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Practical pharmacotherapy for anxiety

David Nutt & Caroline Bell

Anxiety is a very common and disabling condition which has serious consequences for patients, their families and society in general. The past decade has witnessed an increase in the recognition and understanding of the problem but considerable confusion and debate remains over attitudes towards treatment. The background to this controversy dates from the late 1980s when widespread and vehement criticism of doctors and drug companies over the use of benzodiazepines began. Although the litigation was unsuccessful, it resulted in a pervading feeling of uncertainty (both within the medical profession and among patients) about prescribing or taking any drug as a treatment for anxiety. The situation has been further confounded by the split that has occurred between the proponents of pharmacological and psychological approaches to management. These controversies have left the practising clinician in an unenviable position, with few practical or relevant guidelines to follow. Developments over recent years, however, should put an end to this confusion; new pharmacotherapies such as the selective serotonin reuptake inhibitors (SSRIs) and buspirone, and older ones such as the tricyclic antidepressants (TCAs), have emerged as effective alternatives to the benzodiazepines and have been paralleled by a similar growth in effective and available psychological treatments, particularly cognitive and cognitive–behavioural therapy. This progress seems set to continue with the rapid expansion of knowledge about the brain circuits and transmitters regulating anxiety that is now emerging from imaging studies.

This paper aims to give clinicians practical advice on the effective pharmacological management of patients with anxiety. Although we will concentrate on psychopharmacological approaches, it is important to realise that optimal treatment involves more than just prescribing medication. The initial interview is crucial; time invested at this stage will reap benefits later. It is very important to take a thorough history and to make the correct diagnosis as this strongly influences the choice of drug. Patients need to be given a careful explanation of their condition including education about the nature of and the reasons for their anxiety, the likely time course of response, and potential adverse effects. During treatment patients should be seen (at least initially) very frequently (every week or fortnight) for careful monitoring of response and side-effects and for titration of the dose to a therapeutic level. Symptoms should be monitored throughout treatment in a standardised way using self-rating scales of severity, avoidance, etc. There is growing evidence that all these approaches, which have in common the theme of increased patient understanding and compliance, add to drug effects and facilitate recovery.

Although there is no perfect categorisation of anxiety disorders, for practical purposes the diagnostic criteria of DSM–IV (American Psychiatric Association, 1994; Box 1) or ICD–10 (World Health Organization, 1992) are generally used. Both divide anxiety into a series of sub-syndromes with clear operational criteria to assist in distinguishing each. At any time many patients will have symptoms from more than one syndrome, but eliciting the primary diagnosis is important as this markedly influences the choice of treatment.

In this paper we will describe the key features of each anxiety disorder, emphasising important

Professor David Nutt is Professor of Psychopharmacology and Head of Department of Mental Health, University of Bristol. He supports a multi-disciplinary group exploring the mechanisms of action of treatments for anxiety and depression. He has researched the biological basis of anxiety disorders and the mode of action of benzodiazepines and antidepressants. Dr Caroline Bell is Carey Coombs Research Fellow, Bristol Royal Infirmary, United Bristol Healthcare (NHS) Trust and Honorary Lecturer, Department of Mental Health, University of Bristol. She has studied the biological basis of panic disorder and social phobia, and potential new treatments for these disorders. Her current research is in the mode of action of antidepressants, particularly the adaptive changes in 5-HT transmitter function.

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Box 1. DSM–IV classification of anxiety disorders

Panic disorder with or without agoraphobia
Attacks of acute anxiety with pronounced physical and autonomic symptoms (panic attacks); often with marked avoidance of public places such as supermarkets, buses, underground transport (i.e. agoraphobia)

Social phobia
Fear of public scrutiny and possible humiliation; physical symptoms especially blushing, sweaty tremor and speech block

Post-traumatic stress disorder (PTSD)
Anxiety following severe trauma such as assault or accident; symptoms include tension, irritability and startle, insomnia, flashbacks and nightmares, avoidance of things associated with the trauma

Acute stress reaction
Anxiety in response to recent extreme stressor, e.g. loss of job, death of close relative. Can evolve into one of the below

Generalised anxiety disorder (GAD)
Chronic worry about the future with tension, insomnia, autonomic symptoms

Specific phobias
Circumscribed fear of objects such as snakes and spiders

factors that help in diagnosis. We will then give a practical description of the use of medication in the different conditions, including choice of medication, dose and duration of treatment, and what to do if patients fail to respond.

