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Anxiety disorders

— the pharmacological management

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Drugs used to treat anxiety disorders can alleviate symptoms — either on a short- or long-term basis. The second part of this month's special feature describes the drugs commonly used, their potential limitations and side effects

Drug therapy is considered useful in anxiety disorders, either in combination with psychological therapy or alone. Drugs can provide relief both in the short term and on a long-term basis and have the advantage of being immediately available.

This article describes the main agents used in the treatment of anxiety, briefly explaining their likely mode of action and pointing out their potential side effects and limitations.

Short-term treatments

There are four main types of pharmacological treatment for the immediate, severe, disabling symptoms of anxiety: benzodiazepines, beta-blockers, antihistamines and antipsychotics.

Benzodiazepines Benzodiazepines enhance the effects of gamma-aminobutyric acid (GABA) in the central nervous system. GABA is an important inhibitory neurotransmitter in the CNS. Neuronal activity in the CNS is regulated by the balance between GABA inhibitory activity and excitatory neurotransmitters such as glutamate. If the balance swings towards more GABA activity, sedation, ataxia and amnesia occur. When GABA is reduced, arousal, anxiety and restlessness occur.¹ Benzodiazepines bind to the GABA_A benzodiazepine receptor. Benzodi-

azepines allosterically change the receptor complex to increase the efficiency of GABA in opening the GABA_A chloride channel. They cannot enhance GABA transmission beyond that naturally occurring and so are safer than drugs such as barbiturates, chlormethiazole and ethanol, which directly open the GABA_A chloride channel.¹

Benzodiazepines have been used for over 40 years in the treatment of anxiety. They can provide rapid symptomatic relief from acute anxiety states. Concerns over dependence and tolerance led the Committee on Safety of Medicines in 1988 to restrict their use to the short-term relief (up to four weeks only) of severe anxiety, which is disabling or subjecting the individual to unacceptable distress. There may be occasions, however, where long-term use is justified. For example, in patients whose quality of life is much improved with a benzodiazepine, where withdrawal causes severe distress and in patients with epilepsy or spasticity. When using benzodiazepines in anxiety disorders it is advisable to use the lowest effective dose and to use intermittent dosing where possible. For example, diazepam 2mg once or twice a day when required at times of severe symptoms.

Benzodiazepines are useful for relieving acute symptoms in generalised anxiety disorder (GAD) and social phobia.^{2,3} The National Institute for Health and Clinical Excellence recommends that benzodiazepines should not be used to treat panic disorder, as they may reduce the benefits of psychological therapy and may cause dependence.⁴ However, the British Association of

Psychopharmacology suggests that some benzodiazepines (clonazepam, diazepam and lorazepam) are effective in the acute treatment of panic attacks.²

Most benzodiazepines are metabolised by cytochrome P450 enzymes, specifically CYP3A4. Inhibitors of this enzyme, such as erythromycin, some selective serotonin reuptake inhibitors (SSRIs) and ketoconazole, can therefore increase benzodiazepine levels.⁵ Benzodiazepines can cause pharmacodynamic interactions such as increased sedation, confusion and respiratory depression when given with other CNS depressants such as alcohol and methadone.

Around a third of long-term (ie, over four weeks), regular users of benzodiazepines experience problems on withdrawal⁶ and it is difficult to predict who might be affected. Patients who have a history of substance misuse, have severe medical or psychiatric disorders or who lack social support may be more likely to experience withdrawal problems.^{5,6} Withdrawal symptoms can range from mild levels of restlessness, tremor and agitation to severe symptoms such as depression, convulsions or psychosis. Some symptoms can continue for weeks or months after stopping. Withdrawal of a dependent patient should therefore only be considered in a medically well patient with adequate social support and after the risks and benefits to the patient have been considered. The shorter-acting, high potency benzodiazepines such as lorazepam are generally associated with more withdrawal problems than the longer-acting benzodiazepines, such as diazepam

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or chlordiazepoxide. When withdrawing short-acting benzodiazepines in a dependent user, a switch to diazepam is recommended (see Panel 1 for approximate benzodiazepine equivalences).⁶ The substitution of diazepam can usually occur immediately. For example, a patient who has been prescribed temazepam 20mg at night for three months can be switched the next day to diazepam 10mg at night.

