# 6 Benzodiazepines in anxiety disorders: managing therapeutics and dependence

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*The use of benzodiazepines in anxiety disorders must be careful and limited, so as to avoid producing dependence*

*Trees bent in the wind, leaves blowing off and black birds in the corner: typical imagery of anxiety.* Reproduced with permission from the Cunningham Dax Collection of Psychiatric Art in The Mental Health Research Institute of Victoria.

## Synopsis

Treatment for the anxiety disorders should be tailored to the individual patient and the specific disorder present.

- Physical causes of anxiety (e.g., hyperthyroidism) must be excluded by examination and laboratory tests.
- Most anxiety disorders are best treated with cognitive–behaviour therapies.
- Drug therapies are not useful for specific phobias (e.g., arachnophobia), which generally respond to behaviour therapy.
- Among drug therapies, selective serotonin reuptake inhibitors may be the best choice, although the initial effect may be to heighten anxiety (this can be controlled with the use of a benzodiazepine at the start of therapy).
- Benzodiazepines may be indicated for use in generalised anxiety disorder — the anxiety disorder most commonly seen in general practice.
- Benzodiazepine therapy should not be continued in the long term because of the risk of dependence. Courses of two to four weeks, with a tapering withdrawal of the drug, should be used when necessary to control symptoms while psychological treatments are instituted.

Anxiety is a normal emotion experienced at some time by virtually all humans. Pathological anxiety is less commonly experienced and may arise from an anxiety disorder in the context of a depressive or psychotic illness or from one of a number of somatic illnesses, such as hyperthyroidism.

The range of anxiety disorders and appropriate choice of therapies is outlined in Box 1. Most patients with anxiety disorders will be best treated with cognitive–behaviour therapy and/or pharmacotherapy. Cognitive–behaviour therapy in anxiety disorders incorporates a range of verbal interventions and behaviour modification techniques with the aim of correcting habitual errors in thinking. It is based on the premise that an anxious person interprets certain situations as dangerous, causing anxiety symptoms and a desire to escape. The therapy consists of a combination of strategies to change the dysfunctional thoughts, and behaviour modification techniques such as graded exposure (to feared situations) and relaxation techniques. The difficulty of this therapy in general practice is that it requires special training of the doctor and lengthy and repeated consultations with the patient. Most often, therefore, patients requiring cognitive–behaviour therapy will need to be referred to a psychiatrist or psychologist who possesses these skills.

Referral to a specialist will often be dictated by the patient's preference for psychotherapy over pharmacotherapy. Availability of services and cost to the patient may limit the use of cognitive therapy. In cases of partial response to pharmacotherapy, cognitive techniques can be combined with medications to bring about a resolution of symptoms. If pharmacotherapy has failed, or patients have poor medication compliance, or cannot tolerate side effects of medication, or there is evidence of excessive risk (e.g., of dependence) with pharmacotherapy, then cognitive–behaviour therapy is a practical alternative treatment.

The focus of this article is pharmacotherapeutic management, particularly the use of benzodiazepines. This does not mean that benzodiazepines are the treatment of choice for all anxiety disorders. In some, such as obsessive–compulsive disorder, benzodiazepines are ineffective, while in others, such as post-traumatic stress disorder, their usefulness is not established. Because anxiety disorders may be symptomatic of concurrent depression, selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs are often useful and may be the first choice in drug therapy. Indications, doses and safety considerations for antidepressant therapies were discussed in a previous article in this series on managing depression in a community setting.[2]

Despite many legitimate criticisms about their widespread use and problems of withdrawal and dependence, benzodiazepines can be

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## 1 Therapies for anxiety disorders

