Pharmacotherapy for anxiety disorders: drugs available

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The human search for tranquillity has embraced the use of numerous substances of which alcohol is probably the most widely used. Alcohol acts in part by facilitating neurotransmission at γ-aminobutyric acid (GABA) synapses and until recently the pharmacological treatment of anxiety was based principally on drugs that produce similar actions on this neurotransmitter and its receptor complex (Cowen & Nutt, 1982) (Box 1).

Recent advances in the pharmacological management of clinical anxiety disorders reflect two main developments. First, there is now a better clinical delineation of the various anxiety syndromes, together with the recognition that certain drugs are efficacious in some disorders but not others. Buspirone, for example, is effective in generalised anxiety disorder (GAD) but not in panic disorder (Sheehan et al, 1993). Second, it is clear that several classes of antidepressant drugs produce benefit in a range of anxiety disorders even in the absence of significant depressive symptomatology (Box 2). This provides a much wider range of drug treatment options than was previously available (Table 1). In general, drug treatment is used when anxiety causes significant functional impairment and appropriate psychological techniques are ineffective or cannot be properly instituted because of the degree of anxiety. There is some literature to suggest that the provision of psychological treatment may lessen the risk of relapse when drug treatment is discontinued.

**Table 1. Anxiolytic drugs: spectrum of activity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GAD</th>
<th>Panic disorder</th>
<th>Social phobia</th>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>+</td>
<td>+2</td>
<td>?2</td>
</tr>
<tr>
<td>Buspirone</td>
<td>+</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>TCAs</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>SSRIs</td>
<td>?</td>
<td>+</td>
<td>+</td>
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<tr>
<td>MAOIs</td>
<td>?</td>
<td>+</td>
<td>+</td>
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<tr>
<td>β-blockers</td>
<td>?</td>
<td>-</td>
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+, effective; –, not effective; ?, uncertain.
1. With or without agoraphobia.
2. High-potency compound (alprazolam, clonazepam).

**Benzodiazepines**

**Pharmacology**

Of the drugs that enhance GABA neurotransmission, only benzodiazepines will be considered here. Barbiturates are considered obsolete for the treatment of anxiety, and chlormethiazole, zopiclone and zolpidem are not licensed for such treatment.

Benzodiazepines facilitate GABA neurotransmission by binding to a specific receptor which exists...
in a complex with post-synaptic GABA receptors. It is uncertain whether there is an endogenous ligand for the benzodiazepine receptor and, if so, whether it is anxiogenic or anxiolytic. GABA produces its pharmacological effects by increasing conductance through chloride channels. Benzodiazepines are allosteric modulators of this process, which means that while they enhance the effect of GABA they do not affect chloride conductance directly. This accounts for their safety relative to barbiturates.

Clinical use

There are many benzodiazepines available for clinical use but the main distinction of clinical value is the half-life and potency at the benzodiazepine receptor (Table 2). Generally, drugs with high potency at the receptor and short half-lives are more likely to cause withdrawal problems; they are therefore best avoided in the treatment of anxiety. Typically, benzodiazepines act fairly rapidly in anxiety disorders, particularly compared with agents that act primarily on monoamine function (see below).

Benzodiazepines are of established efficacy in the treatment of GAD, for which a drug such as diazepam is suitable. Diazepam is rapidly absorbed and can be used for continuous dosing or on an as-required basis. If benzodiazepines are used to treat panic disorder (with or without agoraphobia), it is generally necessary to use a high-potency agent such as alprazolam or clonazepam. Such drugs ameliorate symptoms of panic more rapidly than tricyclic antidepressants (TCAs) and their efficacy appears to be maintained over several months. Furthermore, benzodiazepine treatment may be better tolerated than a TCA in panic disorder (Schweizer et al, 1993). There are limited data suggesting that clonazepam is effective in the treatment of social phobia, although findings with alprazolam have been more equivocal (Marshall et al, 1994).

Unwanted effects

Despite the undoubted efficacy of benzodiazepines in the management of anxiety disorders, their use is attended by serious drawbacks. During treatment, sedation, cognitive impairment and ataxia may be problematic. Drug discontinuation, even with a slow taper, can cause troublesome withdrawal reactions and rebound anxiety, which may necessitate re-starting treatment. This seems particularly apparent in the use of high-potency benzodiazepines for panic disorder, where withdrawal is often attended by the re-institution of panic attacks (Rickels et al, 1993a). Some patients, particularly those with a history of aggression, may be disinhibited by benzodiazepines.

