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Pharmacotherapy for anxiety disorders: using the available drugs

P. Tyrer

The treatment of anxiety is one of the more contentious issues in therapeutics. It is also one of the most important, as pathological anxiety is such a common symptom in the population. The recent Office of Population Censuses and Surveys survey of psychiatric morbidity indicated that one in eight of all those interviewed had an anxiety disorder of sufficient severity to receive a formal diagnostic label in the week before interview (Meltzer *et al*, 1994). Clearly, only a proportion of these should be treated with drugs, and selection for pharmacotherapy is one of the more difficult issues in clinical practice. It is a matter of some concern that changes in the National Health Service are increasingly shifting the onus of responsibility for treatment from the psychiatrist to the general practitioner. As a consequence, it behoves both disciplines to keep liaison active, so that best practice can be maintained from whatever source it is being provided.

Before discussing the individual drugs used for treating anxiety it is useful to examine when it is appropriate (and when it is inappropriate) to treat anxious patients with drugs (Box 1). The diagnosis of anxiety disorders is still in a somewhat confused state and it is reasonable to concentrate on the main symptoms being treated rather than the specific diagnostic labels attached to each condition (Table 1). In general, it is more appropriate to treat anxiety with drugs when it is symptomatically severe and handicapping, when short-term treatment is predicted, and when there is no past history of drug abuse or dependent behaviour. As this also has a bearing on the choice of anti-anxiety drug it is important to make an adequate assessment of the

Box 1. Questions to ask before prescribing an anti-anxiety drug

Is short-term (<4 weeks) or long-term treatment expected?
Is this patient likely to have difficulty in stopping drug treatment?
What mode of treatment does the patient prefer?

Table 1. Selection of drug treatment in anxiety disorders

Main clinical feature	Psychological treatment	Drug treatment
Severity of symptoms	Preferred in mild to moderate severity	Preferred in most severe forms of anxiety
Dependent personality	Preferred but time-limited	All potentially addictive drugs to be avoided
Panic	Preferred when good cognitive therapy and anxiety management treatment is available	Used as prophylactic for future panic attacks
Worry	Generally preferred	Generally to be avoided
As part of another psychiatric syndrome	Choice dependent on main treatments for underlying syndrome	May be treated symptomatically with drugs in the short term

Peter Tyrer is Professor of Psychiatry, Imperial College School of Medicine at St Mary's, London W2 1PD.

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Table 2. Classification of anti-anxiety drugs

Drug group	Common members of group	Main mechanism of action
Sedative/hypnotic	(a) Benzodiazepines:diazepam, temazepam, triazolam, lorazepam (b) Barbiturates:amylobarbitone sodium (c) Cyclopyrrolones: zopiclone, zolpidem (d) Propanediols: meprobamate (e) Others: chlormezanone, chlormethiazole, chloral hydrate	Facilitation of γ-aminobutyric acid (GABA) transmission
Azospirodecanediones	Buspirone	Partial agonists of 5-HT_{1A} receptors
Beta-blocking drugs	Propranolol	Peripheral beta-blockade
Antihistamines	Promethazine, chlorpheniramine	Histamine receptor blockade
Antipsychotic drugs	Chlorpromazine, flupenthixol	Not fully established but could include dopamine and histamine receptor blockade
Antidepressant drugs	(a) Tricyclic antidepressants: amitriptyline, dothiepin, lofepramine (b) Selective serotonin reuptake inhibitors: fluoxetine, paroxetine (c) Monoamine oxidase inhibitors: phenelzine, moclobemide	Probably linked to changes in noradrenergic and serotonin receptors after regular treatment for three or more weeks. Short-term relief of anxiety may also be noticed immediately with the more sedative tricyclic antidepressants

nature, likely duration and background to the problem before treatment is given.

The main drugs used for treating anxiety (and insomnia) are summarised in Table 2. Although many of these are marketed specifically for anxiety or insomnia, their similarities are too great to justify separate discussion. All anti-anxiety drugs may be effective hypnotics, and all hypnotic drugs are effective in relieving anxiety. There are, however, some important differences, largely concerned with the sensorimotor impairment created by some of the tricyclic drugs discussed below. There has also been an important shift in recent years in attitudes towards treating anxiety. Whereas treatment in the past was largely confined to those drugs which had sedative or hypnotic effects, it is now realised that many other drugs which are not licensed for the treatment of anxiety are also effective anxiolytics and, in some cases, may be better than conventional sedative–hypnotic drugs (Hudson & Pope, 1990; Tyrer & Hallström, 1993).