Panic disorder

The essential feature of panic disorder is the presence of recurrent, unexpected panic attacks. These are discrete periods of intense fear accompanied by characteristic physical symptoms. The first panic attack often occurs 'out of the blue' but may subsequently become associated with specific situations (e.g. a bus, a crowded shop, etc.). Anticipatory anxiety and avoidance behaviour develop in response to this.

The importance of careful history-taking cannot be over-emphasised. Particularly useful areas to cover and questions to ask are listed in Box 2, the answers to which should allow differentiation from social phobia (see below) and generalised anxiety disorder (GAD) (see below). Other conditions that may present with panic attacks and need to be excluded include alcohol withdrawal, caffeinism, hyperthyroidism and, rarely, phaeochromocytoma.

Patients experiencing panic attacks often do not know what is happening to them and, because of the somatic nature of the symptoms, usually present to non-psychiatric services. Consequently, they are either extensively investigated or, at the other extreme, told that there is nothing wrong with them – neither approach being very helpful. Education of the medical profession and public about the symptoms of panic, together with careful history-taking, should reduce the likelihood of this occurring and, therefore, improve patient management.

Treatment

The choice of drug treatment for panic disorder is between a fast-acting benzodiazepine such as alprazolam, and a drug with delayed efficacy but

Box 2. Key questions to help differential diagnosis

Description of where the first panic attack occurred – panic disorder (e.g. bus, shopping centre) *v.* social phobia (e.g. giving a presentation)

Establishing what the patient thinks is the worst thing that could happen to them in the middle of a panic attack – panic disorder (e.g. have a heart attack) *v.* social phobia (e.g. make a fool of themselves)

Are some symptoms particularly prominent, e.g. blushing, trembling, sweating, 'drying up' when speaking – all typical of social phobia

If they have to go into an anxiety-provoking situation, is it better if they have someone with them (typical of panic disorder) or do they prefer to be on their own (more typical of social phobia)

If anxiety is a permanent feature, is it anticipatory anxiety, i.e. fear of having another panic attack (typical of panic disorder), fear of being the centre of attention (indicative of social phobia) or a more general, all-pervasive fear (typical of generalised anxiety disorder)

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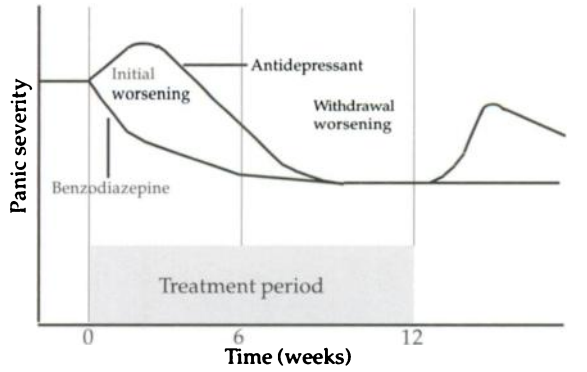

Fig. 1 Time course of panic treatment

fewer problems of withdrawal such as a TCA or SSRI (Klein, 1964; Nutt *et al*, 1995). The different time courses of these two classes of agent in panic disorder is shown in Fig. 1. Benzodiazepines work quickly to reduce panic frequency and severity and continue to be effective for many months, with only a few patients displaying any significant therapeutic tolerance. On withdrawal, however, there is an increase in the symptoms of anxiety and panic attacks in some patients (Rickels *et al*,1990). This is seen even when withdrawal is gradual, and reaches a maximum when the final dose is stopped (Tyrer *et al*, 1983; Schweizer *et al*, 1990). Although a withdrawal syndrome is not seen in all patients, in some it can lead to them continuing to take the drug long-term (Petursson & Lader, 1984; Schweizer *et al*, 1993).

In contrast, antidepressants have almost the opposite profile. On initiation of treatment they can cause an increase in anxiety and panic frequency, which can result in patients stopping their medication after even a single dose. This provoking action usually lasts for only two to three weeks, after which time panic frequency and severity is improved (Fig. 1), but patients need help to stay on the treatment over this period. The doctor needs to give a clear and thorough explanation of the likely time course of events, and to reduce the likelihood of initial exacerbation the antidepressant should be started at half the minimum dose.

Our clinical practice is to use a TCA or SSRI as described above. We get patients to cut the minimum strength tablets in half and to take this for one week, increasing to one tablet and then upwards in weekly increments until a response is achieved or unwanted effects emerge. In addition, if there is anxiety exacerbation, a short course of a long-acting benzodiazepine can be used for the first few weeks. The dose of antidepressant required to treat panic disorder is generally as high or higher than that needed for depression, and maximal benefit may not emerge until 8–12 weeks. Patients should therefore be treated at as high a dose as is tolerated for this length of time. If there is no response, then the monoamine oxidase inhibitor (MAOI) phenelzine should be tried at doses of up to 105 mg/day, with appropriate information about side-effects (especially postural hypotension) and food and drug interactions (Tyrer *et al*, 1973). The MAOIs tend to produce less exacerbation at the beginning of treatment than the other antidepressants but can increase anxiety and panic in more sensitive individuals. The reversible monoamine oxidase inhibitor (RIMA) moclobemide is an alternative, with significant advantages in terms of unwanted effects and safety.