*Therapies are ranked in order of importance. Most anxiety disorders are best treated with psychological therapies, and clinical judgement, based on the severity of the disorder, should be exercised as to whether a pharmacological treatment should be used at all. Psychological therapies can be used irrespective of severity and should be combined with drug therapies for patients with moderate to severe disorders as appropriate. Newer agents (venlafaxine, nefazodone) have not yet been systematically evaluated in the treatment of anxiety disorders.*

| Disorder | Psychological therapies* | Drug therapies |
|---|---|---|
| ***Panic disorder***<br>Unpredictable and unwarranted recurrent attacks of panic characterised by upsetting physical symptoms such as tachycardia, chest pain, sweating, tremor, nausea, and overwhelming sensations of fear or loss of control. | 1. Cognitive–behaviour therapy<br>2. Group therapy (groups of patients with similar problems directed by a trained therapist) | 1. SSRIs<br>2. TCAs<br>3. Benzodiazepines |
| ***Agoraphobia***<br>Unwarranted anxiety about being in certain places (possibly in public, but also possibly alone at home), leading to avoidance of those places; may be accompanied by panic disorder. | 1. Cognitive–behaviour therapy<br>2. Group therapy | 1. SSRIs<br>2. TCAs<br>3. Benzodiazepines |
| ***Social phobia***<br>Extreme and persistent anxiety about certain social situations, leading to avoidance of those situations, or pronounced anxiety attacks on exposure or even on anticipation of exposure to the situation. | 1. Behaviour therapy (i.e., training in exposure to the phobic situation)<br>2. Cognitive–behaviour therapy | 1. Moclobemide†<br>2. β-Blockers† |
| ***Specific phobias*** | 1. Behaviour therapy (i.e., training in exposure to the phobic situation) | ‡ |
| ***Obsessive–compulsive disorder***<br>Anxiety marked by obsessional thoughts (recurrent, intrusive and inappropriate thoughts that cause marked anxiety), and compulsions (repetitive behaviours or mental acts that the person feels driven to perform in order to reduce anxiety). | 1. Cognitive–behaviour therapy | 1. SSRIs<br>2. Clomipramine |
| ***Post-traumatic stress disorder***<br>Anxiety following a severe trauma, marked by intrusive memories, flashbacks, or dreams recalling the trauma, disturbed sleep, hyperarousal, irritability, difficulties in concentrating, depression. | 1. Debriefing<br>2. Cognitive–behaviour therapy<br>3. Eye movement desensitisation and reprocessing<br>4. Group therapy<br>5. Psychodynamic therapy (reconstruction of trauma, abreaction, catharsis; must be individualised) | 1. SSRIs<br>2. TCAs<br>3. Benzodiazepines |
| ***Generalised anxiety disorder***<br>Excessive anxiety and worry, occurring most days for more than six months, with symptoms of motor tension, autonomic hyperactivity, apprehensive expectation, vigilance and scanning. | 1. Support (guidance, advice, developing coping strategies)<br>2. Counselling<br>3. Relaxation therapy<br>4. Stress management (relaxation, meditation)<br>5. Cognitive–behaviour therapy | 1. Buspirone<br>2. SSRIs<br>3. TCAs<br>4. Benzodiazepines<br>5. β-Blockers |

*Psychological therapies remain controversial, as there are few controlled studies evaluating comparative efficacy. We have assessed the relative usefulness of psychological therapies according to experience in our unit.
†Limited studies[1] suggest improvement with moclobemide; β-blockers may be useful in performance anxiety.
‡Drugs alone are generally not helpful.
SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

useful in the management of anxiety disorders. To facilitate their safe and appropriate use for the treatment of patients with anxiety states presenting to general practice, we present some principles for the use of benzodiazepines and some guidelines for managing withdrawal and dependency.

## Benzodiazepines

### *Indications*

Although benzodiazepines possess other biological effects (e.g., anticonvulsant and muscle relaxant properties), their predominant clinical use has been in the treatment of anxiety disorders. The decision to use medication, and a benzodiazepine in particular, must be carefully assessed, taking into account the severity of the patient's symptoms, the length of time the symptoms have been present, the degree of psychosocial impairment caused by the disorder, and the proneness to addiction of the patient. In addition, anxiety may arise due to a number of physical disorders such as hyperthyroidism,[3] which must be excluded by physical and laboratory examinations.