Drug interactions

Benzodiazepines can potentiate the sedative effects of alcohol and other centrally-acting drugs. Respiratory depression has been reported in some patients receiving benzodiazepines with clozapine.

Buspirone

Pharmacology

Buspirone is an azapirone derivative which acts as an agonist at type 1A serotonin (5-HT1A) receptors. The anxiolytic effect of buspirone has been proposed to result from stimulation of inhibitory 5-HT1A receptors on 5-HT cell bodies, an action which decreases 5-HT cell firing and the release of 5-HT in terminal regions (Yocca et al, 1990). Animal studies indicate that this action, however, occurs fairly rapidly, whereas the clinical anxiolytic effect of buspirone can take weeks to manifest. Interestingly, repeated buspirone treatment may desensitise
inhibitory 5-HT_{1A} receptors and this, together with its modest post-synaptic 5-HT_{1A} receptor agonist actions, could lead to an overall increase in 5-HT neurotransmission. This model would be compatible with the anxiolytic effects of selective serotonin reuptake inhibitors (SSRIs), which also increase 5-HT neurotransmission (see below).

**Clinical use**

Buspirone is effective in the treatment of GAD but does not produce useful effects in panic disorder (Ortiz et al, 1987; Sheehan et al, 1993). It may have some modest effect in social phobia (Marshall et al, 1994). In contrast to benzodiazepines, buspirone needs to be administered for several days or weeks before a useful anxiolytic effect is obtained. It is not generally helpful in ameliorating benzodiazepine withdrawal and patients who have undergone previous benzodiazepine treatment may not respond well (Lader, 1991).

**Unwanted effects and interactions**

Unlike benzodiazepines, buspirone does not cause sedation and produces relatively little cognitive impairment at clinical doses. Also, there is little evidence that buspirone causes dependence or tolerance. Withdrawal reactions are not usually problematic (Lader, 1991). The use of buspirone is, however, associated with nausea, dizziness and headache. It should not be given with monoamine oxidase inhibitors (MAOIs) because the combination may lead to elevated blood pressure. This may be a consequence of the buspirone metabolite, 1-(2-pyrimidinyl)piperazine, an $\alpha_1$-adrenoceptor antagonist, which may facilitate noradrenaline release.

**TCAs**

**Pharmacology**

Tricyclic antidepressants are effective inhibitors of noradrenaline reuptake, and the tertiary derivatives, for example, amitriptyline, imipramine and, particularly, clomipramine, also block the reuptake of serotonin. In addition, TCAs block certain post-synaptic neurotransmitter receptors, which accounts for many of their side-effects (Table 3). The anxiolytic effects of TCAs, like their antidepressant effects, are often delayed for a number of weeks.

**Clinical use**

The primary indication for TCAs is the treatment of major depression. However, placebo-controlled studies have shown that imipramine (at about 150 mg daily) is effective in GAD even in the absence of significant depressive symptomatology (Kahn et al, 1986; Rickels et al, 1993b). However, the time-course of its action differs from that of benzodiazepines. For example, Rickels et al (1993b) found that the anxiolytic effect of imipramine appeared somewhat slowly, with significant benefit over placebo becoming apparent only during the third week of treatment. In contrast, diazepam was already more effective than placebo at the end of the first treatment week. Nevertheless, by the eighth week of treatment the anxiolytic effect of imipramine was greater than that of diazepam.

It is well established that imipramine is also effective in the treatment of panic disorder (with or without agoraphobia; Lydiard & Ballenger, 1987). The optimum dosage is probably a little over 2 mg/kg (Mavissakalian & Perel, 1995). As in the treatment of GAD, the effect of imipramine in panic and phobic avoidance appears relatively slowly and there may be significant drop-out rates early in treatment through worsening anxiety and ‘jitteriness’. These problems can be minimised by slow escalation of the dosage (for example, increments of 10 mg every 3–4 days; Clark et al, 1994). In contrast to their efficacy in GAD and panic disorder, studies of TCAs in social phobia have been disappointing (Marshall et al, 1994).

