The pharmacological management of anxiety disorders

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Progress in Neurology and Psychiatry **is running a series of updated articles on the major psychiatric drug groups, produced in association with the College of Mental Health Pharmacy (www.cmhp.org.uk). In this article, Stephen Bleakley and Simon Davies provide an overview of the main types of anxiety disorders, obsessive compulsive disorder and post-traumatic stress disorder. The article focuses on the drug treatment options and supporting evidence base.**

The term anxiety disorder encompasses a variety of complaints, which can either exist on their own or in conjunction with another psychiatric or physical illness. Anxiety generally presents with a combination of psychological, physical and behavioural symptoms.

Anxiety disorders can be broadly divided into: generalised anxiety disorder (GAD), panic disorder, social anxiety disorder, specific phobias, separation anxiety disorder and illness anxiety disorder. Post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) share similar symptoms to anxiety disorders but in the recently published *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) are considered as separate entities (note: DSM-5 is not the only categorisation system currently in use). For completeness they will also be considered in this article. A short description of the clinical features of each disorder can be seen in Table 1.

To meet the diagnosis of an anxiety disorder, the symptoms must be prolonged, cause significant distress and impair social or daily functioning. Most sufferers will have another psychiatric illness, which is commonly depression.[1] Successful treatment of an underlying depression will often improve the symptoms of anxiety. Many patients will also present with more than one anxiety disorder at the same time, which can further complicate treatment. In adults, anxiety disorders as a whole have a lifetime prevalence of approximately 21%,[1] with specific phobias being the most commonly reported.

Treatment options

NICE guidelines cover the treatment of panic disorders with or without agoraphobia, GAD, PTSD, OCD and social anxiety disorder.[2–5] The British Association for Psychopharmacology and the World Federation of Biological Psychiatry have also produced guidelines covering treatment options in anxiety disorders, PTSD and OCD.[1,6]

In all anxiety disorders, psychological therapies are also considered first-line treatment options, the choice between psychotherapy and medications depending on patient preference, previous response and local availability. Psychotherapy and antidepressants have broadly similar efficacy in the acute treatment of anxiety disorders[1,6] and many patients have a preference for psychotherapy. If the patient is unable to tolerate the anxiety or associated distress, then medicines are sometimes used before or while awaiting psychotherapy. The ideal treatment should be tailored to the individual and may involve a combination of both psychotherapy and pharmacotherapy. It is important to note, however, that in many anxiety disorders it is largely uncertain if combining pharmacotherapy and psychotherapy is associated with a better long-term outcome than either treatment alone. The exception may be in panic disorder and OCD where combined treatment has been shown to be more efficacious.[7] The type of treatment should depend on patient preference, symptoms, type of anxiety disorder, speed of response required, long-term goals and previous response or adverse reactions. Specific phobias, illness anxiety disorder and separation anxiety disorder are almost exclusively treated using psychotherapy approaches so will not be discussed further.

Pharmacotherapy

Table 2 provides an overview of the recommended drug treatments for the main types of anxiety disorders. Antidepressants are recommended for patients who prefer medication, are unable to commit or have not responded to psychological therapies. In addition, antidepressants are considered a first-line

treatment option either alone or in combination with cognitive behavioural therapy (CBT) in patients suffering from OCD with moderate or severe impairment.[4] The number needed to treat with antidepressants is around five in GAD and PTSD,[8,9] while in childhood and adolescent anxiety disorders this increases to 14.[10]

The response rate to antidepressants in anxiety is often lower and takes longer than that seen in depression. Up to 12 weeks may be needed to assess the response to an antidepressant.[1] In GAD if no response is seen within four weeks any further improvement with the same treatment and dose is unlikely.[1] A detailed review of the antidepressants including

