Drugs in the treatment of Anxiety

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This paper reviews the use of different drugs for the treatment of anxiety-related disorders. There are four categories of anxiety-related disorders, each of which responds differently to different drugs. These are: 1) simple phobias; 2) complex phobias and panic disorder; 3) generalised anxiety disorder (GAD); 4) obsessive compulsive disorder (OCD). There appear to be three main types of drug action: 1) symptomatic relief of acute anxiety for which benzodiazepine compounds are the most effective; 2) longer-term amelioration of anxiety in GAD, complex phobias and panic disorder brought about equally by tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI); 3) improvement in OCD for which SSRI, (but not TCA or benzodiazepines) are effective. These observations suggest that the four DSM-IV categories of anxiety conditions differ from one another in their pathophysiology.

Anxiety and fear play a vital role in all human societies. To feel anxious in the face of a threatening stimulus is both normal and appropriate; it is only when the anxiety becomes so severe as to be incapacitating, or arises without reasonable cause, that clinical intervention is indicated. Unfortunately this occurs all too frequently. Epidemiological surveys reveal that anxiety symptoms are common to all societies (see Oakley-Brown et al this issue). In western countries 4-7% of the population experience clinically significant anxiety symptoms in any six month period (Wiessman & Merikangas 1986). About a quarter of those afflicted take tranquillisers, mainly benzodiazepines, on a regular basis - that is between 1-2% of the adult population (Mellinger et al 1984). A recent survey in the UK revealed that 7.7% of the population had taken a benzodiazepine over the course of the previous year: approximately half had done so primarily to help them sleep, the other half to counter anxiety; women outnumbered men in the ratio of 2:1. (Dunbar et al 1989). In a random community study of women in Otago, New Zealand conducted in 1988, 3.3% were found to be taking a benzodiazepine either for anxiety relief (2.4%) or as a hypnotic (0.9%), (S.E.Romans - personal communication). Similar findings have been reported from Australia (Lockwood and Berbatis 1990) and Canada (Busto et al 1989).

Within the overall spectrum of anxiety disorders a number of clinical subcategories have been delineated and defined, as described in the 4th edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association (1994). These include generalised anxiety disorder (GAD), panic disorder, phobic disorders, post-traumatic stress disorder, acute stress disorder, and obsessive complusive disorder (OCD).

Generalised anxiety disorder

This is characterised by generalised and persistent feelings of anxiety and foreboding, not restricted to, or even strongly predominating, in any particular environmental circumstance (ie it is 'free-floating'). Increased distractibility and irritability are frequent, as are impairment of concentration and sleep disturbance. Common autonomic accompaniments are palmar sweating, palpitations, tremulousness, dry mouth and flushing. Patients may also experience a wide variety of other somatic symptoms, the physiological basis of which is obscure. These can include light-headedness, paraesthesiae, hot or cold spells, 'butterfly stomach', frequency of micturition and/or defaecation, and a lump in the throat.

Depressive symptoms may also be present, in which case it is often difficult to decide whether the presenting syndrome is primarily one of anxiety or depression. Some authorities even question the wisdom of trying to distinguish between the various sub-types of anxiety, with or without concomitant depressive symptoms; placing them all in a common category of general neurotic syndrome, in which anxiety, depression and panic symptoms occur in varying combination at different times (Tyrer 1989).

When a patient presents with either the psychological symptoms of anxiety (excessive worrying, inability to concentrate, difficulty in getting off to sleep) or its somatic accompaniments (palpitations, tension headaches, sweaty palms), the first step is to establish whether or not there is an

appropriate environmental cause for these symptoms to arise at that particular time. If so, it may be possible for the situation to be adjusted in such a way that the anxiety-provoking circumstances no longer apply. Recognition of the underlying cause may be itself of considerable therapeutic benefit. Furthermore, in many cases remission occurs spontaneously, without any definitive therapeutic intervention.

If, however, as is so often the case, the causal factors cannot be defined or modified, or there are no adequate grounds for the patient's symptoms, symptomatic relief is the next step. Attempts should first be made to effect this using psychological techniques, including explanation and reassurance, supplemented when necessary with self-help literature and training in relaxation techniques. However, the symptoms may be so obtrusive as to make such an approach inappropriate as the initial treatment. In such cases treatment with an antianxiety (anxiolytic) drug is indicated.

