Anxiolytics

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Abstract

Anxiety is both a normal emotion and a disorder which can cause profound distress and functional impairment. The range of treatments available for anxiety has improved substantially in the last 20 years. This has in part been due to improved understanding of the neurobiological mechanisms underlying anxiety. Guidelines are available for the treatment of the various anxiety disorders; selective serotonin reuptake inhibitors (SSRIs) are now considered first-line pharmacological therapy for all the anxiety disorders except simple phobia, for which psychotherapy is most effective. SSRIs may cause anxiety to increase during initial therapy before the anxiolytic effect emerges. Other antidepressants shown to be effective in anxiety disorders include mirtazapine, venlafaxine and, although less commonly used, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Benzodiazepines were used widely in the past for anxiety, but concerns over dependence and withdrawal effects have now greatly limited their use. However, they continue to have a role in those non-responsive to other agents and for short-term use during antidepressant initiation. Several anticonvulsant medications may also be useful in anxiety (e.g. pregabalin). Some atypical antipsychotics also have a limited evidence base to support their use in treatment-resistant anxiety disorders. Psychotherapy has an important role to play in the treatment of anxiety disorders, but this contribution is restricted to discussion of pharmacological treatment.

Keywords anti-anxiety agents; anticonvulsants; antidepressive agents; antipsychotic agents; anxiety; benzodiazepines; psychopharmacology

Anxiety is both a normal emotion and a psychiatric disorder. Excessive anxiety is common, with a lifetime prevalence of ≥15% of the population.[1] Anxiety disorders can cause profound individual distress and functional impairment, yet it was only following the publication of DSM-II in 1980 that anxiety disorders

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What's new?

- Pregabalin has gained a licence for the treatment of generalized anxiety disorder

- New data support the use of escitalopram in several anxiety disorders

- Research into GABA$_A$ subtype selective agonists is ongoing, in an attempt to separate anxiolysis from undesirable side effects

began to be studied systematically. The need for treatment is usually determined by symptom severity and effect on functioning.

All anxiety disorders except simple phobia (which generally responds only to psychotherapy) can be treated with either psychotherapy or pharmacotherapy.[1] The search for effective agents and treatments for anxiety began with the first barbiturate in 1903. Anxiolytics have now been developed to target specific brain neurotransmitter systems (Table 1). A number of pharmacological theories exist which suggest that anxiety is caused by an increase in either amine or excitatory amino acid function.

γ-aminobutyric acid (GABA)

GABA is the main inhibitory neurotransmitter in the brain. There are two types of receptor: GABA$_A$ and GABA$_B$. The GABA$_A$ receptor is the brain's main inhibitory receptor and so regulates the activity of many types of neurone, including dopaminergic, noradrenergic and serotonergic. Benzodiazepines (BZs) reduce anxiety by binding to the BZ receptor and increasing brain GABA$_A$ function. Strong evidence for the role of the BZ receptor in anxiety comes from the close correlation found between the binding affinity of the benzodiazepine and its clinical dose. This is a relationship similar to neuroleptic D2 binding affinity in schizophrenia.

There is considerable evidence that a down-regulation of GABA$_A$ function may underlie some forms of anxiety, some of which comes from imaging studies (see pages 273–278).[2] Other clinical evidence comes from withdrawal states (e.g. from benzodiazepines and alcohol), where GABA$_A$ function is reduced.

Serotonin (5-HT)

There is conflicting evidence about whether 5-HT is increased or decreased in anxiety, but it is now thought that there are two different pathways from the raphe: medial raphe nucleus (MRN) and dorsal raphe nucleus (DRN). MRN is thought to modulate fear and anticipatory anxiety. DRN is thought to modulate cognitive processes associated with anxiety. It is postulated that an excess of 5-HT may be anxiogenic in one pathway and anxiolytic in the other, perhaps through actions at different 5-HT receptor subtypes.[3]

It is clear clinically that selective serotonin reuptake inhibitors (SSRIs) are effective in a wide range of anxiety disorders,[4] although their precise mechanism of action is not yet fully