Anxiety disorder	12-month prevalence (best estimate from expert consensus)	Clinical features
All anxiety disorders	Approximately 14%	Fear or worry, sleep disturbances, concentration problems, dry mouth, sweating, palpitations, GI discomfort, restlessness, shortness of breath, avoidance behaviour, etc
Generalised anxiety disorder	1.7–3.4% (more frequent in older age)	Persistent (free floating), excessive and inappropriate anxiety on most days for at least 6 months. The anxiety is not restricted to a specific situation
Panic disorder (with or without agoraphobia)	1.8% (agoraphobia 2%)	Recurrent, unexplained surges of severe anxiety (panic attacks). Most patients develop a fear of repeat attacks or the implications of an attack. Often seen with agoraphobia (fear in places or situations from which escape might be difficult)
Social anxiety disorder	2.3%	A marked, persistent and unreasonable fear of being observed, embarrassed or humiliated in a social or performance situation, *eg* public speaking or eating in front of others
Specific phobia	6.4%	Marked and persistent fear that is excessive or unrealistic, precipitated by the presence (or anticipation) of a specific object or situation, *eg* flying, spiders. Sufferers avoid the feared object/subject or endure it with intense anxiety
Separation anxiety disorder	Not known	Fear or anxiety concerning separation from attached individuals. For example, excessive distress when separated from home with persistent worries about potential harm to attachment figures
Illness anxiety disorder	Not known	Excessive or disproportionate preoccupations with having or acquiring a serious illness. Excessive health-related behaviour and high levels of alarm about personal health status
Post-traumatic stress disorder	1.1–2.9% (more frequent in younger age)	Can occur after an exposure to a traumatic event that involved actual or threatened death, or serious injury or threats to the physical integrity of self or others. The person responds with intense fear, helplessness or horror. Sufferers can re-experience symptoms (flashbacks) and avoid situations associated with the trauma. Usually occurs within 6 months of the traumatic event
Obsessive compulsive disorder	0.7%	Persistent thoughts, impulses or images (obsessions) that are intrusive and cause distress. The person attempts to get rid of these obsessions by completing repetitive time-consuming purposeful behaviours or actions (compulsions). Common obsessions include contamination while the compulsion may involve repetitive washing or cleaning

Table 1. Prevalence and clinical features of the main types of anxiety disorders[1]

adverse reactions and interactions can be viewed in an earlier article in this College of Mental Health Pharmacy series.[11]

SSRIs

The selective serotonin reuptake inhibitors (SSRIs) have a broad anxiolytic effect and are considered the first drug options in all anxiety disorders, PTSD and OCD.[1–6] Individual SSRIs have varying licensed indications across the anxiety disorders but this does not necessarily mean others have no supporting evidence (Table 2). Where more than one SSRI is licensed in a particular disorder it is not possible to conclude which SSRI would be more effective because of the lack of direct head-to-head trials.[1,12] There is some evidence in GAD however, which suggests that there are small but important differences in efficacy and tolerability between antidepressants and other drug options.[13] In a multiple treatment meta-analysis in GAD, fluoxetine was ranked as first for efficacy while sertraline was ranked first for tolerability.[13] The SSRIs also differ in their interaction potential, side-effect profile and ease of discontinuation.[11] Initial worsening of symptoms is common when starting an SSRI (and other antidepressants such as serotonin and noradrenaline reuptake inhibitors [SNRIs] and tricyclic antidepressants) in GAD, panic disorder and PTSD, so beginning with half the dose of that used in depression is recommended,[14] as is reassuring the patient that this is usually only experienced for the first few weeks of treatment. The NICE guidelines for GAD recommend that patients are reviewed every two to four weeks for the first three months of treatment to monitor for efficacy and tolerability, in view of these concerns.[2]

SNRIs

The SNRI venlafaxine has some evidence to support its use in most anxiety disorders (with the exception of OCD), but it is only licensed for use in GAD and social anxiety disorder. Discontinuation symptoms are common following venlafaxine withdrawal and can even be experienced after missing a single dose. Venlafaxine can increase blood pressure at higher doses so is contraindicated in patients with a high risk of cardiac arrhythmias or uncontrolled hypertension. There is also some evidence that venlafaxine may be less well tolerated than SSRIs.[13,15]