1 Benzodiazepine drugs

Chlordiazepoxide, the first benzodiazepine compound to be marketed, rapidly became very widely prescribed following its launch in 1960. It was followed by diazepam, nitrazepam, medazepam, oxazepam, lorazepam, temazepam, ketazolam and potassium clorazepate. These compounds are 1:4 benzodiazepines and are closely related metabolically to one another. The major metabolite of diazepam is N-desmethyldiazepam (nordiazepam) which is itself pharmacologically active. Metabolites of diazepam and nordiazepam are temazepam and oxazepam respectively, which are also marketed compounds. Potassium clorazepate, is a 'prodrug', that is a compound which is broken down in the gastrointestinal tract to release the active constituent, in this case nordiazepam. It is questionable whether many of these drugs differ significantly from one another, in view of their close metabolic interrelationships. Alprazolam and triazolam are triazalobenzodiazepine derivatives; they are high potency compounds with short half-lives.

It appears that benzodiazepine-GABA receptor complexes at various different brain sites mediate the antianxiety, anticonvulsant, muscle relaxant and hypnotic effects of this group of drugs (see McNaughton, this issue). These complexes are in turn influenced by 5-HT pathways coming from the raphé nuclei, and by noradrenergic pathways from the *locus coeruleus*.

Despite their potential disadvantages (see below), the efficacy of benzodiazepines in the alleviation of anxiety is well-established (Rickels et al 1983, Silverstone & Turner 1995), and they remain the most widely prescribed drugs for anxiety states.

Pharmacokinetics. As might be expected, those 1:4-benzodiazepines that have the common major metabolite nordiazepam, namely diazepam, medazepam, ketazolam and clorazepate, are indistinguishable because the metabolite is active pharmacologically and has a longer half-life than those of the parent compounds. This complicates their pharmacokinetic profiles, because it means that steady-state levels of the parent drugs will be reached before that of nordiazepam, which will continue to accumulate in the plasma and tissues while the drug continues to be administered. These four compounds, therefore, are long-acting and more suitable as antianxiety than as hypnotic agents.

Adverse effects. Overdosage with benzodiazepines, accidentally or for suicidal purposes, produces drowsiness, sleep, confusion, incoordination, muscle weakness, ataxia, diplopia and dysarthria. Serious respiratory depression can occur, but this is unusual in the absence of pre-existing respiratory disease, or unless another central depressant is being taken at the same time. Although relatively safe when taken alone, benzodiazepines may potentiate the central depressant effects of alcohol and barbiturate drugs and such combinations can be dangerous.

Some degree of psychomotor impairment often follows administration of therapeutic doses of benzodiazepines (Hindmarch 1980, Brosnan et al 1986, Woods et al 1992). This has obvious implications for car driving or handling complex machinery (Skegg et al 1979, Silverstone 1988, Brookhuis et al 1990). Many of the relevant studies have been carried out in healthy subjects and do not answer the question whether, in anxious patients, these potentially detrimental effects on psychomotor function outweigh the improvements in performance accompanying a reduction in anxiety (Lader 1993). While some studies show little, if any, impairment of psychomotor function in anxious patients on treatment with a benzodiazepine anxiolytic, other studies do, particularly those carried out in elderly patients (Woods et al 1992).

Benzodiazepine compounds can significantly affect memory processing, mainly by impairing the acquisition of new information, while leaving retrieval process essentially intact (Curran 1991, Lister 1991, Woods et al 1992). This leads to anterograde amnesia, that is, subjects cannot recall information presented to them while in the drugged state. High-potency compounds such as triazolam present a particular risk in this regard, with the elderly being especially susceptible (Bixler et al 1991, Greenblatt et al 1991). In terms of the 'working memory' model, these effects are attributed to impairment of central executive function (Curran 1991). It is uncertain how much of the memory impairment is secondary to the overall sedating action of these drugs, and how much to a more specific action on memory processing (Woods et al 1992). However, benzodiazepines have been shown to affect what is termed 'episodic memory' in normal subjects and in anxious patients, in the absence of any sedative effect (Curran 1991).