It is important to remember that the equivalent dosing is only approximate and benzodiazepines vary in their half-lives and degrees of sedation, so minor alterations of the dose may be required to get the desired effect. The dose of diazepam is reduced by one eighth to one tenth every two weeks depending on the occurrence of symptoms. Lower doses, such as those below 20mg of diazepam, can be particularly difficult to reduce and a slower withdrawal may be required. Patients' tolerance of withdrawal varies, with some patients only requiring four weeks to withdraw and others needing a year or more.

Beta-blockers The usefulness of beta-blockers in anxiety is unclear. They are not mentioned by NICE^{4,7,8} and there is not enough evidence to recommend them in any anxiety disorder.² The non-selective beta-blockers propranolol (40mg to 120mg daily) and oxprenolol (40mg to 80mg daily) are, however, licensed for the relief of the symptoms of anxiety. They are probably only useful to treat the somatic or physical symptoms such as palpitations, tremor, sweating and shortness of breath. One author suggests aiming for a reduction in resting heart rate of around seven beats per minute.⁵ Beta-blockers are generally considered less effective than benzodiazepines, but more effective than placebo, for treating the physical symptoms of anxiety.⁵

Antihistamines The sedating antihistamine hydroxyzine is the only antihistamine licensed for short-term use in anxiety (50-100mg four times a day). Sedating antihistamines are considered by NICE and the British Association of Psychopharmacology for the immediate management of generalised anxiety disorder.^{1,4} They are only

beneficial where sedation is required and are unlikely to treat anxiety in the long term.

Antipsychotics Antipsychotics have limited evidence of efficacy and many adverse effects in anxiety. They are occasionally used at low doses for their sedative and calming effects. Many of the older, typical, antipsychotics eg, chlorpromazine, haloperidol and trifluoperazine, are licensed for use in the short-term management of severe anxiety. Movement disorders such as akathisia are generally more common with the typical antipsychotics, making assessment of agitation in anxiety more difficult. In addition, antipsychotic-induced akathisia has been associated with suicidal behaviour.⁵ The newer, atypical antipsychotics are less likely to cause movement disorders. Of these, olanzapine has been proven useful in social phobia and post-traumatic stress disorder (PTSD)^{2,3}, risperidone in PTSD and obsessive-compulsive disorder (OCD)² and quetiapine in OCD.² In general antipsychotics are used after the failure of conventional treatments and usually in combination with an antidepressant. NICE states that antipsychotics should not be prescribed for panic disorders.⁴

— Long-term treatments

Many antidepressants are useful for the longer-term treatment of anxiety disorders. Buspirone is not an antidepressant but will be discussed here for completeness.

Selective serotonin reuptake inhibitors (SSRIs) The SSRIs cause selective and potent inhibition of serotonin (5HT) reuptake. There are many subtype receptors for the serotonergic neuron. For example, stimulation of serotonin at receptor 5HT_{1A} may account for the anti-anxiety and antidepressant effect while stimulation at 5HT₂ and 5HT₃ may cause some of the common side effects. The SSRIs are considered the first-line choice of medication in all anxiety disorders.^{2,3,4,7,8} They have shown good efficacy in randomised controlled clinical trials, are generally well tolerated and are safer in overdose compared with the tricyclic antide-

pressants (TCAs). The individual indications for the SSRIs in different anxiety disorders vary according to preparation but this probably represents marketing strategies rather than lack of effect. Although chemically different, they have an identical mode of action and a similar adverse effect profile. They are differentiated by their potential for interactions via inhibition of the cytochrome P450 enzyme system and their ability to cause withdrawal problems. For example, fluoxetine and paroxetine are potent inhibitors of CYP2D6 while citalopram and escitalopram are very weak inhibitors at this cytochrome.⁵ Caution must be used with other drugs metabolised by cytochrome CYP2D6 such as TCAs. Fluoxetine has been shown to double or treble plasma levels of amitriptyline, clomipramine and imipramine.⁵ Other cytochrome P450 enzymes may also be inhibited by the SSRIs, for example, paroxetine and norfluoxetine inhibit cytochrome CYP3A4^{5,6}.

