do not respond to the initial interventions, high-intensity psychological interventions (such as cognitive behavioural therapy) or medication are recommended.

Australasian guidelines for panic and agoraphobia<sup>4</sup> identify cognitive behavioural therapy as first-line treatment. As a sole therapy, it can be at least as effective as pharmacotherapy and in some cases more so. Antidepressants alone are less effective than cognitive behavioural therapy alone, or the combination of an antidepressant and cognitive behavioural therapy.<sup>4-6</sup> Additionally, cognitive behavioural therapy is more likely to give lasting benefit. In contrast to depression, efficacy appears to be lost soon after stopping antidepressants, with a recurrence of anxiety being the rule rather than the exception.

**Self-help programs**

Non-facilitated self-help is available through a number of online resources including:

- [www.anxietyonline.org.au](http://www.anxietyonline.org.au) – developed by the National eTherapy Centre at Swinburne University of Technology (Victoria) and funded by the Australian Government Department of Health
- [www.thiswayup.org.au](http://www.thiswayup.org.au) – an initiative of the Clinical Research Unit for Anxiety and Depression at St Vincent's Hospital (Sydney)
- [www.ecentreclinic.org](http://www.ecentreclinic.org) – developed by the Centre for Emotional Health at Macquarie University.

There is increasing evidence to support these web-based programs.<sup>7</sup> Their efficacy has been reviewed by a team at the Australian National University ([www.beacon.anu.edu.au](http://www.beacon.anu.edu.au)). Drop-out rates are reduced by having some contact with a therapist, but this does not have to be an expert. For example, the Clinical Research Unit for Anxiety and Depression program provides verbal scripts that can be used by a practice nurse. Within the stepped-care model, a good quality online anxiety treatment program can be recommended to patients with anxiety disorders of mild to moderate severity if they are comfortable with the technology.

**Pharmacotherapy for anxiety**

Patients with severe symptoms, those demoralised by their anxiety or those with comorbid depression may benefit from drug treatment. If medication

is likely to be required for more than a few days, an antidepressant should be used. Guidelines<sup>8</sup> recommend selective serotonin reuptake inhibitors (SSRIs) as first-line for all anxiety disorders, and serotonin and noradrenaline reuptake inhibitors (SNRIs) for some disorders (Table).

### Choosing an SSRI or SNRI

Clinicians should choose a drug with a favourable tolerability profile and the least potential for drug interactions. Several antidepressants are potent inhibitors of cytochrome P450 enzymes.<sup>9</sup> Combining more than one serotonergic drug, including multiple antidepressants, St John's wort and some analgesics such as tramadol, can give rise to serotonin syndrome. A high index of suspicion is needed for patients who present with hypertension, hyperthermia, autonomic signs and hyperreflexia soon after starting, adding or increasing the dose of a serotonergic drug.<sup>10</sup> Discontinuation syndrome is more common with some antidepressants such as venlafaxine and paroxetine.

### Pre-treatment counselling

Most patients with anxiety, and especially those with health concerns, for example in generalised anxiety disorder and panic disorder with or without agoraphobia, are highly sensitive to the physiological effects of medication. Adverse effects commonly seen when commencing antidepressants, such as nausea, headache and dizziness, may be misinterpreted as signs of serious physical illness or impending loss of mental control. Hence, the increased anxiety often observed when starting SSRIs may reflect a combination of normal (though undesirable) physiological effects, heightened cognitive symptoms of anxiety as a result of fears about the seriousness or permanence of these adverse effects, or more rarely, agitation or akathisia or acute suicidality.

Most patients have had their anxiety symptoms for many years before presenting for treatment and will generally tolerate a few more weeks while they wait for a response. Clinical experience suggests that patients most value information about the nature of their illness and its treatment, and do not expect instant alleviation of their symptoms.

To minimise the chances of a patient stopping medication as a result of these factors:

- start the patient on half the minimum strength tablet available. Continue at this dose for a few days to a week, or until the patient feels confident enough to increase the dose.
- give the minimum recommended dose a chance to work before increasing (at least four weeks)