Outside the laboratory setting, an indication of the detrimental effects these drugs can have on psychomotor function and cognitive processing in daily living, is afforded by the finding that the number of insurance claims for accidents over a six-month period coming from benzodiazepine users was twice the number coming from non users (Oster et al 1990). Similarly, following the passage of a law in New York State limiting the prescribing of benzodiazepines to a 30-day supply on any one occasion (which resulted in a marked reduction in the number of prescriptions for benzodiazepines), benzodiazepine-related admissions to accident and emergency departments in New York hospitals fell by nearly 40% (Brahams 1990).

Dependence. Within a year of the introduction of benzodiazepines into clinical practice in the United States, it became clear that high-dose treatment can lead to physical dependence (Hollister 1961). However, it was not until the late 1970's that it was recognised how frequently this happens, even with more modest doses if taken for long periods. Up to one third of long-term benzodiazepine users were found to be affected, showing the characteristic symptoms of withdrawal when they attempted to stop taking their anxiolytic drugs (Petursson and Lader 1981; Owen and Tyrer 1983). The withdrawal symptoms include insomnia, anxiety, gastrointestinal symptoms, tremulousness, muscle tension, twitchings, distorted perception (such as hypersensitivity to auditory stimuli and abnormal bodily sensations), and depersonalisation; on occasion frank convulsions can occur.

Patients often mistake this syndrome for a recrudescence of anxiety as it has many similar features. They consequently revert to restarting benzodiazepines for relief. However, in contrast to what usually happens in severe generalised anxiety, the withdrawal symptoms gradually abate over the course of the next two to four weeks without further medication being required; although this may take much longer in some patients.

Dependence is thought to reflect a gradual change in the sensitivity of the benzodiazepine receptor sites in the brain, leading to tolerance to the pharmacological effects of these drugs (Lader & File 1987). Chronic use has been shown to be associated with a gradual diminution in their hypnotic and anticonvulsant effects, and this may also be true, if to a lesser extent, of their antianxiety activities.

Withdrawal symptoms have been observed following treatment with virtually all benzodiazepine compounds. The syndrome is particularly severe when high doses have been given, for example 30 mg or more of diazepam daily. While physical dependence is most usually seen in patients who have been taking benzodiazepines for three to six months, it has been reported after much shorter periods of treatment (Murphy et al 1984, Woods et al 1992). Its appearance on stopping or reducing long-term therapy has led many patients to continue taking a benzodiazepine for years. Therefore, when a benzodiazepine drug is prescribed for anxiety, it should be given in as low a dosage and for as short a time as possible. The patient should be warned against increasing the dose without medical instruction, or abruptly discontinuing it.

It is unknown how many people are physiologically dependent on benzodiazepines. A recent survey in the UK revealed that 1.9% of the adult population (ie some 750,000 people) had taken a benzodiazepine on a daily basis for over a year (Dunbar et al 1989). In the US the proportion of the adult population who are long-term users is 1.6% (Mellinger et al 1984). Assuming 20% of these long-term users are physiologically dependent (Owen & Tyrer 1983), this would give a figure of 150,000 who were dependent on benzodiazepines in the UK, and over 500,000 in the US. Worldwide, the estimate is 2-3 million (Edwards et al 1990): a serious epidemiological problem by any standards.

The essential principle in the management of withdrawal from benzodiazepines is gradual reduction of plasma drug concentration. As withdrawal from shorter acting benzodiazepines such as lorazepam and alprazolam is particularly troublesome (Tyrer et al 1981; Ashton 1984; Rickels et al 1990), it is advantageous to switch to a longer-acting benzodiazepine such as diazepam and then slowly tail off the dose over a period of weeks, titrating the rate of reduction against the patient's symptoms. This approach, sometimes called 'tapering', significantly lessens the discomfort of withdrawal (Laughren et al 1982; Fontaine et al 1984; Rickels et al 1986; Busto et al 1986; Schweizer et al 1990). Psychological support, in the form of self-help groups, is often helpful to patients trying to wean themselves off benzodiazepines; other anxiety management techniques may also be beneficial. Pharmacological treatment has little to offer: propranolol reduces some of the somatic symptoms of withdrawal but is of only modest benefit overall; the noradrenergic alpha$_2$ agonist clonidine likewise has only a limited effect; the anti-convulsant carbamzepine has not lived up to its early promise (Roy-Byrne 1991).