Imipramine has been the most widely studied TCA in controlled trials of anxiety disorders. However, amitriptyline and clomipramine are also effective in panic disorder and the latter drug may, in fact, be more effective than imipramine (Modigh et al, 1992). Clomipramine is a particularly potent inhibitor of serotonin reuptake and its efficacy in panic is of interest in view of the fact that the selective noradrenaline reuptake inhibitor, maprotiline, does not appear to possess significant anti-panic properties (Den Boer & Westenberg, 1988). This suggests that potent serotonin reuptake inhibitors may have superior efficacy in the treatment of panic disorder, but whether this extends to GAD is not known.

**Unwanted effects**

The most serious potential problem of TCAs is cardiotoxicity through deliberate overdose. The risk of overdose is generally less in anxiety disorders than major depression, but suicidal behaviour in panic disorder is not uncommon (Appleby, 1994). Possibly agitation and jitteriness early in treatment could predispose to this kind of behaviour (Power & Cowen, 1992), showing the importance of careful
attention to initial dosing schedules. Despite the superficial attraction of sedation in an anxious subject, most patients with anxiety disorders try hard to maintain their usual activities. In these circumstances, imipramine may be a better choice than amitriptyline. While TCAs are undoubtedly useful in anxiety disorders the gains made during treatment are not always maintained following drug discontinuation; where possible, drug therapy should be withdrawn slowly (Clark et al., 1994).

Drug interactions

The sedative effects of TCAs can be increased by other centrally acting drugs. Drugs with effects on cardiac conduction, including antihistamines such as astemizole and terfenadine, should be used cautiously with TCAs. Plasma levels of TCAs may be increased by phenothiazines, calcium channel blockers, disulfiram and cimetidine. TCAs can potentiate the effects of sympathomimetic agents.

SSRIs

Pharmacology

The acute pharmacological action of SSRIs is essentially confined to the blockade of serotonin reuptake. While this action manifests early during treatment, the anxiolytic effects of SSRIs take several weeks to develop fully. It has been proposed that this delay represents the time needed for 5-HT₁₆ inhibitory autoreceptors to desensitise (see Buspirone, above) because it is only when this has occurred that the ability of an SSRI to increase serotonin neurotransmission can be expressed fully.

Clinical use

Studies in major depression have shown that SSRIs produce good relief of associated anxiety symptoms (Cohn & Wilcox, 1992), although whether SSRIs are effective in GAD without significant depressive symptomatology is not established with certainty. It is worth noting here that the antidepressant drug trazodone appears more effective than placebo in GAD (Rickels et al., 1993b). However, while trazodone is purported to block serotonin reuptake, it is unlikely that this action occurs to a significant extent at clinical doses.

There are placebo-controlled trials to show that fluvoxamine and paroxetine are effective in panic disorder (Black et al., 1993; Oehrberg et al., 1995). Open studies indicate that fluoxetine may also produce benefit. As with TCAs the onset of effect may be delayed for a number of weeks and gradual dose escalation is needed to avoid jitters in early in treatment. Effective doses are similar to those used in major depression but may be at the higher end of the range. SSRIs may also be helpful in social phobia. There are open reports of benefit in this disorder with fluoxetine (Marshall et al., 1994), and in one placebo-controlled trial with fluvoxamine (150 mg daily) half of the drug-treated subjects showed significant improvement on measures of social and anticipatory anxiety (van Vliet et al., 1994).

Unwanted effects

Sedation and anticholinergic effects are uncommon but gastrointestinal effects are often experienced. Insomnia, anxiety and jitters may occur early in treatment. Sexual dysfunction, particularly anorgasmia, can be a persistent problem. Rarer but important adverse effects include dystonic reactions, low sodium states, and seizures. As with TCAs, it is not clear how far gains made during treatment are maintained following treatment cessation. SSRIs should be withdrawn slowly to avoid discontinuation reactions (Young & Cowen, 1994).

Drug interactions

SSRIs can potently inhibit hepatic metabolising enzymes and thus are prone to raise plasma levels of co-administered drugs (Taylor & Lader, 1996). Sertraline and citalopram appear to cause fewer such
problems but have been less studied in anxiety disorders. Important clinical interactions have been reported with SSRIs and warfarin, antipsychotic drugs, TCAs, carbamazepine, phentoyin, aminophylline, benzodiazepines and terfenadine (Taylor & Lader, 1966). SSRIIs should not be given with MAOIs because of the risk of a toxic serotonin syndrome. This reaction may occur with selective type A inhibitors and type B inhibitors, as well as the non-selective agents.