Withdrawal problems with SSRIs, and indeed with all antidepressants, may be partly associated with the length of the half-life of the antidepressant and the presence of active metabolites. Paroxetine, for example, has a relatively short half-life of approximately 24 hours and has been associated with a greater number of discontinuation reports than other antidepressants. Fluoxetine has a half-life of four to six days while its active metabolite norfluoxetine has a half-life of six to 16 days. These long half-lives mean that fluoxetine causes very few withdrawal problems. A common strategy to reduce the risk of discontinuation symptoms with all antidepressants is to reduce the dose every week by 20 to 25 per cent over at least four weeks.⁶ Problems on discontinuation are less likely if the antidepressant has been taken for less than eight weeks. In these circumstances, a faster discontinuation may be appropriate.⁶

A transient increase in anxiety symptoms has been reported when starting SSRIs in panic disorder, GAD and OCD.^{4,7} This increase in anxiety can be particularly difficult for the sufferer and cause early non-compliance. To prevent this the starting dose should be half the normal dose used in depression and then increased at weekly intervals.^{4,6,7} Standard antidepressant doses are usually well tolerated in social phobia.³ Other transient and dose-related side effects of the SSRIs include nausea (which may be caused by stimulation at 5HT₃ receptors), diarrhoea and insomnia. Sexual dysfunction such as decreased libido and delayed orgasm are also commonly reported with SSRI treatment (60 to 70 per cent prevalence).⁶ This may in part be the result of 5HT_{2A} receptor-stimulation. Spontaneous remission of sexual dysfunction can occur, but if the condition is persistent, the dose should be reduced or an alternative class of antidepressant should be tried.⁶

Panel 1: Benzodiazepine equivalents (approximate values)⁶

Benzodiazepine	Dose (mg)	Half-life in healthy adults (hours)
Diazepam	10	20-54
Chlordiazepoxide	25	10-48
Clonazepam	1-2	30-40
Lorazepam	1	12
Nitrazepam	10	24-29
Oxazepam	30	3-9
Temazepam	20	3-18

SSRIs may increase the risk of suicidal thoughts and self-harm in younger adults with depression. It is unclear whether this risk also occurs in anxiety disorders. It would be prudent to monitor any patient at risk of self-harm or suicide every one to two weeks and to only supply a small quantity of medicines to them.

Tricyclic antidepressants The TCAs are named after their three-ring chemical structure. They block the reuptake pumps for both serotonin and noradrenaline. Clomipramine has a more potent action at serotonin pumps than noradrenaline reuptake pumps. Amitriptyline and imipramine have similar potencies at both serotonin and noradrenaline reuptake pumps. The TCAs block many other neurotransmitters both centrally and peripherally which may explain their adverse effects. Histamine blockade can cause sedation, anticholinergic effects may cause dry mouth, blurred vision, constipation and cognitive impairment and alpha-1 blockade accounts for postural hypotension. TCAs also lower seizure threshold and commonly cause weight gain.^{5,6} Of particular concern is their toxicity in overdose, usually as a result of QTc prolongation or anti-arrhythmic effects.⁶ This multitude of adverse effects can limit the

usefulness of the TCAs. Ideally they should be avoided in patients at risk of suicide and those with cardiac disease. However, when used cautiously in medically well patients the sedative effects can prove useful in anxiety disorders. Only a few TCAs have proven efficacy in anxiety disorders. Clomipramine is used in panic disorder and OCD and is considered slightly more efficacious but less well tolerated than the SSRIs in OCD.² Clomipramine is the only TCA licensed for anxiety under the indications of phobic and obsessional states. Imipramine is supported by placebo controlled trials in GAD, panic disorder, PTSD and OCD and amitriptyline has shown some efficacy in PTSD.² There is no evidence for the use of TCAs in social phobia.^{2,3} NICE recommends specific TCAs, usually only after an adequate trial and failure of at least one SSRI. Amitriptyline is only recommended by NICE for initiation by mental health specialists in PTSD. Imipramine or clomipramine are recommended by NICE for the treatment of panic disorder and clomipramine alone is recommended by NICE for the treatment of OCD.^{4,8,9}

Monoamine-oxidase inhibitors (MAOIs) and reversible MAOIs Monoamine-oxidase (MAO) is one of the principal enzymes responsible for the breakdown of

serotonin, noradrenaline and dopamine. The MAOIs irreversibly bind to the MAO and destroy its function. Enzyme activity only returns when a new enzyme is synthesised. MAOIs are much less frequently prescribed than both SSRIs and TCAs. They have problematic drug interactions and dietary restrictions and therefore use is limited to severely resistant cases when other treatment has failed. NICE recommends phenelzine in PTSD for initiation by mental health specialists only.⁸ The Cochrane Collaboration recommends phenelzine as a second line agent in social phobia.³ Moclobemide is a reversible MAO inhibitor which can be displaced from the MAO by noradrenaline allowing the enzyme to regain its function. Moclobemide therefore causes fewer drug and dietary interactions. Moclobemide is licensed and recommended for the treatment of social phobia.^{2,3} However, moclobemide is considered less effective than the SSRIs for social phobia so is probably most useful when the SSRIs are poorly tolerated.³ There is little to no evidence to support moclobemide use in other anxiety disorders.