With a comprehensive treatment programme most patients will succeed in coming off benzodiazepines completely, and the majority of them will stay off (Rickels at al 1986). Of 46 patients treated at a specialist centre over a 5-year period 25 (54%) were not taking benzodiazepines when followed up 1-5 years later, although many were still experiencing anxiety symptoms (Golombok et al 1987).

In some cases it may be inappropriate to undertake withdrawal. After pointing out that the evidence for irreversible damage from long-term benzodiazepine use is "weak", Onyett (1989) goes on to suggest that: "Where a patient is suspected of being dependent but shows little motivation to stop...enforced withdrawal may be a disservice". Similarly: "Despite the general recognition that long-term use is undesirable, benzodiazepines remain relatively safe drugs...For some patients long-term use of benzodiazepines is a 'lesser evil' than its alternatives" (Holden 1989).

Clinical use. If drug treatment for an acute exacerbation of anxiety is indicated a benzodiazepine, prescribed for a short period (not exceeding a few weeks so as to avoid the risk of dependence), may well reduce anxiety symptoms sufficiently for the patient to cope more effectively with any associated or causal life problems, and allow him or her to learn other strategies for dealing with stress over the longer term. When used in this way for short-lived episodes of severe anxiety interfering with normal function, the benzodiazepines can play a useful therapeutic role (Lader 1993).

Whenever a benzodiazepine is prescribed the patient must be warned of the potential sedative effects and be cautioned against driving a motor vehicle or operating complex machinery should such effects be experienced. It is therefore wise to advise patients not to drive for a day or two after starting on a benzodiazepine so that the degree of day-time sedation can be gauged and dosage adjusted accordingly. It is also essential to notify patients about the dependence-producing potential of benzodiazepines, cautioning them not to take any of these drugs continuously for more than a week or two.

The most widely prescribed benzodiazepine for the relief of anxiety is undoubtedly diazepam, and when used with due circumspection it is very effective in the majority of patients. In view of its long half-life it can be administered on a daily basis. However, some patients prefer the flexibility which multiple dosage gives them; this may reflect the fact that the peak plasma level occurs within an hour or so after oral administration and is followed by a rapid redistribution phase in which plasma levels fall. Lorazepam, 1-2.5 mg given twice daily has been found to be equally effective, but it carries a greater risk of causing dependency, probably because of its shorter half-life. Fine adjustment of dosage can often be left to individual patients who are usually in the best position to judge the optimum dose for their own symptom relief. It is illogical and unnecessary to prescribe more than one benzodiazepine compound at a time, and there is no justification for prescribing a short-acting benzodiazepine to relieve insomnia if the patient is already taking a longer-acting drug to counter anxiety. The administration and dosage of the longer-acting drug should be adjusted appropriately instead.

Guidelines for the use of benzodiazepine compounds in the treatment of anxiety have been published in the UK by the Royal College of Psychiatrists (1988), in the US by the American Psychiatric Association (1991), and in Australasia by The Royal Australian and New Zealand College of Psychiatrists (1991).

2 Buspirone

Buspirone is an azopirone antianxiety drug. In contrast to the benzodiazepines it is non-sedative and lacks anticonvulsant and muscle-relaxant properties. It does not appear to act on the benzodiazepine-GABA receptor complex, but rather it is a partial agonist at the $5HT_{1A}$ receptor, and also a weak antagonist at the dopamine D_2 receptor. It is completely absorbed after oral administration, but has a low systemic bioavailability because of a large hepatic first-pass uptake. Its plasma elimination half-life is short (2-8 hours), but some of its metabolites may be active. It probably acts in a manner similar to antidepressant drugs, many of which enhance serotoninergic neurotransmission (see McNaughton, this issue).

Buspirone has been shown to be useful in the treatment of anxiety when given at a daily dose of 15-30 mg (Rickels et al 1988). However, its therapeutic effect can be modest, and it usually takes up to two weeks to become fully effective (Deakin 1993). While some controlled trials show it to be as effective as diazepam others do not (Goa and Ward 1986). Furthermore, the high drop-out rate seen in longer-term trials raises questions about its long-term efficacy (Fineberg and Drummond 1995).