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Current evidence-based treatment of the anxiety disorders

Anxiety disorder	First-line treatment	Second-line treatment	Other treatments	Augmenting agents
GAD	SSRI (e.g. escitalopram 20 mg/day, paroxetine 20 mg/day)	Venlafaxine 75–225 mg/day or imipramine 150 mg/day	Benzodiazepines, psychotherapy	Combine with CBT
OCD	SSRI (e.g. fluoxetine 20–60 mg/day, fluvoxamine 50–300 mg/day, paroxetine 20–40 mg/day, sertraline 50–200 mg/day)	Clomipramine 150–250 mg/day	Deep brain stimulation, neurosurgery	Psychological interventions. Atypical antipsychotics (e.g. risperidone 1–3 mg/day, quetiapine 25–600 mg/day)
Panic disorder	SSRI (e.g. citalopram 20–60 mg/day, paroxetine 10 mg/day increasing to 50 mg/day)	Clomipramine 150 mg/day, imipramine 150 mg/day	Benzodiazepines (e.g. diazepam 5–30 mg/day)	Limited evidence for pharmacological augmentation (e.g. antipsychotics or benzodiazepines). Addition of CBT shown to be useful. Combination of paroxetine or buspirone with CBT shown to be superior to CBT alone
PTSD (chronic)	SSRI (e.g. paroxetine 20–50 mg/day, sertraline 50–200 mg/day)	Mirtazapine 30–45 mg/day, phenelzine 30–60 mg/day, venlafaxine, amitriptyline 150–200 mg/day		Tiagabine of benefit in one small study. Atypical antipsychotic (e.g. olanzapine 2.5–5 mg/day), risperidone
Social anxiety disorder	SSRI (e.g. escitalopram 20 mg/day, paroxetine 20–50 mg/day)	Switch to venlafaxine if no response to SSRI. Add buspirone 20–40 mg/day if partial response to SSRI	Phenelzine 30–60 mg/day, olanzapine 2.5–5 mg/day. Benzodiazepines (e.g. diazepam 5–30 mg/day)	Augmentation of SSRI with buspirone shown to be beneficial
Specific phobia	Psychological therapy	Consider adding paroxetine 20 mg/day or benzodiazepines (e.g. diazepam 5–30 mg/day) in those unresponsive to psychological approaches		

Table 1

understood. Tryptophan depletion (TD), which causes an acute, temporary and reversible reduction in brain 5-HT levels, has been used to study this.[5] Combined with a challenge, TD tends to increase anxiety and the rate of panic attacks and social anxiety symptoms in patients with the respective disorders. Studies of TD in obsessive–compulsive disorder (OCD) have failed to show significant effects, suggesting that SSRIs have a different mode of action in OCD.[6,7]

Noradrenaline (NA)

Noradrenaline is an excitatory neurotransmitter involved in modulating awareness of the outside world, particularly to threats. Noradrenergic neurones have their cell bodies in the locus coeruleus in the brain stem with projections throughout the brain. There are three types of NA receptor: α_1, α_2 and β. β NA receptors in the periphery are involved in mediating the physical symptoms of anxiety. Their role centrally has yet to be determined. α_2-NA receptors occur both pre- (feedback) and post-synaptically (arousal, blood pressure and GH release).[3]

The sympathetic nervous system is linked to arousal (e.g the 'fight or flight' response). NA levels have been studied in anxious patients and, at rest, have not been found to be statistically different. However, when challenged (e.g. after a panic attack), both adrenaline and NA release were elevated in anxious patients, although this was confined to the heart. The evidence for an abnormality in noradrenergic function is most compelling for panic disorder (PD) and post-traumatic stress disorder (PTSD).[3]

Neuroimaging

Many neuroimaging studies have been performed across the range of anxiety disorders. In general terms, increased anxiety (in patients or healthy volunteers) causes metabolic changes in the brain that can be mapped. Some of these regions are activated in several anxiety conditions. Resting brain metabolism

has been shown to be altered in patients with anxiety disorders compared with controls. These areas of altered metabolism often correspond to areas activated in the presence of pathological emotions, such as OCD and PD (see pages 273–78).

