



## THEME

Mental health



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# Depression and anxiety

## Pharmacological treatment in general practice

### BACKGROUND

Depression and anxiety are common presentations in general practice and medications are one of the key treatment strategies.

### OBJECTIVE

This article provides an overview of important practical issues to consider when prescribing medications for anxiety and depression.

### DISCUSSION

Key questions for the general practitioner to consider are:

- Are medications the best option?
- Which is the best medication for this patient?
- What are the practical aspects of prescribing this medication?
- What is the next step if it doesn't work?

**General practitioners are the main providers of treatment for anxiety and depression in our community and medications are often prescribed as part of the treatment plan. The BEACH study (Bettering the Evaluation and Care of Health Program)<sup>1</sup> showed that GPs treat psychological problems at a rate of 11.5 per 100 encounters, and medications are recommended in 70% of contacts for psychological problems. Depression is the first, and anxiety the second commonest psychological disorders seen in general practice, and they often co-exist. This article aims to provide a practical approach for GPs in prescribing psychotropic medications for depression and anxiety, and recommends four key questions for GPs to consider.**

### Are medications the best option?

Treating anxiety and depression is as much about common sense and practicalities as it is about evidence and science. Successful clinical practice combines both.

The single most important factor in ensuring a good outcome from medication is making the correct diagnosis. This may require more than one interview with the patient, and sometimes consultation with family members or significant others. If possible hold off from prescribing at the first interview. Depression needs to be distinguished from the vicissitudes of life while anxiety is often a

symptom of other disorders such as physical illness. From a prescribing point of view, separating depression from anxiety and vice versa, is less crucial as they often occur together, and the pharmacological first line for both is often the same (an antidepressant).

Following diagnosis, the next important issue is the patient's attitude to medication. What are their preferences with regard to psychological and/or pharmacological treatment? Do they think medication will be helpful or harmful? Up to 50% of patients discontinue medication within 3 months of starting a drug, while a small number of patients never have the prescription filled.<sup>2</sup> Adherence to therapy is crucial – if the patient has doubts about medications, the doubts need to be discussed openly.

The next concern is the severity of the anxiety or depression. Antidepressants are clearly indicated as the first line treatment in severe depression, have approximately equal efficacy to the main psychotherapies in moderate depression, and are not indicated in mild depression, where supportive clinical care, psycho-education, problem solving and counselling are the appropriate strategies.<sup>3</sup> For anxiety disorders, the rules are not quite as simple. There are more agents to consider (anti-anxiety and antidepressant medications – see later) and the rules about severity and comparisons with psychological therapies are less clear. In general, for mild to moderate anxiety disorders, focused psychological

**Table 1. The newer antidepressants**

Antidepressant	Usual dose range (mg)	Class	Sedation
Citalopram	20–40	SSRI	Unusual
Escitalopram	10–20	SSRI	Unusual
Fluoxetine	20–40	SSRI	Sometimes
Fluvoxamine	100–200	SSRI	Sometimes
Paroxetine	20–40	SSRI	Unusual
Sertraline	50–100	SSRI	Sometimes
Venlafaxine	75–150	S&NRI	Sometimes
Mirtazepine	30–45	Tetracyclic/NaSSA	Usually, often at lower doses
Reboxetine	8–10	SNRI	Rarely
Moclobemide	300–600	RIMA	Unusual
Mianserin	60–90	Tetracyclic	Nearly always

SSRI = selective serotonin reuptake inhibitor  
S&NRI = serotonin and noradrenaline reuptake inhibitor  
SNRI = selective noradrenaline reuptake inhibitor  
RIMA = reversible inhibitor of monoamine oxidase A  
NaSSA = Noradrenaline and specific serotonin antidepressant

therapies such as cognitive behaviour therapy are considered slightly advantageous and have better long term outcomes than medications alone, while in severe anxiety disorders medications are usually warranted, and usually in combination with psychological therapies.

Finally, the age of the patient also influences choice. In adolescents the role of medications in anxiety and depression is poorly established and there is an increased risk of agitation leading to suicidal thinking; hence medications are often reserved as a last resort, and usually in conjunction with specialist opinion. In the elderly, side effects are more pronounced, in particular the risk of falls, and so caution should be exercised.

### Which is the best medication for this patient?

As a general rule, antidepressants are the pharmacological treatment of choice for both anxiety and depressive disorders. Anti-anxiety agents are reserved for transient anxiety (associated with a short term stressor), or for brief, interrupted courses in chronic anxiety disorders.