The adverse effects of buspirone appear to be less of a problem than those of benzodiazepines (Goa and Ward 1986, Fineberg and Drummond 1995). Headaches, dizziness and gastrointestinal symptoms are the most troublesome, and may occur in up to 10% patients. It does not impair psychomotor function, nor does it appear to promote physical dependence.

3 Antidepressants

There is increasing evidence that a range of antidepressant drugs have an anxiolytic activity independent of any antidepressant effect (Johnstone et al 1980, Kahn et al 1986, Tyrer et al 1988, Rickels et al 1993). Imipramine, phenelzine, a number of selective serotonin reuptake inhibitors, and the reversible monoamine oxidase-A inhibitor moclobemide have all been shown to be effective in the treatment of anxiety disorders.

In fact long-standing anxiety-symptoms often respond better to treatment with an antidepressant than with an anxiolytic. Certainly antidepressants are preferable to the benzodiazepines when longer term treatment is required. Selective serotonin reuptake inhibitors (SSRI), while possibly no more effective than tricyclic antidepressant drugs (TCA) such as imipramine and amitriptyline in GAD, are better tolerated and less toxic in overdose.

4 Beta-adrenergic blockers

The subjective experience of anxiety is usually accompanied by widespread sympathetic discharge together with a steep rise in circulating catecholamines. These autonomic responses can reinforce the central awareness of anxiety and thus compound the symptoms' severity; such cardiovascular concomitants often make the patient seek medical advice.

Some patients certainly find that the degree of anxiety which they experience is modulated by their awareness of autonomic symptoms, particularly tachycardia. For them simple reduction of the tachycardia, by peripheral beta-adrenergic receptor blockade with a drug such as propranolol, affords significant symptomatic relief (Peet & Ali 1986). However, this applies to only a minority of anxious patients; particularly those with performance anxiety. Most other anxious patients require lowering of their state of heightened arousal by a centrally acting compound.

Relatively small doses of propranolol such as 20 to 40 mg six- or eight-hourly may be used together with small doses of a benzodiazepine drug or buspirone. It must be remembered that, in some patients, bronchial asthma is a manifestation of anxiety; when this happens propranolol and other beta blockers are contraindicated.

Panic disorder (episodic paroxysmal anxiety)

This condition is characterised by recurrent attacks of severe anxiety (panic attacks), which are not restricted to a particular place or circumstance. They are often accompanied by an inexplicable but overwhelming sensation of imminent death. The attacks typically arise without warning and with no obvious precipitant. Further convincing the patient that the worst is about to happen are the frequent sensations of choking and smothering together with a rapid tachycardia and profuse sweating. There is a pronounced tendency to overbreathe which in turn brings on paraesthesiae, and dizziness.

When an attack occurs in a specific situation, it can prompt the patient to avoid that situation in future. Some patients even become frightened of leaving home altogether

for fear of having a panic attack (panic disorder with agoraphobia).

Panic disorder was first distinguished from other types of anxiety disorder on account of what was then thought to be its unique responsiveness to the tricyclic antidepressant drug imipramine (Klein & Fink 1962). Subsequent studies have shown that this response is not limited to panic disorder, nor is imipramine the only compound which has this therapeutic activity. As we have already seen, other forms of anxiety disorder respond to a wide range of antidepressant drugs, and a number of different psychotropic compounds have been shown to be effective in panic disorder (Johnson et al 1995).

Four categories of drugs have been shown to be effective: tricyclic antidepressants (TCA); selective serotonin reuptake inhibitors (SSRI); monoamine uptake inhibitors [both the non-reversible type (MAOI) and the reversible (RIMA)]; benzodiazepines (Fineberg and Drummond 1995).

1 Tricyclic antidepressants

Imipramine was the first tricyclic antidepressant drug to be shown to be effective in panic disorder (Klein & Fink 1962). When given at a dose of 150-300 mg daily, it has been found in a number of studies to reduce significantly the frequency and severity of recurrent panic attacks. Other tricyclic antidepressants appear to exert a similar therapeutic effect (Liebowitz 1989).

2 SSRI

Fluvoxamine has been the most widely studied of the SSRI in this condition. A three-way comparison with placebo and cognitive therapy showed it to be more effective than either comparator (Black et al 1993). In another trial it was more effective than the noradrenergic antidepressant maprotiline (Den Boer and Westenberg 1988). Preliminary studies have indicated that a range of other SSRI (citalopram, fluoxetine, paroxetine) are also likely to be effective in the management of panic disorder. Because of their more acceptable side effect profile, SSRI are currently the treatment of choice for panic disorder.