Drugs acting via amino acid transmission

Benzodiazepines
These were developed in the 1950s as a safer alternative to barbiturates. All known actions of benzodiazepines are mediated by the $GABA_A$ receptor complex. This consists of five protein subunits (α, β, γ, δ, ϱ) arranged around a central pore. The binding site for benzodiazepines is found at the interface of the α and γ subunits. Benzodiazepines act to increase Cl- conductance of the $GABA_A$ receptor, causing increased inhibitory neurotransmission. Other psychoactive compounds, such as alcohol, also act on the $GABA_A$ receptor, with similar effects.[3]

The most important (and most prevalent) $GABA_A$-BZ receptor in the brain is made up of α_1, β and γ_2 subunits, encoded by the same cluster of genes on chromosome 5. Studies in mice of different receptor subtypes have shown that the different actions of benzodiazepines can be separated and that compounds acting on the $GABA_{A2/3}$ subtypes are theoretically anxioselective without being sedative. Clinical trials of such compounds are eagerly awaited.[7]

Benzodiazepines are effective predominantly in PD, generalized anxiety disorder (GAD) and social phobia, and have a rapid onset of action. They also offer patients the flexibility to change their dose in line with their symptomatology.[4]

Adverse effects: although benzodiazepines are generally well tolerated, concerns regarding their potential for misuse and dependence have led to controls on their use in most countries. In many studies, 20–25% of patients have a worsening of anxiety when discontinuing benzodiazepines: this is likely to be both a reflection of the persistence of the underlying illness and a withdrawing effect.

Benzodiazepines have important sedative side effects, including daytime drowsiness and impaired balance and motor performance,[8–10] which may cause problems with daily tasks such as driving. As they are metabolized by the CYP450 system there is a potential for drug interactions; for example, some SSRIs can inhibit CYP450.[8] Sedation and impaired motor performance could be increased by concurrent use of other drugs that cause these effects, such as antihistamines and alcohol.

Although their use in anxiety remains controversial in some quarters, they are still often indicated as a first-line drug treatment in anxiety, particularly for short periods. They may be used to treat the increased anxiety that some patients experience during SSRI initiation. Long-term monotherapy or combination therapy is most likely to cause problems with discontinuation and is thus reserved for those resistant to treatment with an SSRI alone.[4]

Partial agonists such as pagoclone and bretazenil act through the same site to reduce anxiety. Because they are partial agonists they have fewer maximal side effects than full agonists such as diazepam, however clinical trials have been generally disappointing.

Anticonvulsants
Most anticonvulsant drugs act via GABA and glutamate neurotransmission and so offer promise for novel anxiolytic therapies;

however, although preclinical research shows anxiolytic properties for these drugs the evidence in humans is less impressive.

Gabapentin and pregabalin are effective in certain anxiety disorders. Pregabalin, which works via voltage-gated Ca^{2+} channels, causing decreased release of several neurotransmitters, has shown short-term efficacy in GAD.[1] The anticonvulsant properties of lamotrigine are mediated via NMDA glutamate receptor antagonism. Efficacy has been shown in PTSD.[1] Tiagabine, topiramate and vigabatrin also have some effect on anxiety. Long-term use of vigabatrin is restricted due to visual field constriction. Tiagabine, a GABA reuptake inhibitor, has had mixed results in clinical trials but has shown efficacy in GAD as well as in PD. Further research is ongoing.

Drugs acting via monoaminergic neurotransmission

Antidepressants
The efficacy of the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the treatment of anxiety disorders has been established for a number of decades. In the 1990s there was enormous growth in the use of safer antidepressants, the SSRIs, for the treatment of anxiety disorders.