Clinical use

Anxiety is a common symptom in psychiatric disorder but is rarely continuous and persistent at the same level of severity. In view of this, and the general principles outlined in Box 2, it is wise to keep the dosage and duration of treatment under regular review. It has been unfortunate that for much of the history of anti-anxiety drug treatment in the past 30 years these general principles have not been acknowledged adequately. As a consequence, for far too long patients were assumed to have 'chronic' anxiety and had long-term identical prescriptions.

Benzodiazepines

These drugs continue to be the most popular anti-anxiety drugs although their use has declined steadily over the past decade because of concerns over dependence. This concern has been fuelled more by

Box 2. General principles of anti-anxiety drug treatment

All centrally acting anti-anxiety drugs that have immediate effect should be regarded as addictive

Tolerance to anti-anxiety effects is common after repeated dosage

Anxiety is a fluctuating mood and does not need continuous treatment

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media interest than by psychopharmacologists, and is illustrated in Fig. 1. This shows that the major reduction in prescription of benzodiazepines in the 1980s was in those benzodiazepines prescribed as anxiolytics, whereas later in the decade concern over temazepam and triazolam led to reduction in the prescriptions of benzodiazepines normally prescribed for insomnia. As the risks of these drugs are almost identical for both indications it would have been expected that both groups of drugs would show similar rates of decline.

Although the main uses of benzodiazepines are for treating insomnia and anxiety, they are also useful in reducing aggression, where they have formed a major part of rapid tranquillisation policies (Pilowsky *et al*, 1992). Their muscle relaxant and anticonvulsant properties are also clinically useful. Intravenous diazepam remains one of the important mainstays of treatment for status epilepticus. They are also used for premedication in anaesthesia and some short-acting benzodiazepines (e.g. midazolam) are used for this purpose only.

Benefits

If treatment of anxiety is contemplated for a short time only, benzodiazepines are the most effective drugs available and are generally superior to psychological treatments (American Psychiatric Association Task Force, 1990). Once treatment continues beyond two weeks in regular dosage, however, both psychological and other drug treatments, particularly antidepressants, become more effective (Kahn *et al*, 1986; Tyrer *et al*, 1988). This is not only because other forms of treatment have a delayed onset of action, but also because tolerance develops to all the effects of benzodiazepines at a variable rate after repeated treatment (File, 1985). Benzodiazepines are therefore most appropriate for the emergency or planned short-term treatment of anxiety and insomnia, rather than long-term use. Despite their speed of action, however, they are still insufficiently rapid in their onset of clinical effects to treat attacks of panic which reach a peak within a few minutes of symptoms first manifesting.

Benzodiazepines are very safe when taken singly in overdosage, have few adverse effects in normal dosage and are liked by patients. This last feature is often forgotten by authorities who are not day-to-day practitioners, but is extremely important. Compliance is seldom a problem with benzodiazepines; although this can be viewed negatively (as a problem of dependence), it is valuable if a short-term, reliable treatment for anxiety or insomnia is needed.

Risks

As already indicated, in acute dosage there are few risks with benzodiazepines. This group as a whole