A frequent initial response to treatment with SSRI is a short-lived increase in anxiety, which subsides after the first week or two in parallel with the more definitive action of these drugs beginning to take effect. To minimise the early activating effect of SSRI in the treatment of panic disorer it is advisable to start with a small dose (eg 10mg fluoxetine or paroxetine) and gradually titrate upwards (Johnson et al 1995).

3 Monoamine oxidase inhibitors

Phenelzine was found to be superior to placebo in reducing panic attacks, with a trend for phenelzine to be better than imipramine (Sheehan et al 1980). The efficacy of the RIMA compound, moclobemide, which has a better side-effect profile than the older MAOI, is currently being evaluated.

4 Benzodiazepines

Although benzodiazepines were thought to be ineffective in panic disorder, more recent clinical trials have shown this not to be the case. Alprazolam, a high potency triazolobenzodiazepine compound, was found to be at least as effective as the standard antidepressant drugs, and more rapid in its anti-panic action (Cross National Collaborative Panic Study 1992). In addition, a benzodiazepine can prove useful in covering the initial stages of treatment while waiting for an SSRI or TCA to take effect (Johnson et al 1995). However, longer-term use raises the problem of physical dependence with subsequent withdrawal symptoms.

In the light of the clear-cut efficacy of antidepressant drugs, especially SSRI, in panic disorder, it is perhaps surprising that the 5-HT_{1A} agonist buspirone was found to be lacking in any useful therapeutic effect (Sheehan et al 1993).

Phobic anxiety disorders

Phobias can be regarded as the irrational avoidance of a particular set of situations or objects which evoke severe anxiety in the subject. The fear often arises out of a learned experience. The phobic disorders are usually classified as falling into one of three categories, specific phobias, social phobias and agoraphobia.

(a) Specific (isolated) phobias.

These include avoidance of particular objects (frequently a particular type of animal, e.g. spiders, snakes) or situations (e.g. heights). They often begin in childhood. Behaviour therapy, in the form of graduated exposure to the feared object or situation, is the treatment of choice. It is usually very effective, with up to 90% of patients showing benefit. The majority of patients can be taught self-exposure techniques, which are quick and cost-effective (Fineberg and Drummond 1995).

(b) Social phobias.

These take the form of avoidance of social situations in which the individual is exposed to the scrutiny of others (e.g. eating in public).

The non-reversible monoamine oxidase inhibitors (MAOI) phenelzine (Liebowitz et al 1986) and tranylcypromine (Versiani et al 1988), as well as the reversible inhibitor of monamine oxidase A (RIMA) moclobemide (Versiani et al 1992), have been shown to be superior to placebo in the management of social phobias. Treatment should continue for several weeks.

Evaluation of SSRI and of buspirone in social phobias is ongoing.

(c) Agoraphobia.

This is the most pervasive and restricting form of phobic disorder in which the sufferer finds great difficulty in leaving the security of his or her own home. Crowded shopping areas and bustling streets are particularly avoided. A companion may be required for even the shortest forays into the world outside; with some patients becoming completely housebound. There is usually a history of a life-long tendency to experience heightened anxiety.

The pharmacological treatment of agoraphobia is similar to that for panic disorder (see above), with which it is frequently associated. Antidepressant drugs are the treatment of choice. Of these imipramine, phenelzine, selective serotonin reuptake inhibitors *(SSRI)*, and moclobemide (a reversible inhibitor of monoamine oxidase-

A [RIMA]) have all been shown to be effective. The SSRI and moclobemide have fewer side-effects and are less toxic. The anti-anxiety activity of these compounds appears to be independent of any effect on depression, which is often not present.