Antidepressants differ from benzodiazepines in the speed of onset and course of their actions. Most are associated with an increase in anxiety on initiation of therapy and a delayed anxiolytic effect. The newer antidepressants tend to have better long-term tolerability due to fewer effects on psychomotor performance. Withdrawal effects, particularly rebound, tend to be less problematic. In contrast to the benzodiazepines, these drugs are also effective at treating depressive comorbidity.

Tricylic antidepressants
The benefits of imipramine on panic attacks were noted as early as the 1960s. Their antidepressant efficacy is related predominantly to the reuptake inhibition of serotonin and noradrenaline. However, their use is limited by their side-effect profile due to blockade of brain receptors.[4] Side effects include:
- anticholinergic effects (e.g. drowsiness, dry mouth)
- antihistaminergic effects (e.g. drowsiness, weight gain)
- α_1 adrenergic blockade (e.g. postural hypotension).

TCAs are highly toxic in overdose. They interact adversely with a number of drugs, particularly those that act as CYP2D6 inhibitors.[4]

Monoamine oxidase inhibitors
These increase the synaptic availability of serotonin, noradrenaline and dopamine by inhibiting breakdown following reuptake from the synapse. The traditional MAOIs bind irreversibly to monoamine oxidase; however, reversible inhibitors are now available (e.g. moclobemide).

Like TCAs, the MAOIs are associated with a significant side-effect profile. Initiation can cause dizziness, insomnia, postural hypotension and anticholinergic effects. During long-term use, weight gain and sexual dysfunction may occur. The use of MAOIs is further limited by the risk of a hypertensive crisis following the ingestion of foods containing tyramine (e.g. yeast products), therefore dietary restrictions are necessary. A similar reaction can occur with drug interactions (e.g. sympathomimetics, antihypertensives) and most psychostimulant drugs. A drug-free

period of 2 weeks is advised when switching from MAOIs to other antidepressants.[4]

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs increase synaptic 5-HT by selectively blocking the 5-HT reuptake transporter. There are 6 different SSRIs available:
- citalopram/escitalopram (its active enantiomer)
- fluoxetine
- fluvoxamine
- paroxetine
- sertraline.

As a class they are considered to be first-line therapy for each of the major anxiety disorders and are licensed in the UK for all anxiety disorders except simple phobia. Short-term efficacy ($\leq$ 6 months) has been clearly demonstrated in RCTs, but evidence is lacking concerning the treatment duration. Guidelines suggest treating for 12–24 months and longer if relapse risk is high.[4]

Although the side-effect and safety profiles of SSRIs are much superior to the TCAs and MAOIs, they are not without problems. Patients often feel more anxious after treatment initiation (the 'jitteriness' syndrome), which can lead to their stopping treatment. This can be overcome by prn use of benzodiazepines for a period of 2–3 weeks, after which the SSRI anxiolytic efficacy becomes apparent. SSRIs also can cause discontinuation symptoms (e.g. nausea, dizziness, headache and rarely 'electric shocks'). This is more common with drugs such as paroxetine which have a shorter half-life. Other side effects include sexual dysfunction, sedation and sweating.[4]

Venlafaxine

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI); however, below 150 mg serotonergic effects predominate. The best evidence for its efficacy in anxiety is in GAD, although evidence for its efficacy in treating social anxiety disorder has recently become available. Side effects on treatment initiation are similar to those with SSRIs and venlafaxine is also associated with discontinuation symptoms.[4] There is some emerging evidence that duloxetine, another SNRI, has efficacy in GAD.

Mirtazapine

Mirtazapine increases synaptic release of serotonin and noradrenaline by blockade of presynaptic inhibitory α_2 adrenoreceptors. It also blocks postsynaptic 5-HT$_2$, 5-HT$_3$ and H$_1$ receptors. It has shown efficacy in mixed anxiety and depression,[9] and early small-scale studies in anxiety disorders have been positive, especially in PTSD, where its sleep-promoting properties may help. Important side effects include sedation and weight gain.[1]

Buspirone

Buspirone is a partial agonist at postsynaptic 5-HT$_{1A}$ receptors in the limbic system and a full agonist at presynaptic 5-HT$_{1A}$ receptors in the raphe. Acute doses cause inhibition of serotonin release, which recovers with continued administration. Buspirone has well established efficacy in the treatment of GAD and anxiety symptoms in depression, but is ineffective in other anxiety disorders.[1] When compared with benzodiazepines as treatment for GAD, the onset of anxiolytic effects is slower for buspirone but it equates to benzodiazepines at 4–6 weeks.