Venlafaxine Venlafaxine blocks serotonin, noradrenaline and dopamine reuptake. These effects are dose-dependent, with serotonin reuptake inhibition prominent at all

Panel 2: Overview of recommended treatments^{2,3,4,6,7,8}

Treatments	Anxiety Disorders				
	Generalised anxiety disorder	Panic disorder	Social phobia/social anxiety disorder	Obsessive-compulsive disorder	Post-traumatic stress disorder
Non-drug treatments	Cognitive behavioural therapy (CBT)	CBT	CBT	CBT including exposure and response prevention	Trauma focused CBT or eye movement desensitisation and reprocessing
Benzodiazepines	Often used, recommended for short term use only (2-4 weeks)	Have a rapid effect but may worsen outcome in the long term. NICE do not recommend	Often used, recommended for short term use only (2-4 weeks)	Not recommended	Not recommended
First line pharmacotherapy*	Escitalopram Paroxetine	Citalopram Escitalopram Paroxetine	Escitalopram Paroxetine	Citalopram [†] Fluvoxamine Fluoxetine Paroxetine Sertraline	Paroxetine Mirtazapine [†]
Other treatments in resistant cases (which are less well tolerated or have a weaker evidence base)	Buspirone Hydroxyzine Imipramine Venlafaxine [†] (max 75mg daily)	Clomipramine Imipramine Mirtazapine Moclobemide	Moclobemide Phenelzine Propranolol, oxprenolol (performance anxiety only) Augmentation with olanzapine	Clomipramine Augmentation with risperidone Quetiapine	Amitriptyline [†] Phenelzine [†] Sertraline (in women) Imipramine Augmentation with olanzapine Risperidone

* ** means that the licensed preparation is indicated but other SSRIs may also be beneficial, † means that the treatment is currently unlicensed but recommended by NICE^{7,8} and †† means that the treatment is recommended by NICE for use by a specialist in mental health only

Advice to patients

Patients with an anxiety disorder often have many concerns about starting psychotropic medicines. They should be reminded that the response to antidepressants is not immediate, initial worsening of symptoms is common with SSRIs and venlafaxine (in panic disorder, GAD and OCD) and that antidepressant therapy is long-term (at least 12 months in PTSD, OCD and social phobia and at least six months in GAD and panic disorder).^{3,4,7,8} This is to reduce the risk of the symptoms returning. Longer courses may be required for patients with multiple relapses or severe symptoms.

It is also important to educate the patient that tolerance, dependence and addiction do not occur with antidepressants but withdrawal symptoms are possible. Slowly reducing the antidepressant over at least four weeks may reduce these symptoms. Patients should be reminded that benzodiazepines can cause dependence so should be taken for no longer than four weeks, ideally intermittently and at the lowest effective dose. There may however be occasions when longer courses are justified.

dose ranges but noradrenaline reuptake only significant after 150mg per day and dopamine reuptake inhibition above 225mg per day.⁵ Venlafaxine has fewer sedative and anticholinergic effects than the TCAs and has evidence to support its use in all the anxiety disorders, although the evidence in OCD is minimal.² Venlafaxine is only licensed in GAD and NICE suggests it could be considered after the failure of two SSRIs or psychological therapy.⁴ Since there are concerns about the effects of overdose, the CSM currently recommends that venlafaxine treatment should only be started by a specialist mental health medical practitioner. Monitoring, such as a baseline ECG and regular blood pressures are also required.² The dose of venlafaxine in GAD is 75mg per day.

Mirtazapine Mirtazapine, an α_2 antagonist, increases both noradrenaline and serotonin neurotransmission by blocking the α_2 autoreceptors that inhibit noradrenaline neurons. It also blocks two specific serotonin receptors, 5HT₂ and 5HT₃, and histamine receptors. This reduces the risk of sexual dysfunction and nausea seen with SSRIs, but mirtazapine may instead cause weight gain and sedation through histamine blockade. It is recommended by NICE in the treatment of PTSD.⁸ There are few studies supporting the use of mirtazapine in other anxiety disorders.