Table Efficacy of drug treatments for anxiety disorders

Drug (daily dose)	Efficacy from meta-analyses or consistent positive findings in more than one randomised controlled trial *
<b>Selective serotonin reuptake inhibitors</b>	
escitalopram (10–20 mg) †	all anxiety disorders
paroxetine (20–60 mg)	
sertraline (50–150 mg, up to 200 mg in OCD)	
fluoxetine (20–40 mg, up to 60 mg in panic disorder and 80 mg in OCD)	panic/agoraphobia, social phobia, OCD, PTSD
fluvoxamine (100–300 mg)	panic/agoraphobia, social phobia, OCD
citalopram (20–40 mg) †	panic/agoraphobia, social phobia
<b>Serotonin and noradrenaline reuptake inhibitors</b>	
venlafaxine (75–225 mg, higher doses are sometimes used in specialist practice)	all anxiety disorders except OCD
duloxetine (60–120 mg)	GAD
<b>Benzodiazepines</b>	
alprazolam	GAD, panic/agoraphobia
clonazepam	panic/agoraphobia, social phobia
diazepam	GAD, panic/agoraphobia
lorazepam	GAD, panic/agoraphobia
<b>Tricyclic antidepressants †§</b>	
amitriptyline (75–200 mg)	PTSD
clomipramine (75–250 mg)	OCD, panic/agoraphobia
imipramine (75–250 mg)	GAD, panic/agoraphobia
<b>Monoamine oxidase inhibitors</b>	
phenelzine (45–90 mg)	panic/agoraphobia, social phobia
<b>Antipsychotics</b>	
quetiapine (50–150 mg) §#	GAD

GAD generalised anxiety disorder      OCD obsessive compulsive disorder  
PTSD post-traumatic stress disorder

\* If several members of an antidepressant class have demonstrated efficacy, it is highly likely that all members of the class will, however there may be limited studies of individual drugs. Differences in efficacy of benzodiazepines have sometimes been reported between low potency and high potency members of the class.

† Note the maximum dose recommendations have been revised following reports of dose-dependent QT interval prolongation. Citalopram has a greater effect than escitalopram on the QT interval ([www.fda.gov/Drugs/DrugSafety/ucm297391.htm](http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm)).

‡ Relatively few tricyclics have been studied extensively, and there are no studies of this class in social phobia.

§ ECG monitoring of QTc interval may be indicated. Avoid concomitant use with other drugs known to cause electrolyte imbalance or QT prolongation.

# The upper limit of the dose range is based on findings that the efficacy of a 300 mg dose was unreliable compared to lower doses in placebo-controlled trials and was associated with more adverse effects and treatment dropouts. Another recent trial found quetiapine 150 mg was effective in generalised anxiety.<sup>1</sup>

- inform the patient about common and expected adverse effects before prescribing. See them again soon and encourage them to telephone should they have any concerns. Appropriate reassurance can be helpful.
- provide information about the expected time frame of response.

Occasionally patients describe intolerable, persistent or unusual adverse effects. In such cases another SSRI (or SNRI) should be tried. The routine use of benzodiazepines when starting SSRIs is not recommended and not usually required if the above strategies are used.

### *Dose and duration*

Approximately 75% of patients respond to the initial minimum dose of antidepressant, with the exception of obsessive compulsive disorder which shows a dose-response relationship.<sup>8</sup> However, for anxiety the onset of action is generally slower than in depression and may take 4–6 weeks.

There is little research about how long treatment should be continued. In practice, I recommend patients take

antidepressants for a year in the first instance (similar to guidelines for the first episode of depression). Ideally, patients should also have cognitive behavioural therapy to protect against relapse. In severely anxious patients or those with comorbid depression, cognitive behavioural therapy may be added after some symptomatic improvement has occurred.

### *Other antidepressants*

Tricyclic antidepressants are effective in panic disorder, and clomipramine – a relatively serotonergic tricyclic – is effective in obsessive compulsive disorder. There is also some evidence for their use in post-traumatic stress disorder. However, tricyclics have a significant adverse effect profile rendering them far down the list of options. They are highly toxic in overdose, potentiate the sedating effects of alcohol, and can prolong the QT interval. If a general practitioner is considering prescribing a tricyclic, it may be preferable to seek a specialist opinion first.

Similarly, while non-reversible monoamine oxidase inhibitors have been shown to be effective for panic and social anxiety disorders, they carry a high burden of risks and adverse effects and, in general, should only be initiated with specialist review. Common adverse effects include nausea, postural hypotension, insomnia, anticholinergic symptoms and weight gain. They may interact with tyramine or dopa-

containing foodstuffs, sympathomimetic drugs, and some alcoholic beverages, with the potential for life-threatening hypertensive crisis. Other serious interactions involving hypertension or hypotension and hyperthermia may be seen with a range of other drugs, including other antidepressants, opioids, levodopa and anaesthetics. For some patients, the foods that must be avoided, such as mature cheese, aged meat or liver products, and yeast extracts, may represent a significant part of their normal diet.