### MAOIs

#### Pharmacology

There are two forms of monoamine oxidase (type A and type B) in the brain, which are encoded by separate genes. In general, type A metabolises intraneuronal noradrenaline and serotonin, whereas dopamine and tyramine are metabolised by both type A and type B. Conventional MAOIs such as isocarbocacid, phenelzine and tranylcypromine irreversibly inhibit both types of the enzyme. This gives rise to serious reactions with tyramine-containing foodstuffs, requiring strict dietary precautions. In contrast, moclobemide is a selective and reversible inhibitor of monoamine oxidase type A only. This results in a lack of significant interactions with foodstuffs and a quick offset of action (Priest, 1990).

#### Clinical use

Soon after their introduction, it was recognised that MAOIs had anxiolytic properties in patients with phobic anxiety syndromes (Kelly et al, 1970). It is not established with certainty whether or not MAOIs are effective in GAD but it seems likely that they are. There is evidence from controlled trials that MAOIs are effective in both panic disorder and social phobia (Lydiard & Ballenger, 1987; Liebowitz et al, 1992).

Because of the dangers of food and drug interactions, conventional MAOIs are used as second-line drugs when safer agents have proved ineffective. Moclobemide has definite safety advantages over the conventional MAOIs, but its efficacy in anxiety disorders has not been widely studied. There is, however, evidence that it is effective in social phobia. In a placebo-controlled study of 78 subjects with social phobia, Versiani et al (1992) found similar response rates at 16 weeks for moclobemide (87%) and phenelzine (91%) and both were significantly better than placebo (43%). Phenelzine had a quicker onset of action but was less well tolerated.

### Unwanted effects

Conventional MAOIs cause a number of side-effects including insomnia, dizziness and postural hypotension. Weight gain, oedema and sexual dysfunction can be problematic long-term effects. Moclobemide is better tolerated, but insomnia, headache and nausea can occur. There is a strong clinical impression that withdrawing conventional MAOIs often leads to relapse of anxiety symptoms.

### Drug interactions

MAOIs can cause dangerous hypertensive reactions with sympathomimetics, L-dopa and opiate analgesics. A serotonin syndrome can be provoked if MAOIs are combined with SSRIs or clomipramine. MAOIs can potentiate the effects of anti-diabetic agents. Moclobemide should not be used with serotonergic antidepressants and caution is needed with opiates. The pressor effects of sympathomimetics may be enhanced by moclobemide.

### Other drugs

Certain other drugs are sometimes used to treat anxiety symptoms. For example, β-adrenoceptor antagonists such as propranolol are often helpful in ameliorating the physical symptoms of performance anxiety in otherwise healthy subjects. Although it has been suggested that β-adrenoceptor antagonists may have a role in the treatment of social phobia, recent studies have been rather disappointing (Marshall et al, 1993). There is no systematic evidence that β-adrenoceptor antagonists are useful in the treatment of other anxiety disorders such as panic disorder (Hayes & Schulz, 1987), although many patients receive them from general practitioners.

Antipsychotic drugs in low doses are also used to treat anxiety symptoms, often in patients who have comorbid disorders such as substance abuse or aggressive personality disorders. In this situation the use of antipsychotic drugs presumably reflects the wish to avoid the dependence-producing or disinhibiting effects of benzodiazepines. While short-term benefit often seems to occur, this practice is not supported by many trial data. It does appear, however, that low doses of antipsychotic drugs such as haloperidol and trifluoperazine may decrease anxiety and tension in subjects with borderline personality disorder (Soloff et al, 1986). However, the risk of movement disorders is a disincentive to long-term use of antipsychotic drugs for these indications.
References


Multiple choice questions

1. The following drugs potentiate GABA neurotransmission:
   a) clonazepam
   b) fluvoxamine
   c) zopiclone
   d) alcohol.

2. Tricyclic antidepressants are of proven benefit in:
   a) generalised anxiety disorder
   b) social phobia
   c) panic disorder
   d) agoraphobia.

3. In treating panic disorder, benzodiazepines:
   a) act more quickly than TCAs
   b) have higher drop-out rates than TCAs
   c) can be discontinued without difficulty
   d) improve panic but not phobic avoidance.

4. Irreversible, non-selective MAOIs:
   a) are second-line drugs in panic disorder
   b) are effective in social phobia
   c) do not require a tyramine-free diet
   d) are as well tolerated as RIMAs.