Bupirone Buspirone has a complex mechanism of action, which is not fully understood. It may act as a partial agonist at 5HT_{1A} receptors.⁵ It is not a benzodiazepine and therefore does not treat or prevent benzodiazepine withdrawal problems. It is licensed for short-term use in anxiety but has a slow onset of action. To be effective it needs to be given for at least four weeks at a dose of 10mg, three times a day or more.⁵ There is some supporting evidence for using buspirone in GAD, where it is occasionally used in resistant cases.²

Prescribing considerations

Any concurrent depressive symptoms usually improve more quickly than anxiety symptoms when treating with an antidepressant. In anxiety alone it can take up to 12 weeks to respond to an antidepressant although an earlier response is often seen.^{2,4,7} The response rate to antidepressants is lower in anxiety compared with depression. Across the range of anxiety disorders approximately 50 per cent of patients in primary care significantly improve over six or more months with active treatment.² Any medication used for anxiety should be gradually titrated depending on adverse effects and continuing symptoms. The evidence to support a higher response rate with higher doses of antidepressants in anxiety is limited. However, there is evidence that a higher dose is

more effective in GAD, panic disorder and OCD, but a dose dependent response is not proven in social phobia or PTSD.² The evidence base, current national guidelines and type of anxiety disorder should determine the choice of a particular drug. In anxiety disorders the absence of a licensed indication does not always mean there is no evidence of effectiveness but for medico-legal reasons if a licensed drug with good evidence exists then this should be the preferred option. Medical co-morbidities and concurrent medicines must also be considered before choosing drug therapy.

Anxiety in the medically ill

Many medical conditions have anxiety as a clinical symptom, for example, hyperthyroidism, alcohol withdrawal syndrome and hypoglycaemia. Having an anxiety disorder increases the risk of some medical conditions. For example several studies have shown a link between anxiety disorders coronary heart disease and hypertension.⁹ Many prescribed medicines and illicit drugs have also been reported to cause symptoms of anxiety, for example, aminophylline, isoniazid, high dose caffeine, cocaine and prednisolone.^{5,6} Before treating anxiety, medical conditions, prescribed medicines and illicit drugs should be ruled out as the cause.

Conclusion

Anxiety disorders are common, chronic, cause considerable distress and disability and are often poorly treated. A range of treatments are available which can dramatically improve quality of life and social functioning. These are summarised in Panel 2 (p121). Medication is considered useful after psychological treatment such as cognitive behavioural therapy. The SSRIs are the recommended first line therapy in all anxiety disorders. The response rate to treatment in anxiety is less than that seen with depression and time to response is often longer. Successful treatment often involves a

combination of psychological and pharmaceutical approaches. The benzodiazepines still have a role in the severe, immediate symptoms in GAD and social anxiety disorder but are not routinely recommended in other anxiety disorders. Antidepressants such as some TCAs, phenelzine, moclobemide, venlafaxine and mirtazapine have a role in the treatment of specific anxiety disorders usually after the failure of or intolerance to the SSRIs.

References

1. Nutt D, Malizia A. New insights into the role of the GABA_A- benzodiazepine receptor in psychiatric disorders. *British Journal of Psychiatry* 2001; 179:390-6.
2. Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson J et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2005;19:567-96.
3. Stein DJ, Ipser JC, van Balkom AJ. Pharmacotherapy for social anxiety disorder. *The Cochrane Database of Systematic Reviews* 2000, Issue 4.
4. National Institute for Health and Clinical Excellence. Anxiety management of anxiety (panic disorder with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London: the institute; 2004.
5. Bazire S. *Psychotropic Drug Directory 2005 — The professionals' pocket handbook & aide memoire*. Wiltshire:Fivepin;2005.
6. Taylor D, Paton C, Kerwin R. *The South London and Maudsley NHS Trust and Oxleas NHS Trust 2005-06 Prescribing Guidelines*. 8th edition. Oxon: Taylor & Francis;2004.
7. National Institute for Health and Clinical Excellence. *Obsessive-compulsive disorder. Clinical Guidelines* 31. London: the institute; 2005.
8. National Institute for Health and Clinical Excellence. *Post-traumatic stress disorder (PTSD). Clinical Guidelines* 26. London: the institute; 2005.
9. Davies SJC, Jackson PR, Potokar J, Nutt DJ. Treatment of anxiety and depressive disorders in patients with cardiovascular disease. *British Medical Journal* 2004;328:939-43.