There is no doubt that in the past these agents have been too freely prescribed, but if the disorder is of sufficient severity to require pharmacological interventions patients should not be denied access to benzodiazepines.

Benzodiazepines are indicated for use in **generalised anxiety disorder**, which is the anxiety disorder most likely to be seen in primary care. A differential diagnosis of major depression or borderline personality disorder must be ruled out, as these disorders are often inappropriately treated with benzodiazepines alone.[4] In major depression, short-term management of anxiety with benzodiazepines in addition to an antidepressant is frequently used.

**Panic disorder,** with or without **agoraphobia**, has been shown to respond to benzodiazepines, but usually at higher doses than those recommended for generalised anxiety disorder.[5] Alprazolam has been the best studied drug for this indication, but other drugs have been reported to be equally effective.[6] As many as 15% of the population may have an isolated panic attack without a recurrence. Panic disorder has a high co-morbidity with major depression, while panic attacks may occur in the context of another psychiatric disorder.

Psychological adjuncts to treatment[7] should be introduced with drug therapy with the aim of using these alone when drug therapy stops.

Antidepressant drugs (tricyclics, monoamine oxidase inhibitors and SSRIs) have been shown to be effective in treating panic disorder and may be preferable to benzodiazepines from the point of view of the dependence liability.[8,9] They may heighten anxiety initially and a benzodiazepine may be required as well for 2–4 days. Cognitive and behaviour therapies are also effective treatments and result in longer lasting remissions than drug treatment alone.[10]

Benzodiazepines are also used in some **medical illnesses** (e.g., gastrointestinal or cardiovascular disease) in which anxiety may be a prominent secondary feature. In these cases the drugs can be useful in alleviating symptoms without having an effect on the underlying disease process.

**Adjustment disorder** with anxious mood and **substance use disorders** have also been treated with benzodiazepines, but in view of the proneness to addiction of these groups of patients, a strong case for the use of non-pharmacological management can be made.

### Case history: Panic disorder responding to benzodiazepine and cognitive therapy

A 48-year-old woman presented with a two-year history of a sense of dread and nervousness about leaving home. She attributed the onset of the disorder to a period of being confined to her hotel room for three days on an overseas trip due to a bout of gastroenteritis.

On questioning she described panic attacks characterised by breathlessness, sweating, shaking, palpitations, "jelly" legs, faintness and a fear of loss of control. The attacks were experienced whenever she left the house, leading to avoidance behaviour. There was some associated depressed mood and sleep disturbance, which fluctuated. A probable family history of agoraphobia was noted in the patient's mother and in her 20-year-old daughter. The patient was not taking any drugs at the time of consultation. She reported having received relaxation training, which helped her relax but did not reduce the frequency of panic attacks. Routine biochemical investigations were normal, including thyroid function tests and electrocardiography.

A diagnosis of panic disorder with agoraphobia was made. The patient kept a diary of panic attacks over the next week and noted six attacks. She was prescribed alprazolam 1 mg at bedtime for the first two days, and the dose was titrated to 1 mg twice a day for three days, then 1 mg three times a day for three days. During this time the patient maintained her diary of panic attacks.

On reassessment after a week's treatment, the patient's panic attacks had diminished but were still present. The dose of alprazolam was increased to 4 mg/day in divided doses and the patient was reviewed at weekly intervals. By six weeks there were no further panic attacks. Medication was continued for a further eight weeks.

The patient's phobic avoidance behaviour was addressed by specifically encouraging her to confront phobic situations during drug therapy and by instituting a behavioural management plan, including homework tasks, cognitive restructuring and education about the nature of panic disorder and attacks. At the end of 14 weeks' treatment, a tapered withdrawal schedule for alprazolam was instituted.

An important element of the treatment was the recognition by the patient that the drug therapy would be for a limited time only and that the taper schedule would be flexible depending on the degree of difficulty experienced during the withdrawal process. Withdrawal was successful and the patient did not experience a return of her agoraphobia. The patient's condition over the six months after withdrawal was reviewed regularly.