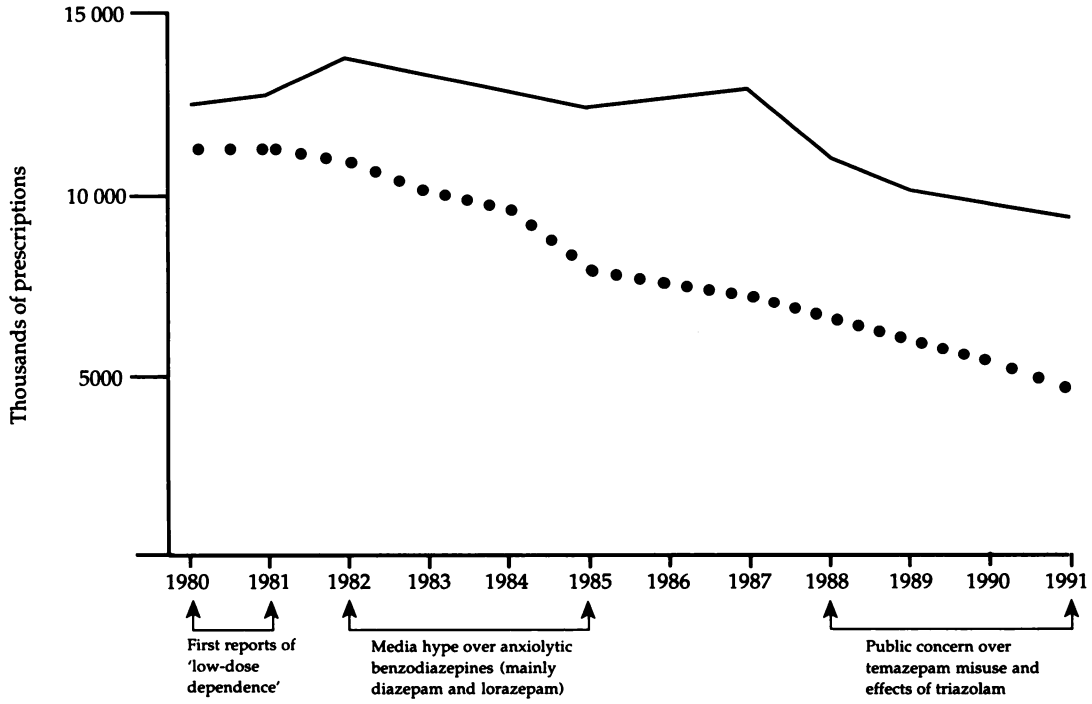

Fig. 1 Factors affecting the decline in number of prescriptions for benzodiazepines in England, 1980–1991. ——, hypnotics; • • , anxiolytics. Data courtesy of the Department of Health.

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is remarkably safe, although there can be additive effects with alcohol and other depressant drugs, particularly other drugs of the sedative–hypnotic type. A major indication of excessive dosage is drowsiness. Anterograde amnesia (i.e. amnesia from the time of onset of drug action) may also be a problem in higher dosage, although it may be a beneficial effect in some conditions (e.g. premedication for dental phobia).

All benzodiazepines have the propensity for psychomotor impairment. This affects in particular tasks which need coordination and vigilance (e.g. driving, monitoring machinery) and performance of these may be impaired by treatment. Because anxiety fluctuates considerably from hour to hour, unwanted effects such as psychomotor impairment may be noted after acute anxiety has passed but the effects of the drug persist. This is more likely with long-acting benzodiazepines (see below) and is most marked in the demonstration of 'hangover' effects of hypnotic benzodiazepines.

The risks with benzodiazepines become much more prominent once regular prescription is continued for four weeks or longer. This is mainly because of the risk of dependence. Dependence on benzodiazepines is shown mainly by the exhibition of a withdrawal syndrome after reduction or discontinuation of the drug (Hallström, 1993). The other major features associated with dependence (craving, drug-seeking behaviour, escalation of dosage and marked tolerance) are not nearly so marked, although it is now becoming appreciated that tolerance is a much greater problem than was once thought. There is also some evidence that the more potent benzodiazepines, particularly those with a short elimination half-life such as triazolam and lorazepam, may carry greater risks of dependence than others (Tyrer & Murphy, 1987).

The withdrawal syndrome is characterised by symptoms that roughly fall into three categories:

(a) those that are typical of anxiety, such as palpitations, trembling, panic, dizziness, nausea and other bodily symptoms, together with depressed mood;

(b) symptoms of perceptual disturbance, including depersonalisation and derealisation, hypersensitivity to all the senses, particularly to auditory stimuli, and distorted perception of height and space, tinnitus, itching sensations, a peculiar taste in the mouth, and influenza-like symptoms; and

(c) epileptic seizures, confusional states or paranoid psychotic episodes.

The third of these is unequivocal evidence of a withdrawal syndrome, the second is likely evidence when two or more symptoms are present, and the first is not in itself indicative of a withdrawal reaction. However, if any of the symptoms occur only shortly after withdrawal or reduction it is likely that such symptoms are those of a withdrawal reaction.