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) follows the experience of major and distressing psychological trauma. It is a persistant condition characterised by recurrent intrusive recollections of the traumatic event in the waking state ('flashbacks') and/or as nightmares. Irritability, tension and depression are usually present, and phobic avoidance of objects or situations which remind the patient of the traumatic event is likely. Treatment of PTSD is multimodal, with drugs playing a potentially important part (Davidson 1992). The tricyclic antidepressant drugs amitriptyline and imipramine have been shown to be more effective than placebo in controlled trials involving combat veterans, although the overall improvement was modest. In another study phenelzine (an MAOI) was more effective than imipramine, particularly in reducing intrusive symptoms (Frank et al 1988). Uncontrolled reports suggest that the SSRI drugs fluvoxamine and fluoxetine may be of benefit, at least in some patients (Fichtner et al 1994). Treatment should continue for several months, as it may take that long for the maximum benefit to be derived (Davidson 1992).

Acute stress disorder

This is, as its name implies, an acute reaction to a frightening traumatic event which threatened the patient's life or safety. It is characterised by many of the same symptoms as PTSD, but is of shorter duration (lasting 2 days to 4 weeks by DSM-IV definition). Pharmacological treatment is usually not required. However, if the anxiety symptoms are so severe as to be incapacitating, or to interfere with daily activities, short-term administration of a benzodiazepine such as diazepam can afford relief.

Obsessive-compulsive disorder (OCD)

Patients suffering from OCD are plagued by recurrent thoughts (obsessional thoughts or ruminations) and/or preoccupied by the need to perform recurrent acts (compulsive acts [obsessional rituals]). The obsessional thoughts are typically distressing, often being violent or obscene. Compulsive acts are repetitive behaviours, which patients recognise as unnecessary, but which they are powerless to resist because of the resultant fear that some disaster will occur should they desist.

Many authorities do not regard OCD as being a true anxiety disorder (Montgomery 1993). They argue that the anxiety which is seen in OCD arises as secondary to the obsessional ideas: it is not, as in the case of other anxiety disorders, a primary feature. Furthermore, unlike anxiety disorders, which are more common in women, the prevalence of OCD is as high in men as in women.

Psychophysiology and pharmacology

Imaging studies using MRI and PET, have revealed changes in the size and activity of the basal ganglia (particularly the caudate nucleus) in some, though not all, patients with OCD (Baxter et al 1988). The relationship of such brain findings to the psychopathology of OCD is as yet unclear.

Abnormalities in central serotoninergic (5-HT) neurotransmission have been implicated in the pathogenesis of OCD on the basis of neuroendocrine and pharmacological findings (Barr et al 1992). Consistent with an involvement of 5-HT is the observation that oral (but not intravenous) administration of the post-synaptic 5-HT receptor agonist mCPP can exacerbate the symptoms of OCD in some patients. Furthermore, the 5-HT receptor blocking drug metergoline reverses the therapeutic benefits brought about by serotonin reuptake inhibitors. Yet, the relationship of obsessional symptoms to changes in brain 5-HT is by no means clear-cut: metergoline alone has no effect on OCD symptoms, and lowering brain 5-HT using a tryptophan-depleted diet does not reverse the therapeutic benefits of treatment with SSRI antidepressants, (in contrast to what is seen in depressive illness).

Drug treatment

There is a substantial body of evidence, derived from a large number of placebo-controlled clinical trials, to indicate that drugs which preferentially block the reuptake of serotonin into pre-synaptic neurones are effective in ameliorating the symptoms of OCD in the majority of patients (Fineberg et al 1992, Montgomery 1993). Such drugs include: clomipramine (50-150mg daily), fluoxetine (20mg daily), fluvoxamine (100-200mg daily) and sertraline (100-200mg daily); all appear to be equally effective. By contrast, treatment with antidepressant compounds without a selective effect on serotonin reuptake (eg desipramine), produces little clinical benefit. This is another point in favour of the view that serotonin is involved in the pathogenesis of OCD, and that the pathophysiology is likely to differ from that of major depressive illness where both TCA and SSRI are equally effective.

In patients who fail to respond to treatment with 5-HT reuptake inhibitors given in adequate dosage for a sufficient length of time (at least 10 weeks), further enhancement of central serotoninergic neurotransmission may help (Rasmussen et al 1993). Drugs which can affect this include lithium, tryptophan and dexfenfluramine, all of which have proved effective adjuncts to SSRI. It is generally recommended that drug treatment of OCD be undertaken in conjunction with behaviour therapy.