A sub-group of patients seem only to benefit from the long-term use of combination treatment such as an antidepressant and a benzodiazepine, and should therefore be treated with this, but only after the other options have been tried. Although antidepressants are effective in the treatment of panic disorder in the absence of depression, when the two conditions do coexist the arguments for the use of antidepressants rather than benzodiazepines are very strong.

Social phobia

The essential feature of social phobia is a marked and persistent fear of performance situations when patients feel they will be the centre of attention and will do something humiliating or embarrassing. The situations that provoke this fear can be quite specific, (e.g. fear of public speaking) or general, involving fear of most social interactions (e.g. initiating or maintaining conversations, participating in small groups, dating, speaking to anyone in authority). Exposure to the feared situation almost invariably provokes anxiety. Symptoms are similar to those experienced by patients with panic attacks but some seem to be particularly prominent and difficult – blushing, tremor, sweating and a feeling of 'drying up' when speaking. The differentiation of social phobia from panic disorder can at first appear difficult but this need not be the case. A careful history should make the diagnosis clear and should include the following details: the occurrence of these symptoms; the focus of the fear; establishing which situations are particularly anxiogenic; and other key questions such as whether being accompanied makes things better (the patient with social phobia finds having someone with them makes everything much worse), what is the most difficult part of a supermarket checkout queue (the social phobic will find being at the front and paying most stressful) and where they sit in a restaurant (the patient with social phobia will sit at the side or back to avoid being

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noticed, whereas the patient with panic disorder will sit near the door).

Treatment

Issues involving the treatment of social phobia have been hampered not only by the lack of recognition of the condition but also by the fact that clinicians have tended to view social phobia as a personality trait related to shyness and not as a condition responsive to medication. The drugs with established efficacy in social phobia are the MAOI, phenelzine, and the RIMA, moclobemide. These both achieve equivalent degrees of improvement, the differences between them being the faster onset of action of the MAOI and its much greater incidence of adverse effects (Versiani *et al*, 1992). Other drugs that have also been reported to be beneficial include the SSRIs and some high-potency benzodiazepines but the evidence for their use is so far less conclusive. Beta-blockers continue to be widely used despite the fact that they have no proven efficacy in social phobia. Their only place is in the treatment of specific performance anxiety, for example in musicians, when management of the tremor is crucial.

Our practice is to use moclobemide as the drug of choice because of its tolerability and the lack of requirement for dietary restrictions. The starting dose should be 150 mg b.d., increasing to 450 mg/day after one week, and then to 600 mg/day a week later. This should be continued for at least 12 weeks because improvements are often delayed for this length of time. If there is no response, the patient should be changed to an SSRI, and this used as in panic disorder but without the initial half-minimal dose. Again, treatment should be continued for at least 12 weeks.

Post-traumatic stress disorder

The essential feature of post-traumatic stress disorder (PTSD) is the development of characteristic symptoms following exposure to an extreme traumatic stressor. The symptoms include persistent re-experiencing of the traumatic event, persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness, and persistent symptoms of increased arousal. In taking a history the association with the event is usually obvious. PTSD is differentiated from acute stress disorder by its persistence – the symptoms of acute stress disorder resolve within four weeks. Depression quite commonly coexists with PTSD and should be enquired for in the history.

In the current climate of litigation it is likely that PTSD will be cited frequently in the courts. If it is to retain its validity as a serious and disabling disorder, we need to ensure that the diagnosis is not in doubt and that clear criteria for its diagnosis are fulfilled.

Treatment

The treatment of this condition is poorly researched; there have been no properly controlled trials and almost all open trials have been conducted on patients a long time after the causative incident, which may explain the poor outcome. A range of drugs have been reported to be helpful, including benzodiazepines, TCAs, SSRIs and MAOIs. Treatment immediately following the incident should probably be a short course of a benzodiazepine to promote sleep and to help minimise mental rehearsal of the trauma that may lead to long-term problems. Long-term therapy appears to be indicated, with doses in the same range as for other anxiety disorders. Our practice is to use an SSRI or TCA as first-line treatment, with the addition of a benzodiazepine for more enduring cases.