Duloxetine, another SNRI, is also licensed for GAD and can similarly increase blood pressure. Of the licensed treatments for GAD, duloxetine was ranked first for response but fourth for remission in a multiple-treatment meta-analysis.[13]

Tricyclic antidepressants

Certain tricyclic antidepressants (TCAs) – clomipramine, imipramine, lofepramine and amitriptyline – are efficacious in some anxiety disorders (Table 2).[1] They are, however, associated with a greater burden of adverse reactions such as anticholinergic effects, hypotension, sedation and weight gain. Of particular concern is their cardiac toxicity in overdose, which relegates their use to second-line options following the failure of an SSRI. In those with a serious risk of cardiovascular disease it would be prudent to either avoid a TCA or consider electrocardiogram and blood pressure monitoring before and during prescribing. TCAs should also be avoided or supplied in very small quantities to any patient at risk of suicide. Clomipramine may be marginally more effective, but not as well tolerated in OCD compared with SSRIs.[1]

Other antidepressants

The monoamine-oxidase inhibitors (MAOIs) are rarely used in practice because of their potentially life-threatening interactions with other serotonergic medicines and tyramine in the diet. Strict advice on avoiding tyramine (which is found in dairy products, aged or cured meats and yeast extracts for example) and over-the-counter medications containing ephedrine is required when prescribing an MAOI because of the potential for a hypertensive crisis.[16] Moclobemide is a reversible MAOI so causes fewer problematic drug and dietary interactions. Phenelzine and moclobemide are occasionally used by specialists in social anxiety disorder following the failure of an SSRI.[1,5] Phenelzine also has supporting evidence, as a third-line treatment option in PTSD.[3,17]

Mirtazapine, an alpha2-adrenoreceptor antagonist, is recommended by NICE as an option for PTSD if sufferers do not wish to participate in trauma-focused CBT.[3] This pragmatic recommendation is based on a rather limited evidence base which may account for mirtazapine not appearing in other PTSD treatment guidelines.[1,6,17] Mirtazapine has a lower incidence of nausea, vomiting and sexual dysfunction than the SSRIs but is commonly associated with weight gain and sedation.

Agomelatine has a novel mode of action with an agonist effect at melatonin 1 and 2 receptors and an antagonist effect at 5-HT_{2c}. The affect on melatonin is thought to improve circadian rhythm and sleep quality while the 5-HT_{2c} blockade increases noradrenaline and dopamine release.[11] Agomelatine is associated with a lower rate of discontinuation symptoms than the SSRIs or SNRIs.[1] It does, however, elevate hepatic enzymes in just over 1% of patients so

	Generalised anxiety disorder	Panic disorder	Social anxiety disorder	Obsessive compulsive disorder	Post-traumatic stress disorder
Short-term treatment with benzodiazepines	Benzodiazepines • Alprazolam • Diazepam • Lorazepam (where possible 2–4 weeks only)	Benzodiazepines • Alprazolam • Diazepam • Lorazepam • Clonazepam (NICE recommends avoiding benzodiazepines due to poor long-term outcomes)	Benzodiazepines • Clonazepam (2–4 weeks only)	Avoid. Benzodiazepines have not been shown to be effective	Avoid. Benzodiazepine given immediately after the trauma may interfere with the recovery process
First-line pharmaco-therapy	SSRI • Sertraline • Citalopram • Escitalopram • Paroxetine	SSRI • Citalopram • Escitalopram • Paroxetine • Fluoxetine • Sertraline • Fluvoxamine	SSRI • Sertraline • Escitalopram • Paroxetine • Citalopram • Fluoxetine • Sertraline • Fluvoxamine	SSRI • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline • Citalopram	SSRI • Paroxetine • Sertraline • Fluoxetine
Other drug treatments with supporting evidence	• Venlafaxine • Duloxetine • Pregabalin • Buspirone • Imipramine • Agomelatine • Quetiapine • Hydroxyzine • Trazodone	• Clomipramine • Imipramine • Venlafaxine • Lofepramine • Mirtazapine • Moclobemide	• Moclobemide • Phenelzine* • Venlafaxine • Pregabalin • Gabapentin • Olanzapine	• Clomipramine • Augmenting the SSRI or clomipramine with an antipsychotic or 5-HT_3 antagonist* • Augmenting the SSRI with lamotrigine or topiramate*	• Venlafaxine • Mirtazapine • Phenelzine* • Augmenting the antidepressant with: olanzapine, risperidone or prazosin*
Duration of antidepressant treatment following response	Up to 18 months	At least 6 months	At least 6 months	At least 12 months	At least 12 months
* Usually prescribed by mental health specialists only.					