Choosing a first line antidepressant is relatively easy, as their similarities far outweigh their differences. They are all equally effective in treating depression, with approximately 65% responding, compared to a placebo response rate of 35%.<sup>3</sup> Although the specific side effect profiles differ, the tolerability of virtually all the antidepressants is similar. In clinical trials, patients drop

out at similar rates for almost all antidepressants. Hence the choice of medication relates to which adverse events the patient would prefer, which is often related to the issue of sedating versus non-sedating drugs. Of course predicting sedation is not exact, as there is a degree of chance involved as to whether a patient will experience sedation on any given drug. *Table 1* shows the chances of sedation with each drug.

Exceptions to the above are the older tricyclic and monoamine oxidase inhibiting (MAOI) antidepressants. These are not as well tolerated and are also dangerous in overdose, hence apart from patients who have been on them long term or have a particularly good past response, these should be relegated to treatment resistant cases in the specialist setting.<sup>3</sup>

In the primary care setting, a clinician should familiarise themselves with two or three drugs from different classes. This allows expertise with each drug, while also giving a representative choice of the compounds available, and giving one or two options for change should the first choice prove ineffective. Two failed trials of an antidepressant should trigger reconsidering the diagnosis or referring for a specialist opinion.

Choosing a benzodiazepine is also straightforward. There is no clinical evidence that one benzodiazepine is superior to another, but some drugs are more likely to be used as anxiolytics and others as hypnotics (sleep inducing) (*Table 2*). Drugs with longer half-lives (eg.

diazepam) are usually chosen for anxiety disorders, while drugs with shorter half-lives are used as hypnotics (eg. temazepam or triazolam). There are some exceptions, such as flunitrazepam, which has a long half-life, however plasma levels of the drug are not sustained above a minimum effective dose for more than a few hours, and hence it is mainly used as a sleep inducing agent.

The efficacy of benzodiazepines in the long term treatment of anxiety or insomnia is controversial. Evidence for efficacy beyond 4 months is lacking. Brief interrupted courses of treatment should be proposed from the outset. The drugs should be tapered on withdrawal to avoid a withdrawal syndrome.<sup>4</sup>

The primary role of benzodiazepines is in the management of generalised anxiety disorder (GAD), panic disorder and insomnia. Use in other anxiety related disorders is more often due to clinical desperation than proven efficacy. Even in GAD and panic disorder, benzodiazepines have fallen from favour due to problems of dependence and withdrawal syndromes.

Medication alone is rarely sufficient to provide complete relief from anxiety, and psychosocial interventions should always be included in the treatment plan.

## What are the practical aspects of prescribing this medication?

### Antidepressants – golden rules for prescribing

#### Starting an antidepressant

For selective serotonin reuptake inhibitors (SSRIs), starting at half the recommended dose is a good way to minimise the adverse effects. If there are no problems after 4 days increase to the full tablet. Adverse effects mostly settle after 2 weeks. A low dose of benzodiazepine is often useful in the first 2 weeks to help with the initial agitation, especially if the antidepressant is being used for an anxiety disorder.

#### Things to tell the patient

Treating depression, especially when it is moderate or severe, may require a degree of negotiation. Patients usually have trouble accepting the idea that depression can be viewed as an illness, and they often feel hopeless, meaning that they do not deserve help and that nothing will help anyway. Furthermore, many see medication for mood as a sign of weakness or 'surrendering' to one of life's challenges. Consequently, it is easy to fall

**Table 2. Anti-anxiety medications**

Drug	Usual dose range	Drug trade names	Elimination half life
<b>Benzodiazepines</b>			
<b>Predominantly anxiolytic</b>			
Alprazolam	0.5–4.5 mg/day	Alprax, Kalma, Xanax	9–20 hours
Bromazepam	6–9 mg/day	Lexotan	8–30 hours
Clobazam	10–30 mg/day	Frisium	20–40 hours
Clonazepam	2–6 mg/day	Rivotril, Paxam	19–60 hours
Diazepam	5–40 mg/day	Antenex, Ducene, Valium, Valpam	14–70 hours
Lorazepam	1–10 mg/day	Ativan	8–24 hours
Oxazepam	45–90 mg/day	Alepam, Murelax, Serepax	3–25 hours
<b>Predominantly hypnotic</b>			
Flunitrazepam	1–2 mg/day	Hypnodorm	24 hours (see above)
Nitrazepam	5–10 mg/day	Alodorm, Mogadon	15–48 hours
Temazepam	10–30 mg/day	Euhypnos, Normison, Temaze, Temtabs	3–25 hours
Triazolam	0.125–0.5 mg/day	Halcion	1.5–5 hours
<b>Nonbenzodiazepines</b>			
Buspirone	20–30 mg/day	Buspar	1–11 hours
Zopiclone	Up to 7.5 mg/day	Imovane	3–6.5 hours
Zolpidem	5–10 mg/day	Stilnox	1.5–4.5 hours

into the trap of failing to adequately inform the patient regarding the medication issues for fear of scaring them away from treatment.