Dependence can begin after as little as four weeks in regular dosage and there have been claims for withdrawal symptomatology following a single dose of the short-acting drug triazolam (Morgan & Oswald, 1982), in which symptoms the day following a nightly hypnotic dose can be regarded as those of withdrawal. This is not generally agreed but after stopping regular treatment after four to six weeks there is unequivocal symptomatic change indicative of a withdrawal reaction (Power *et al*, 1985). Symptoms of withdrawal normally begin within 24 hours of stopping short-acting benzodiazepines and up to six days after stopping a long-acting one. The terms 'rebound insomnia' and 'rebound anxiety' are sometimes used in the context of withdrawal reactions (e.g. Kales *et al*, 1978). However, there is no fundamental qualitative difference between the symptoms of rebound and those of withdrawal. It is just more common to use the term withdrawal when drugs have been taken for a longer period when the symptoms are greater after stopping the drug. 'Rebound' is also a somewhat unfortunate word to describe withdrawal phenomena. The word 'overshoot' is perhaps a better one, as it is only in those cases where the symptoms after withdrawal are worse than those before treatment that an unequivocal withdrawal reaction can be identified. The withdrawal syndrome lasts for up to five weeks after stopping the drug and there is some evidence that a 'post-withdrawal syndrome' exists, with symptoms persisting for up to two years after all traces of the drug have been eliminated from the body (Tyrer, 1991).

The risks and benefits of benzodiazepines in the treatment of anxiety are summarised in Box 3.

Non-benzodiazepine sedatives

Because all these drugs act primarily by facilitating GABA transmission, they have the same risks as benzodiazepines as well as some of their advantages. All carry the major risk of pharmacological dependence and it is likely that they will not differ significantly from the benzodiazepines in this respect. These risks have been established for the propanediols such as meprobamate and for chlormethiazole but not for chlormezanone, which, despite its apparent efficacy, has not been popular as an anxiolytic. The cyclopyrrolones such as zopiclone and zolpidem (both used as hypnotics) and suriclone (used for anxiety) have shown fewer sedative effects,

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Box 3. Risks and benefits of benzodiazepines

Benefits
Quick-acting
Wide safety margin
Liked by patients

Risks
Sensorimotor impairment
Pharmacological dependence
Anterograde amnesia

but there is little evidence that they are less likely to cause dependence (Goa & Heel, 1986).

Azaspirodecanediones

These comprise several members, of which the best known is buspirone, which have anti-anxiety (and possibly antidepressant) properties. They differ from sedative hypnotics in having no muscle relaxant or anticonvulsant effects, no obvious risk of dependence and a delayed onset of clinical action (Lader, 1988).

For reasons that are not fully understood, patients who have previously taken benzodiazepines tend to do badly on buspirone. This may be because buspirone differs from benzodiazepines in producing a dysphoric rather than a euphoric effect after initial administration, although there may be other factors also, including the possibility that benzodiazepines have a long-term influence on benzodiazepine receptors that continues long after the drug has been eliminated from the body (Hallström, 1993). It is therefore not surprising that buspirone is not a good benzodiazepine alternative and tends to be ineffective for treating benzodiazepine withdrawal symptoms (Ashton *et al*, 1990).

Beta-blocking drugs, antihistamines and other anti-anxiety drugs

Beta-blocking drugs have been in use for the treatment of some forms of anxiety for the past 30 years and they now have an established place in the treatment of anxiety in clinical psychiatric practice. This remains a relatively limited one even though they are demonstrably more effective than placebo (Kathol *et al*, 1980; Tyrer, 1992). It is likely that their major effects are peripheral and symptoms mediated through beta-receptors are most likely to be helped. These include awareness of fast heart beat, flushing, palpitations and tremor. The most obvious use of beta-blockers is in the treatment of performance anxiety in acute stress situations, such as speaking in public and playing a musical instrument. If avoidance of tremor is particularly important (e.g. playing the violin) beta-blocking drugs may be of particular help. The main advantage of beta-blockers is that they have no sedative effects or sensorimotor impairment and have no risk of dependence (Morgan & Tyrer, 1994).

Antihistamines are well-established drugs with a long history of successful use in the treatment of mild anxiety and insomnia from childhood onwards. The sedative effects are rapid in onset but drowsiness is common in doses therapeutic for anxiety. Although the dependence risk of these drugs is low there is still some potential for abuse, with both cyclizine and diphenhydramine being reported as addictive. However, problems of withdrawal following long-term low-dose treatment have not been reported. The main effects of anti-anxiety drugs are summarised in Table 3. Because of the dependence risks of the sedative–hypnotic group it is wise to restrict treatment to several weeks as a maximum or to use the drugs in intermittent dosage to avoid the development of dependence. If longer-term treatment is required, the antidepressants (see below), buspirone or beta-blocking drugs (for the special forms of anxiety indicated above) are preferable.