It is well tolerated, the main side effects being dizziness, anxiety, nausea and headache on treatment initiation. These may be minimized by slow dose titration.[1] It does not cause sexual dysfunction or psychomotor impairment, lacks addictive potential and is safe in overdose. Neither drug interactions nor withdrawal are a significant problem.

β-blockers

These were used historically, but evidence from RCTs is lacking. They have significant side effects, cannot be used in asthmatics and are toxic in overdose, so are not generally prescribed. However, they do have a role in the treatment of performance anxiety where tremor is a problem (e.g. for musicians).[1]

Antipsychotics

These were used historically as major tranquillizers, but now have a limited role in treating refractory anxiety disorders due to their side-effect burden and limited evidence base.[10] There is conflicting evidence from trials for the use of newer atypical drugs such as olanzapine, risperidone and quetiapine in treatment-resistant OCD and GAD.[4]

D-cycloserine

This is an indirect agonist at the NMDA glutamate receptor system that has been shown to increase learning to overcome anxiety in rats. Recent human studies in height and social phobic patients have shown that it can accelerate the action of behaviour therapy.[1] We can expect more studies of this sort in future and the use of drugs to improve psychotherapy may be one of the major growth areas.

Conclusion

In recent times the anxiety disorders have become better recognized and prescribing practices have shifted. Drugs acting via GABA have been surpassed by antidepressants, particularly SSRIs. This partly reflects the controversy surrounding benzodiazepines because of their dependence-producing potential. The shift is supported by extensive and growing clinical evidence of antidepressant efficacy in the treatment of anxiety disorders and evidence of the role of NA and 5-HT in anxiety disorders.

Recognition of the role of the GABA$_A$-BZ receptor in the pathogenesis of anxiety has also grown with the help of neuroimaging and molecular biology. Further research should help to develop anxiolytic drugs that target this receptor but have fewer undesirable side effects. Further research is required to address:
- the optimal duration of treatment
- the benefits of combining psychotherapy with pharmacotherapy
- suitable treatments for those resistant to first-line therapies. ◆

REFERENCES

1 Nutt D. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectrums* 2005; **10:** 49–56.
2 Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain GABA$_A$-benzodiazepine receptor binding in panic

disorder: preliminary results from a quantitative PET study. *Arch Gen Psychiatry* 1998; **55:** 715–20.

3 Nutt DJ, Ballenger JC, eds. Anxiety disorders. Oxford: Blackwell Science Ltd, 2003.

4 Baldwin D, Anderson A, Nutt D, et al. Evidence based guidelines for the pharmacological treatment of anxiety disorder: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2005; **19:** 567–96.

5 Hood SD, Bell CJ, Nutt DJ. Acute tryptophan depletion. Part I: rationale and methodology. *Aus N Z J Psychiatry* 2005; **39:** 558–64.

6 Bell CJ, Hood SD, Nutt DJ. Acute tryptophan depletion. Part II: clinical effects and implications. *Aus N Z J Psychiatry* 2005; **39:** 565–74.

7 Basile A, Lippa A, Skolnick P. Anxioselective anxiolytics: can less be more? *Eur J Pharmacol* 2004; **500:** 441–51.

8 Kaplan E, DuPont R. Benzodiazepines and anxiety disorders: a review for the practicing clinician. *Curr Med Res Opin* 2005; **21:** 941–50.

9 Nutt DJ. Care of depressed patients with anxiety symptoms. *J Clin Psychiatry* 1999; **60**(suppl 17)**:** 23–27.

10 Blier P. Psychpharmacology for the clinician. *Rev Psychiatr Neuroscience* 2005; **30:** 304.