The key issues to emphasise are:

- the onset of action is at least 2 weeks, probably more like 4 weeks (otherwise patients will discontinue after a week, thinking the medication is not working)
- for benefits to occur, the medications must be taken every day
- the clinical course of improvement fluctuates ('three steps forward, one step backward'). The patient should expect this, and not get disheartened and discontinue when these inevitable setbacks occur
- medications must be continued once the symptoms have resolved
- the side effects profile: while not all patients want to know about side effects, it is important to tell them that they are common, mostly self limiting, and that they should let you know about any they experience. It is often helpful to reframe adverse effects as a good sign, such as 'unfortunately the adverse effects come before the good effects, but at least it's a sign that the drug is getting into your brain and has its best chance of working.' Of course full lists, including pregnancy warnings, come with each packet, including sample packs. It is worth reminding patients of these lists, and reminding them to discuss any concerns with you before making any decisions to cease medication.

### Measure what you are treating – targeting symptoms

Once the patient starts on the medication a range of changes occur. There will be some symptom improvement, some side effects, and other psychological symptoms that were initially not prominent may be revealed. Hence, gauging improvement can be difficult. To counter this, it is useful to pick two or three of the symptoms that are most prominent at the outset and label these as the target symptoms. On review of the patient, measure these (perhaps rate them out of 10, or even better ask the patient to keep a diary of them) so that you can titrate the dose of antidepressant against them, or alternatively use one of the simple psychometric tools now widely available.<sup>5</sup>

### How and when to increase the dose

For most antidepressants there is a lack of evidence to guide dosing. As a general rule, the recommended starting dose should be maintained for 2–4 weeks. If the symptoms are failing to respond, or the response is equivocal, try increasing by half to a whole tablet, and

wait 2 weeks. Keep increasing the dose until a response is reported or the maximum dose is reached (or limited by adverse effects). If the maximum dose (or maximum dose tolerated) fails after 2 weeks, then the trial is considered to have failed, and switching to another class is the next step (after an appropriate withdrawal regimen and drug free interval).

It should be noted that for anxiety disorders a higher dose is usually required, hence you should tend to increase the dose earlier.

### When to cease

There is a lack of evidence for guiding duration of treatment. Short term studies suggest 12 months treatment after the first episode of depression, and expert consensus supports treatment for 3 years for recurrent depression.<sup>6</sup> Most antidepressants are associated with withdrawal reactions and so gradual withdrawal is usually the safest option (eg. halving the dose each week).

### Serotonin syndrome

The serotonin syndrome consists of abdominal cramps, sweating, diarrhoea and agitation, progressing to myoclonus, hyponatraemia or hypernatraemia, confusion, fever and coma. It usually occurs secondary to a drug overdose, but can occur as a result of drug interactions and as an idiosyncratic response to a single serotonin increasing drug. It is often difficult to distinguish the serotonin syndrome from self limiting adverse effects, discontinuation syndromes and drug interactions (in the context of ceasing one antidepressant and starting another) and even depression itself. If symptoms suggest a serotonin syndrome, urgent assessment in an emergency department is advisable.

## Anti-anxiety medications

### Benzodiazepines

As previously stated, many anxiety disorders can be managed by psychotherapeutic means alone or by antidepressants. If a decision is made to use a benzodiazepine, consideration should be given to the proneness of the patient to addiction or abuse of the agent. There is little doubt that these were once prescribed too freely, but if the patient's anxiety is of sufficient severity, short term access to these drugs should not be denied.

The initial choice of drug may be based on previous response or on the convenience of use for the patient (eg. long half-life drugs require once daily dosing). Initially, dose titration may be required, with the bulk of the dose given at night to aid with sleep disturbance.

## Special issues

### Benzodiazepine dependence

Tolerance to the sedative effects of the drugs develops rapidly but whether there is tolerance to the anxiolytic effects is controversial. Some clinical studies have suggested no anxiolytic tolerance even after a year of continuous use. Periods off the drugs and strict monitoring of scripts and doses is the most effective guard against the gradual dose increases that promote tolerance and dependence.

### Withdrawal syndromes

Both high and normal dose use has been implicated in the withdrawal syndrome, as has short or long duration of use. In general, higher doses of short acting drugs are more likely to cause problems than are longer half-life agents. Symptoms of the syndrome include anxiety, tremor, muscle twitching and in severe cases, seizures. They are often pronounced 3–7 days after cessation of medication, with up to 4 weeks or longer required for the patient to return to normal. It can be difficult to distinguish the withdrawal syndrome from the return of the original anxiety disorder. Referring back to the original symptom list can sometimes help sort this out.