Acute stress disorder

This is anxiety in response to a recent extreme stress. Although in some respects it is a normal and understandable reaction to an event, the problems associated with it are not only the severe distress the anxiety causes, but also the risk that it may evolve into a more persistent state.

Treatment

Short-term benzodiazepines are the agents of choice for treating patients with overwhelming anxiety that needs to be brought under rapid control. They are particularly useful for the anxiety and sleep disturbance that commonly occur and which, if left untreated, severely affect the individual's ability to cope after a trauma (Forster & Marmar, 1991). It may well be that treating these symptoms when they are severe reduces the likelihood of their progression to a more persistent anxiety state. Drugs with a slow onset of action such as oxazepam cause less dependence and withdrawal than those with fast brain entry such

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as diazepam and lorazepam, and so are probably the drugs of choice. There is the risk, however, that some patients once started on a benzodiazepine will find it hard to stop; benzodiazepines should therefore be reserved for patients where extreme distress is disrupting their normal coping strategies.

Generalised anxiety disorder

The essential feature of GAD is chronic anxiety and worry. To the non-sufferer the focus of the worry often seems to be trivial, such as getting the housework done or being late for appointments, but to the patient it is insurmountable. The anxiety is often associated with other symptoms including restlessness, difficulty concentrating, irritability, muscle tension and sleep disturbance, which may complicate the presentation. The course of the disorder is typically chronic with exacerbations at times of stress, and is often associated with depression.

In establishing the diagnosis it is important to exclude medical conditions such as hyperthyroidism and caffeinism, as well as other anxiety disorders, particularly panic disorder. This can be done from the history by establishing whether the anxiety is in the form of panic attacks with associated anticipatory anxiety (panic disorder) or of a more chronic nature with worsening at times of stress (GAD).

Treatment

Historically, benzodiazepines have been seen as the most effective treatment for GAD. They rapidly reduce anxiety and improve sleep and somatic symptoms. Consequently, patients like taking them. They do, however, have problems associated with them including side-effects, cross-tolerance with other CNS depressants and the contentious issues of tolerance, dependence and withdrawal reactions, factors which may be particularly relevant in view of the chronic nature of GAD.

Buspirone was the first non-benzodiazepine to demonstrate efficacy in GAD but is generally less effective and slower in action than benzodiazepines and tends to cause insomnia rather than sedation. Its advantages are that it does not seem to cause dependence or withdrawal reactions and does not interact with alcohol. It appears to be less effective in patients who have previously received benzodiazepines and is therefore probably best used in benzodiazepine-naive patients.

A number of studies have shown that TCAs are effective in GAD (Rickels *et al*, 1993) and seem to be particularly good for chronic tension. Compared with benzodiazepines they have a slower onset of action and tend to be less well tolerated by patients but they are not associated to the same extent with the problems of dependence and withdrawal. It is likely that the SSRIs might be similarly beneficial with fewer side-effects than the TCAs. No controlled studies have as yet been carried out with

Table 1. Benzodiazepines, buspirone and antidepressants compared in the treatment of anxiety

	Benzodiazepines	Buspirone	Antidepressants
Onset	Fast	Slow	Slow
Exacerbation	No	Rarely	Sometimes
Tolerance	Rarely	No	No
Withdrawal			
Acute	Yes (@ 30%)	No	Yes (?%)
Chronic	Probable (@ 10%)	No	No
Abuse liability	Low	Zero	Zero
Interactions			
Ethanol	Marked	Slight	Slight
MAOIs	No	Not known	Marked
Side-effects			
Sedation	Yes	No	Yes (TCAs)
Amnesia	Marked	No	Mild
Cardiovascular	No	No	Marked (TCAs)
Depression	Sometimes	No	No
Anti-panic	Rarely	No	Yes

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SSRIs in this disorder, although our clinical experience suggests that they are helpful. The risks and benefits of each of these treatments is summarised in Table 1.