### *Treatment considerations*

***Choice of drug:*** Clinical efficacy of the various benzodiazepines is the same, but pharmacokinetic characteristics vary considerably. Rapidity of onset of action is determined by the rate of absorption and distribution, which for most benzodiazepines is rapid and complete after oral administration. Duration of action depends in part on the half-life of the drug and the presence or absence of active metabolites. Drugs with long half-lives (e.g., diazepam) can be administered once daily; drugs with intermediate to short half-lives (e.g., alprazolam) require more frequent administration. Drugs with a long elimination half-life usually have a long duration of action and are generally advantageous for continuous therapy.

Box 2 lists some commonly used benzodiazepines with their usual dose ranges in both young and elderly patients and their indications for use. Dose titration will be required at the start of therapy but the bulk of the dose can be administered at night, thereby aiding sleep. In some patients the entire dose of a longer duration drug can be given at night.

***Duration of treatment:*** The efficacy of benzodiazepines for long term treatment of anxiety or insomnia is controversial. Evidence of continued efficacy beyond four months is not well documented.[11,12] Brief, interrupted courses of treatment should be proposed at the start of therapy, perhaps of two to four weeks' duration, with a tapered withdrawal of the drug. Constant assessment of the efficacy of treatment and the need for continued medication must be made. Failure to respond to treatment when other causes of non-response have been eliminated (e.g., non-compliance, inadequate dose) suggests that an alternative diagnosis may need to be considered. Some patients report sustained benefits from continued treatment with benzodiazepines. In panic disorder, continuous medication, perhaps for as long as six months to a year, may be necessary.[4] Provided there is no gradual escalation of the dose or evidence of drug seeking from multiple sources, there does not appear to be any long term harm from this practice. Periodic breaks from treatment with gradual dose reduction are useful in determining whether continued drug use is necessary. Medication alone is rarely sufficient to overcome anxiety completely, and drugs cannot change elements of the psychosocial environment that contribute to an individual's problem.

***Contraindications:*** Because of their muscle relaxant properties, benzodiazepines are contraindicated in patients with myasthenia gravis. Respiratory depression is not a problem in physically healthy patients but in those with respiratory disorders the benzodiazepines can aggravate the problem.[13] Use in pregnancy must be carefully considered. Benzodiazepines are not usually recommended in the first trimester of pregnancy.[14] In late pregnancy, benzodiazepines may cause respiratory depression and feeding difficulties in the baby.[15] Moderate to high dose use in the mother may cause withdrawal symptoms in the infant 2-3 weeks after birth. Benzodiazepines are excreted in breast milk and infants are particularly susceptible to their effects.[16]

***Side effects and drug interactions:*** The main side effect is excessive sedation. Fatigue, poor concentration, ataxia, dysarthria and confusion may also occur. In elderly patients falls and hip fractures have resulted from benzodiazepine oversedation. The ability to drive or operate heavy machinery may be impaired while using benzodiazepines, and their combination with alcohol may exacerbate motor incoordination.[17] Disinhibition reactions (when patients report feeling angry, irritable or agitated) occur in occasional patients, while rage reactions occur rarely. Given for night sedation, antianxiety agents decrease the amount of rapid eye movement (REM) sleep, with a rebound effect noticeable after discontinuing