Withdrawal can usually be managed using a tapered withdrawal schedule and occasionally changing to an equivalent dose of diazepam before withdrawal may be useful, as the plasma concentrations of the drug decline more slowly. The tapering schedule should be individualised to the patient's need. If patients have been on benzodiazepines for years, then up to 6 months may be required. It is important to implement some psychological aids (eg. relaxation therapy) with the withdrawal process. There should be close contact with the patient throughout the withdrawal period. It is useful to remember that benzodiazepines are cross tolerant with alcohol, which may be used by patients as a substitute for relief of anxiety.

### Adverse events and drug interactions

The commonest adverse event is sedation, which in the elderly may also be associated with falls. Sedation is also problematic for driving or operating machinery. Fatigue, concentration difficulties, ataxia, dysarthria, confusion and impaired memory may all occur during benzodiazepine use, particularly at higher doses, and particularly in the elderly. Disinhibition reactions occur infrequently. In patients with compromised respiratory function, benzodiazepines may aggravate the problem.

There are few clinically important drug-drug

interactions with benzodiazepines. The most important is the potentiation of the sedative effects of other central nervous system depressants, most notably alcohol. Digoxin plasma levels may be increased by co-prescription with some benzodiazepines. Co-administration with L-DOPA may worsen the symptoms of Parkinson disease.

### Other anti-anxiety medications

Buspirone is another medication that GPs should be familiar with. It is unusual in that it is an anxiolytic that is less sedative than benzodiazepines, but like antidepressants, takes longer for the therapeutic effect to begin. Furthermore it has less potential for psychomotor disturbance, abuse and dependence. In clinical trials buspirone has been shown to be as effective as the benzodiazepines in treating generalised anxiety disorder. It does not appear to be effective in panic disorder. The main side effects of treatment are dizziness, drowsiness, nausea, headache, fatigue, nervousness and insomnia. The drug usually has a benign drug-drug interaction profile, but serotonin syndrome is a possibility when it is co-administered with SSRIs or MAOIs.

In recent years, both zopiclone and zolpidem have been introduced for the management of sleep disturbance. Neither drug is a benzodiazepine; however, they do appear to act through similar receptor mechanisms in the brain, ie. the GABA chloride ion channel. Their role is for treating insomnia, not anxiety.

### What is the next step if medications do not work?

If medications fail to work, the first step is to ask yourself these questions:

- Is the diagnosis correct?
- Has comorbidity (particularly alcohol related disorders) been missed?
- Has the patient been adherent to the medication?
- Has the trial been of adequate dose and duration?

Once these issues have been resolved, consider the role of psychological therapies, and/or seeking an opinion from a psychiatrist.

In terms of medication options, the first step is to ensure the drug was trialed for an adequate dose and duration. For antidepressants, at least 2 weeks at the maximum dose is required to declare the trial a failure. Next consider an antidepressant from a different class. Given that about 65% of patients respond to any given antidepressant, it is a common experience for patients to need to trial two, or even three medications before they get the one that is right for them.

After this consider the more heroic options such as combinations of medications. Some are relatively well established, such as the addition of a mood stabiliser in depression (particularly lithium), while others are more controversial, such as combination antidepressants. Given that combinations are a third or fourth line approach (after two or three trials of individual agents), and given the risks of drug interactions, these approaches should come after a specialist opinion, if at all.

## Conclusion

Depression and anxiety are common presentations in general practice. Medications are an important treatment option if symptoms are moderate, but only after clarifying the diagnosis, considering the patients attitudes to treatment, and combining any pharmacological treatment with appropriate psychological therapies. In severe disorders medications are almost always required. Antidepressants are first line, and benzodiazepines have a role for brief, focused periods where symptoms require a rapid response. If symptoms fail to respond, reconsider the diagnosis, comorbidity, and adherence. Two failed trials of medication should trigger a specialist opinion.

## Further reading

This article was based on: Ellen SR, Norman TR. Psychotropic medication in general practice. In: Common problems in general practice psychiatry. Blashki G, Judd F, Piterman L, editors. McGraw-Hill Australia Pty Ltd, 2006.

Conflict of interest: Trevor R Norman serves or has served on advisory boards for various companies whose products are mentioned in this article. He provides or has provided educational talks, is in receipt of or has received research funding and travel grants from these companies. In particular he has or has had associations with Alphapharm, Astra-Zeneca, Aventis, Bristol-Myers-Squibb, Eli-Lilly, Glaxo-Smith-Kline, Lundbeck, Organon, Wyeth and Pfizer. Between 2003–2005 Dr Grant Blashki provided CBT training to GPs which was in part funded by Pfizer Pharmaceuticals.

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