Moclobemide, a reversible monoamine oxidase inhibitor, has been associated with inconsistent findings in efficacy studies for anxiety. A relatively small number of trials support the use of mirtazapine. It might be considered for anxious patients given its relatively sedating profile, but once anxiety has been relieved and the patient is in the maintenance phase, weight gain and persistent sedative effects can be a problem. There is no robust literature for reboxetine or agomelatine.

### *Benzodiazepines*

Benzodiazepines reduce the somatic and psychological symptoms of anxiety in panic disorder, generalised anxiety disorder and, for high potency benzodiazepines, in social anxiety disorder. However, some evidence suggests that patient function may not improve to a similar extent.<sup>11</sup> Because they can cause cognitive impairment and have a potential for dependence, benzodiazepines are not first-line treatments. Alprazolam may have a greater potential for dependence than other benzodiazepines because of its rapid onset of anxiolysis and short half-life. Its use has increased in recent years, even while use of other benzodiazepines has declined or remained stable.<sup>12</sup> Clinicians intending to prescribe alprazolam should carefully consider how likely it is that its use will remain restricted to the very short term – that is, a few days to a week – to see a patient through a crisis.

An additional consideration when using benzodiazepines is that the withdrawal syndrome is frequently mistaken by patients as indicating that the anxiety for which the drug was originally started has returned. In the case of alprazolam, the short half-life means that some regular users may begin to experience withdrawal symptoms in the morning following the last night-time dose, thus seeming to confirm the continuing need for the drug. Benzodiazepines do have a place for patients for whom other drugs and non-pharmacological interventions have failed to bring relief.

### *Other drugs*

There is some evidence of efficacy for buspirone in generalised anxiety disorder, although results

## a stepped-care model for the management of anxiety is recommended

are inconsistent. Nausea is common and dosing is inconvenient at three times daily.

Several randomised controlled trials have shown quetiapine to be effective in relieving symptoms of generalised anxiety disorder over the eight-week period of the studies.<sup>1</sup> However, given the risk of weight gain, metabolic adverse effects, the low but real risk of tardive dyskinesia, and concerns regarding possible adverse cardiac effects of atypical antipsychotics,<sup>13</sup> long-term use of antipsychotics is inadvisable.

Pregabalin has been shown to be effective in generalised anxiety disorder and was included as a second-line drug in UK guidelines. However, it is not subsidised for this indication in Australia. Beta blockers have little evidence to support their use in anxiety disorders, including social anxiety disorder.

### Failure to respond

If a patient does not respond to treatment, the first step is to review their diagnosis and any changes in their medications (for example drugs recently started or stopped). Patients with anxiety disorders may be particularly susceptible to the anxiogenic effects of caffeine. Substance abuse (including alcohol) can exacerbate or cause anxiety. As anxiety is frequently seen in major depression, consider the possibility of an agitated depression.

Personality style can be a potent cause of anxiety, and is unlikely to respond to drug treatment alone. For example, individuals with an obsessive compulsive personality style (perfectionistic, hypermoral, need for routine and certainty) may become anxious when their normal routine is disrupted. Those with a dependent personality style may become highly anxious if there is a threat to an important relationship.

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Secondly, review medication adherence and whether sufficient time has been allowed to see a response. Also ask about their environment – is there a source of chronic worry? Finally, consider adding or revisiting cognitive behavioural therapy or other non-pharmacological strategies, such as mindfulness-based strategies. Specialist assessment is advised before employing medication augmentation strategies.

### Suicide risk and anxiety

Patients with anxiety disorders may experience suicidal ideation, so this risk should always be assessed. Research suggests that the risk of a suicide attempt is most likely to be elevated when there is a comorbid depression. Agitation and akathisia are potential adverse effects of SSRIs and may also be associated with an increased risk of suicide.

### Conclusion

Anxiety occurs on a spectrum from normal and short-lived to persistent, distressing and disabling. Effective treatments are available and a stepped-care model is advocated, linked to the severity of the anxiety and any comorbidity. SSRIs are recommended as first-line pharmacotherapy for all anxiety disorders, with SNRIs also a valuable first-line treatment for many of them. Response is typically slower than is seen in depression. Benzodiazepines should be reserved for short-term use or treatment refractoriness, and are not routinely required as adjunctive therapy when starting antidepressants. ◀

*In the past three years, Dr Lampe has received speakers' honoraria from AstraZeneca, Lundbeck, Pfizer and Servier.*



### SELF-TEST QUESTIONS

True or false?

- Antidepressants used on their own are less effective than cognitive behavioural therapy for anxiety disorders.
- Benzodiazepines are first-line therapy for anxiety disorders.

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