**2 Commonly used benzodiazepines, half-lives, age effects and indications for use**

| Drug | Usual indication | Range of daily doses (mg) | | Elimination half-life (hours) | Effects of increasing age |
|---|---|---|---|---|---|
| | | Young, healthy | Elderly | | |
| ***Long elimination half-life*** | | | | | |
| Clobazam | Anxiety, panic attacks* | 30–80 | 10–20 | 12–60 | Elimination half-life decreased |
| Diazepam | Anxiety, panic attacks* | 6–80 | 2–40 | 20–90 | Elimination half-life increased |
| Flurazepam | Insomnia | 15–60 | 15–30 | 1–2 | Toxicity increased |
| ***Intermediate elimination half-life*** | | | | | |
| Alprazolam | Anxiety, panic attacks* | 1–4 | 0.25–1 | 6–20 | Elimination half-life decreased |
| Flunitrazepam | Insomnia | 0.5–2 | 0.5–2 | 20–30 | Little effect |
| Lorazepam | Anxiety | 2–4 | 2–4 | 10–20 | Little effect |
| Nitrazepam | Insomnia | 5–20 | 5–10 | 20–30 | Elimination half-life increased |
| Oxazepam | Anxiety | 45–90 | 15–30 | 4–14 | No effect |
| Temazepam | Insomnia | 10–30 | 10–20 | 8–22 | Little effect |
| ***Short elimination half-life*** | | | | | |
| Triazolam | Insomnia | 0.5–2 | 0.5–1 | 5–10 | Elimination half-life increased |

*The doses used for the control of panic attacks may need to be higher than those for other anxiety states (e.g., 6–10 mg/day of alprazolam to control panic disorder is not uncommon).

therapy.[18] Other adverse effects are few. Side effects and suggested management are summarised in Box 3.

Few clinically important drug interactions occur with the benzodiazepines; these are summarised in Box 4.

### *Benzodiazepine dependence*

In Western societies it is estimated that 10%–20% of adults regularly take benzodiazepines. When initially introduced they were believed to be devoid of dependence-inducing properties. Recent studies suggest that a substantial proportion of patients receiving benzodiazepines will develop some form of dependence, both high and normal doses of the drugs being implicated.

Tolerance (the escalation of the dose to achieve the same effect) develops readily to the sedative effects of the benzodiazepines. Initial drowsiness usually diminishes soon after starting therapy, even though the dose may be continuing to increase. Tolerance to the therapeutic effects may occur, but some studies suggest continued anxiolytic effects after a year of continuous benzodiazepine use.[19]

It is not clear what minimum dose or duration of treatment is necessary before withdrawal effects occur, or who are the vulnerable users.[20] It has been suggested that withdrawal phenomena (Box 5) are most severe after high-dose treatment and the use of short-acting drugs. Symptoms of the withdrawal syndrome are often most pronounced three to seven days after cessation of medication, with perhaps two to four weeks required for the patient to return to normal.[21,22] Most patients complain of somatic anxiety symptoms and may experience sleep and perceptual disturbances. The rate of decline of benzodiazepine plasma concentrations has been equated to the severity of withdrawal and is advanced as the reason to switch patients from a short-acting drug to diazepam during the withdrawal process.

Prevalence, severity and duration of the withdrawal syndrome are influenced by factors such as the duration of drug use, the doses used, half-life, individual personality style and the expectations of both patient and doctor. Withdrawal is probably best accomplished using a tapered reduction of the dose over a period of four to eight weeks, and by using a benzodiazepine with a long elimination half-life (e.g., diazepam).

An unfortunate trend in benzodiazepine use in recent years has been their unprescribed recreational use with amphetamines, cocaine and heroin. In this context, benzodiazepines (mainly diazepam, temazepam and flunitrazepam) may be used to reverse or reduce the withdrawal effects of stimulants. Escalating doses, novel modes of administration (including intravenous use), and drug combinations characterise benzodiazepine use in this group. This emerging pattern of recreational use poses a major medical and social problem. The toxicity associated with the use of high doses over a protracted period is largely unknown and requires systematic research. Strategies to reduce recreational use of benzodiazepines need to be devised.