Table 2. Overview of the recommended drug treatments for the main types of anxiety disorders[1–6,21]

monitoring of liver function tests is recommended in the first six months of treatment.

To reduce the risk of symptoms returning, patients should be advised to continue the antidepressant for at least six months following improvement of symptoms in panic disorder and social anxiety disorder, for 12 months in PTSD and OCD, and for up to 18 months in GAD.[1] Those with an enduring and recurrent illness may need to continue antidepressants for longer. Most antidepressants have been associated with discontinuation symptoms on abrupt withdrawal (fluoxetine and agomelatine are reported to have a lower risk) so patients should be reminded of the importance of a slow, gradual withdrawal when discontinuation is appropriate.[1,14] In some patients, to prevent relapse and intolerable discontinuation symptoms, this withdrawal may take up to three months.[1]

Benzodiazepines

Benzodiazepines enhance the effects of gamma-aminobutyric acid (GABA) in the central nervous system (CNS). 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.

Conversely, when GABA is reduced, arousal, anxiety and restlessness occur.[18] Benzodiazepines bind to the $GABA_A$ benzodiazepine receptor and allosterically change the receptor complex, which in turn increases the efficiency of GABA in opening the $GABA_A$ chloride channel.[18]

The benzodiazepines have been used for many decades in the treatment of anxiety and can provide rapid symptomatic relief from acute anxiety states. There is robust evidence supporting certain benzodiazepines in the acute treatment of GAD, social anxiety disorder and panic disorder (Table 2).[19] Benzodiazepines have not been found to be effective in OCD, and in PTSD are not recommended in the first few hours following trauma as they may interfere with the spontaneous recovery process.[6,19] Concerns over abuse, dependence and tolerance led the Committee on the Safety of Medicines in 1988 to restrict their use to short term only (up to four weeks). Despite this guidance, in 2002, 30% of prescriptions for benzodiazepines indicated long-term use, which is known to be associated with road traffic accidents, dependence, tolerance and a risk of falls in the elderly.[20] The message of short-term use was repeated in a Chief Medical Officer bulletin in 2004,[20] which recommended that benzodiazepines should be prescribed for just two to four weeks for relief of severe or disabling anxiety that is subjecting the patient to unacceptable distress.

There may be some people, however, where alternative treatments are ineffective, they have no history of drug dependence and they have gained significant improvements in quality of life that long-term benzodiazepine use may be appropriate.[19] Once the time is appropriate for withdrawal from long-term treatment it must be done sympathetically and gradually to avoid potentially dangerous and distressing withdrawal symptoms (such as rebound anxiety, insomnia, restlessness, confusions and seizures).[21]

Guidelines from NICE further state that benzodiazepines are not recommended for those with panic disorder as the long-term outcome is poor.[2] Some patients, for example, reported worse panic attacks after the benzodiazepines were stopped.