In view of the chronic nature of GAD, a delayed response is not as critical as with acute situational anxiety. Taken together with the drawbacks of long-term benzodiazepine use, this suggests a sensible approach (especially in benzodiazepine-naive patients) is to start with a trial of buspirone for 6–8 weeks at a dose of at least 30 mg/day. The dose should be built up gradually over two to three weeks to minimise any unwanted actions, and patients should be warned not to expect an immediate benefit. Those not responding should probably be tried with an antidepressant (TCA or SSRI), again for 6–8 weeks at the full therapeutic dose. In patients who remain unresponsive or in those with a previous long history of benzodiazepine use, benzodiazepines may be the only medication that provides any relief and in this group can be used as the sole treatment, although attempts to switch to buspirone or an antidepressant should be made before coming to this decision. The duration of treatment depends on the nature of the underlying illness. If symptoms are intermittent, and are triggered by anxiety-provoking situations, then intermittent benzodiazepines for a few weeks may be sufficient to treat these exacerbations. More typically, GAD requires longer-term treatment over a period of 6–8 months with gradual tapering of medication after this. In some patients this will be sufficient but in others symptoms may return. The latter group of patients often experience severe, unremitting anxiety and require maintenance benzodiazepines in an analogous way to their long-term use in epilepsy. If benzodiazepines are not prescribed, these patients will treat themselves using the most widely accessible, easily available anxiolytic – alcohol. Since alcohol is highly toxic to many body systems, clinically supervised benzodiazepine use is definitely preferable.

Specific phobias

A specific phobia is a fear of a particular object or situation. The diagnosis is not usually in doubt.

Treatment

Although there have been few controlled trials (none of the newer drugs) it is generally accepted that phobias do not respond to drug treatment unless they occur secondarily to another anxiety disorder or depression. Exposure therapy is the treatment of choice and can be very effective. It does, however, produce severe anxiety, which in some patients limits their ability to fully engage in therapy. In these patients benzodiazepines may have a facilitating role.

Common themes in the pharmacological treatment of anxiety disorders

Pharmacological treatment options for the different anxiety disorders are summarised in Table 2.

The dose of antidepressant medication required for the effective treatment of anxiety is typically higher than that needed for depression. It also takes longer for improvements to be seen, usually at least 4–8 weeks (rather than the 2–3 weeks' delay in depression). It is also important to maintain the patient on as high a dose as can be tolerated for at least 8 weeks before changing medication. Patient education is crucial in obtaining this cooperation.

Duration of treatment is often a tricky issue. The prevailing tendency, derived from concerns about

Table 2. Pharmacological treatments of anxiety

Anxiety subtype	Treatment	Comments
Acute stress	Benzodiazepines	For a few weeks only
Generalised anxiety disorder	Buspirone	More effective in benzodiazepine-naive patients
	Benzodiazepines	
	TCAs/SSRIs	
Panic disorder	TCAs	May exacerbate anxiety at start of treatment
	SSRIs	May exacerbate anxiety at start of treatment
	Benzodiazepines	Problems on withdrawal
Social phobia	MAOIs/RIMAs	Continue at least 12 weeks
	?SSRIs	
Post-traumatic stress disorder	?TCAs/?SSRIs/?RIMAs	Start as soon as possible after trauma
	Benzodiazepines	Can be used acutely

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benzodiazepines, has been to use short courses of treatment, usually 6–10 weeks. However, for many anxiety states this is not long enough to maximise response. Our clinical practice is to apply the same rules as in the treatment of depression. Thus, for the first episode we treat patients for at least 6 months and then tail off medication over a further 4–8 weeks if they are well. We treat patients with recurrent illness for one to two years to enable them to learn and utilise psychological approaches to their problems. In many cases, however, the illnesses are life-long and so maintenance treatment is justified if it has made a significant improvement in the patient's well-being and function.

The combination of medication with psychological techniques is likely be most beneficial, especially in resistant cases. We often see patients who are so incapacitated by their anxiety that they are quite unable to participate in any group or individual work. Medication may allow them to attend these and so benefit from the psychological approaches.

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Multiple choice questions

1. Established effective treatments for social phobia include:
   a TCAs
   b MAOIs
   c self-help groups
   d RIMAs
   e relaxation.

2. Guidelines for effective treatments of panic disorder include:
   a TCAs – start at low dose
   b SSRIs – start at high dose
   c behavioural therapy
   d treatment with antidepressants for 2 months
   e β–blockers.

3. Antidepressant treatment of anxiety compared with depression typically:
   a requires higher doses
   b requires equal or longer duration of treatment
   c therapeutic response is quicker
   d the proportion of patients reporting jitteriness is higher in depression
   e the sedative TCAs are more effective than SSRIs.

4. Effective treatments for GAD include:
   a benzodiazepines
   b buspirone
   c TCAs
   d β–blockers
   e high-dose neuroleptics.

5. Effective treatments for specific phobia include:
   a relaxation
   b cognitive therapy
   c buspirone
   d exposure therapy
   e flooding.

MCQ answers

1	2	3	4	5
a F	a T	a T	a T	a F
b T	b F	b T	b T	b F
c F	c T	c F	c T	c F
d T	d F	d F	d F	d T
e F	e F	e F	e F	e T

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