### 3 Adverse effects of the benzodiazepines and their management

***More frequent effects***

Autonomic nervous system: dry mouth, blurred vision, urinary retention, excessive perspiration
- ➤ *Reassure patient that effect usually diminishes within a few weeks; and/or decrease the dose*

Central nervous system: drowsiness, excessive sedation, ataxia
- ➤ *Tolerance usually develops; decrease dose*

***Less frequent effects***

Nausea, vomiting, constipation
- ➤ *Reassure patient that effect usually diminishes within a few weeks; and/or decrease the dose; exercise, increase fluids, mild laxative*

Skin rashes
- ➤ *Rare; multiple aetiologies; may require withdrawal of drug*

Weight gain
- ➤ *Diet*

Blurred vision
- ➤ *Reduce dose*

Jaundice (hypersensitivity)
- ➤ *Cease medication*

### 4 Drug interactions recorded for the benzodiazepines[11]

| Interacting drug | Mechanism of interaction | Clinical effect |
|---|---|---|
| Alcohol, other CNS depressants | Additive effect | Increased sedation |
| Antacids, anticholinergics | Decreased absorption | Delayed onset of acute clinical effects of benzodiazepine |
| Oral contraceptives, isoniazid | Reduction in metabolism | Prolongation of elimination half-life and effect of benzodiazepine |
| Cimetidine | Inhibition of metabolism | Increased toxic effects due to elevated plasma concentrations of diazepam |
| Rifampicin | Increased metabolism | Elimination half-life benzodiazepine shortened |
| Digoxin | Protein binding diazepam altered | Increased digoxin levels |
| L-dopa | Unknown | Exacerbation of parkinsonian symptoms |
| Disulfiram | Decreased metabolism | Increased effects of benzodiazepine |

**5 Benzodiazepine withdrawal**[30]

***Symptoms***

| | |
|---|---|
| Anxiety | Somatic symptoms of anxiety |
| Depressed mood | Depersonalisation, derealisation |
| Sleep disturbance | Hypersensitivity to touch, pain |
| Tremor, shakiness | Paranoid reaction |
| Headache | Muscular aches, pains, twitches |
| Convulsions | |

***Management***

- ➤ Usually manageable as an outpatient, with frequent supervision
- ➤ Inpatient care for high doses, previous seizures, psychosis
- ➤ Dose must be tapered, usually over several weeks depending on the initial dose, and titrated according to withdrawal symptoms
- ➤ Taper in steps of 2 mg diazepam equivalent daily (or slower, if not coping)
- ➤ Enquire about increased alcohol or nicotine consumption during withdrawal
- ➤ Watch for emergent depression, relationship difficulties
- ➤ Implement relaxation, cognitive techniques if these are not already in place
- ➤ Use self-help groups where available
- ➤ Educate patients about withdrawal
- ➤ Maintain close contact with patient during the withdrawal phase.

## Buspirone

An alternative to the benzodiazepines for the treatment of anxiety is buspirone. This drug is a member of the class of azapirone agents which owe their anxiolytic action to a partial agonist effect at $5HT_{1A}$ receptors.[23] Other members of this class of drug are not approved as anxiolytic agents in Australia. These drugs do not bind to the benzodiazepine–GABA receptor complex.[23] Compared with the benzodiazepines, buspirone has less potential for producing sedation and psychomotor impairment.[24] Furthermore the potential for abuse and dependence appears to be less than with the benzodiazepines.[25]

Buspirone has equivalent efficacy to the benzodiazepines in the treatment of generalised anxiety disorder.[23] The usual dose range is 15–30 mg/day, while up to 60 mg/day has been used in some studies. Buspirone seems not to be effective in reducing panic attacks.[26] Its major side effects are dizziness, drowsiness, nausea, headache, nervousness, fatigue and insomnia. These effects were reported by 10% or less of patients in clinical trials based on pooled data.[23]

Buspirone may have a slower onset of action than the benzodiazepines, with significant improvement noted within one to two weeks and further improvement over four to six weeks.[27] This may be because the sedative–muscle relaxant effects of the benzodiazepines, which buspirone lacks, lead to a perception of faster onset of action. Some studies suggest that previous benzodiazepine treatment predicts a less favourable outcome with buspirone than in patients with no such treatment history.[28]

Buspirone has few clinically relevant interactions with other drugs, although the combination with an SSRI may lead to serotonergic syndrome or worsening of anxiety symptoms.[29] Buspirone should not be co-administered with MAOIs.

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