Pregabalin

Pregabalin is a structural analogue of GABA but has no acute effects at GABA receptors. Instead it binds in a state-dependent manner to the Type 1 and Type 2 proteins of the alpha-2-delta sub-unit of voltage-gated calcium channels in the CNS. By changing the conformation of the calcium channel, pregabalin is proposed to: reduce the release of excitatory neurotransmitters such as glutamate, reduce the synthesis of excitatory synapses, and block the progression of new calcium channels to the cell surface.[22] Pregabalin has robust evidence in the treatment of GAD both in the acute phase and in relapse prevention.[1,22] It has evidence of efficacy in young patients and the elderly, and may enhance the effects of an SSRI or SNRI.[22]

NICE recommends pregabalin as a treatment option if the SSRIs or SNRIs are poorly tolerated in GAD.[2] Although unlicensed and not recommended by NICE, there are also trials supporting pregabalin in social anxiety disorder.[1,22] Pregabalin is quick acting (often within a few days) and is generally well tolerated across the daily dose range of 150–600mg. The two most frequently reported adverse effects are dizziness and somnolence.[22] Pregabalin is almost completely excreted unchanged so is not affected by pharmacokinetic (CYP) P450 drug interactions however; the dose needs to be adjusted in people with renal impairment.

Recently, there have been a few reports of pregabalin abuse, which usually involve those with a previous history of substance misuse.[23] This may be in part related to its occasional adverse effect of euphoria, seen in 1–10% of users.[22] The abuse potential of pregabalin is considered much less than that seen with benzodiazepines.[22]

Other medicines occasionally used in anxiety disorders

Hydroxyzine, a sedating antihistamine, is licensed for the short-term treatment of anxiety in adults at a dosage of 50–100mg four times daily. The clinical evidence only supports its use in the acute treatment of GAD (for up to four weeks) if sedation is required.[1,24]

Although antipsychotics are often used in anxiety disorders, the evidence base is still developing and only supports quetiapine monotherapy in GAD and in the augmentation of antidepressants in OCD and PTSD.[1,6] The first-generation antipsychotics are associated with movement disorders such as akathisia and tardive dyskinesia so should be avoided. The second-generation antipsychotics are less likely to cause movement disorders but are associated with other physical health concerns. An extensive review of antipsychotics was the subject of a previous article in this series.[25]

Buspirone is probably a $5\text{-}HT_{1A}$ partial agonist and is licensed for short-term use in anxiety. It is not a benzodiazepine so does not treat or prevent benzodiazepine withdrawal problems. A Cochrane review on GAD found buspirone and other azapirones

to be superior to placebo in short-term studies (four to nine weeks), but less effective or acceptable than benzodiazepines.[26] The current evidence base only supports buspirone use in the acute treatment of GAD.[1,6]

Propranolol and oxprenolol are both licensed for anxiety symptoms, but are probably only useful for occasional physical symptoms such as palpitations, tremor, sweating and shortness of breath. There is no evidence supporting their use in the acute or long-term treatment of anxiety disorders but, intriguingly, small pilot studies indicate that giving an immediate course of propranolol following a traumatic event may prevent emerging PTSD.[27,28] Of concern is that people with anxiety often report dizziness or postural hypotension which can be exacerbated with beta-blockers.

Conclusion

Clinicians are reminded to actively seek psychotherapy approaches based on cognitive and behavioural techniques when first treating an anxiety disorder. Pharmacotherapy has an important role either in conjunction with psychotherapy or as an alternative if appropriate.

Drugs can provide immediate relief, as with the benzodiazepines, or longer-lasting remission, as with the antidepressants. If benzodiazepines are being considered, they should be prescribed for short courses, up to a month and at the lowest effective dose, to avoid the development of tolerance and dependence. Antidepressants such as the SSRIs and SNRIs can provide longer-term control but may cause an initial worsening of symptoms so should be initiated cautiously. Pregabalin is a suitable alternative in GAD and has an emerging evidence base in social anxiety disorder. Whichever treatment strategy is employed, close monitoring for symptom improvement, adverse effects and adherence is necessary.

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Declaration of interests

There are no conflicts of interest declared.

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