Choice of treatment in anxiety

When deciding what to prescribe for an anxious patient the clinician needs to have good knowledge of the context, the nature and the likely duration of symptoms.

Context

All too often anxiety as a symptom is treated in isolation from its context. Anxiety is ubiquitous and easily identified, but may often hide other more important symptoms. When depression is noted together with anxiety it is reasonable to treat both conditions with an antidepressant; when anxiety is linked to the fear arising from psychotic symptoms it is equally appropriate to use an antipsychotic drug for anxiety relief; and when associated with overeating an SSRI such as fluoxetine is indicated.

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Table 3. Comparison of the issues determining the choice of an anti-anxiety drug

Drug group	Speed of action	Sedation and sensorimotor impairment	Risk of dependence	Efficacy	Main indications
Sedative/ hypnotic	Fast (<2 hours)	Significant but dose-related	Relatively high in long-term treatment	Excellent	Time-limited treatment (e.g. alcohol withdrawal)
Azospiro-decanedione	Fairly slow (2–5 days)	Very little	Very low	Good	Anxiety in abuse-prone situations (e.g. chronic alcohol abuse)
Antipsychotic	Fairly slow	Little in low dosage	Very low	Fair	Anxiety in presence of psychotic symptoms
Antihistamine	Fast	Present to some degree	Low	Fair	Mild anxiety and insomnia
TCAs	Slow (2–5 weeks)	Variable	Very low	Good	Persistent anxiety/panic associated with chronic insomnia
SSRI and reversible MAOI	Slow (2–5 weeks)	Very little	Low	Very good	Yet to be determined
Beta-blockers	Fast	None	None	Good in some instances	Performance anxiety

Nature of symptoms

Anxiety includes the symptoms of fear, panic, worry, tension and situational anxiety (phobias). It is also divided into different diagnostic groups that this author does not feel are particularly helpful in choosing treatment. However, the choice of a beta-blocking drug for performance anxiety when sedation must be avoided, of an antidepressant for persistent and incapacitating generalised anxiety, of a benzodiazepine for acute anxiety associated with a traumatic event, and of buspirone for patients with known risk of dependence (Table 3) are logical and supported both in practice and from formal trials.

Duration of symptoms

It is often extremely difficult to hazard the likely duration of symptoms at the time a drug treatment is first prescribed but it is none the less a worthwhile enterprise. Put more simply, the question, "Will I be able to stop treatment before the end of four weeks?" is one that will answer the most important question. If the answer to the question is "No", it is best to avoid a sedative–hypnotic drug because of the risk of dependence. If the answer is "Yes", a benzodiazepine or similar drug may well be preferred.

This decision becomes more complex after chronic treatment, when a patient may well have been tried on a range of psychological and physical treatments. If a good response has been made to a benzodiazepine, clinicians can rightly argue that long-term benzodiazepine use is justified even if dependence follows.

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Multiple choice questions

1. The following drugs have proven effectiveness as anxiolytics:
   a beta-blocking drugs
   b lithium carbonate
   c tryptophan and related drugs
   d tricyclic antidepressants
   e phenothiazines.

2. Buspirone:
   a acts by stimulating GABA receptors
   b is liable to lead to dependence in regular dosage
   c is effective in generalised anxiety disorder
   d is helpful in withdrawing patients from benzodiazepines
   e does not interact significantly with alcohol.

3. Tricyclic antidepressants:
   a are not effective in anxiety disorders unless depression is present
   b may reduce anxiety by sedation
   c are more effective than benzodiazepines in long-term treatment
   d require a lower dose for treatment of anxiety compared with depression
   e are superior to SSRIs in the treatment of anxiety.

4. Beta-blocking drugs:
   a are preferred treatment for panic disorder
   b are thought to act mainly by peripheral rather than central beta-blockade
   c have no risk of pharmacological dependence
   d lead to impaired vigilance and concentration
   e may help anxiety within one hour of administration.

5. A schizophrenic patient becomes extremely anxious because of fears created by paranoid delusions. Which of the following treatments might be given to good effect:
   a propranolol 40 mg b.d.
   b droperidol 10 mg b.d.
   c lorazepam 1 mg i.m.
   d promethazine 25 mg b.d.
   e fluoxetine 20 mg o.d.

MCQ answers

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

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