Conclusions

Clinical studies reveal that there are four categories of anxiety-related disorders, each of which responds differently to centrally acting drugs. These are: 1) simple phobias; 2) complex phobias and panic disorder; 3) generalised anxiety disorder (GAD); 4) obsessive compulsive disorder (OCD).

In reviewing the drugs themselves there appear to be three types of action: 1) symptomatic relief of acute anxiety for which benzodiazepine compounds are the most effective; 2) longer-term amelioration of anxiety in GAD, complex phobias and panic disorder brought about equally by tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI); 3) improvement in OCD for which SSRI, (but not TCA or benzodiazepines) are effective.

These observations suggest that the four DSM-IV

categories of anxiety conditions differ from one another in their pathophysiology (as discussed by McNaughton, this issue). Continued examination of their differential response to centrally acting drugs should afford an increased understanding of the brain abnormalities underlying each. This in turn will lead to further improvements in treatment

References

American Psychiatric Association. (1990) *Benzodiazepine Dependence, Toxicity and Abuse: A Task Force Report of the American Psychiatric Association.* Washington, D.C., A.P.A.

American Psychiatric Association. (1994) *Diagnostic and Statistical Manual, 4th edition.* American Psychiatric Association, Washington, D.C., A.P.A.

Ashton H. (1984), Benzodiazepine withdrawal: an unfinished story. *British Medical Journal, 28,* 1135-1140.

Barr , L.C., Goodman, W.K., Price, L.H., McDougle, C.J. & Charney, D.S. (1992) The serotonin hypothesis of obsessive disorder: Implications of pharmacologic challenge studies. *Journal of Clinical Psychiatry, 53* (4, supp), 17-28.

Baxter, L.R., Schwartz, J.M., Mazziotta, J.C.,Phelps, M.E., Pahl, J.J., Guze, B.H. & Fairbanks, L. (1988) Cerebral glucose metabolic rates in non depressed obsessive-compulsives. *American Journal of Psychiatry, 145,* 1560-1563.

Bixler, E.O., Kales, A., Manfredi, R.L., Vgontzas, A.N., Tyson, K.L. & Kales, J.D. (1991). Next-day memory impairment with triazolam use. *Lancet, 337,*

Black, D.W., Wesner, R., Bowers, W. & Gabel, J. (1993) A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. *Archives of General Psychiatry, 50,* 44-50.

Brahams D. (1990), Medicine and the law: benzodiazepine over-prescribing - successful initiative in New York State, *Lancet, ii,* 1372-1373.

Brookhuis K.A., Volkerts E.R. & O'Hanlon J.F. (1990), Repeated dose effects of lormetazepam and flurazepam upon driving performance, *European Journal of Clinical Pharmacology, 39,* 83-87.

Brosan C., Broadbent D., Nutt D. & Broadbent M. (1986), Performance effects of diazepam during and after prolonged administration, *Psychological Medicine, 16,* 561-571.

Busto, U., Lanctot, K.L., Isaac, P. & Adrian, M. (1989) Benxodiazepine use and abuse in Canada. *Canadian Medical Association Journal, 141,* 917-921.

Curran, H.V. (1991) Benzodiazepines, memory and mood: a review. *Psychopharmacology, 105,* 1-8.

Cross-National Collaborative Panic Study, Second Phase Investigators. (1992) Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine and placebo. *British Journal of Psychiatry, 160,* 191-202.

Davidson, J. (1992) Drug therapy of post-traumatic stress disorder. *British Journal of Psychiatry, 160,* 309-314.

Deakin, J.F.W. (1993) 5HT1A agonists in anxiety and depression. *Journal of Psychopharmacology, 7,* 283-289.

Den Boer, J. & Westenberg, H. (1990) Serotonin function in panic disorder: a double-blind placebo controlled study with fluvoxamine and ritanserin. *Psychopharmacology, 102,* 85-94.

Dunbar G.C., Perera M.H. and Jenner F.A. (1989), Patterns of benzodiazepine use in Great Britain as measured by a general population survey, *British Journal of Psychiatry, 155,* 836-841.

Edwards J.G., Cantopher T. and Olivieri S. (1990), Benzodiazepine dependence and the problems of withdrawal, *Postgraduate Medical Journal, 66,* (Suppl. 2), S27-S35.

Fichtner, C.G., Arora, R.C., O'Connoer, F.L. & Crayton, W.J. (1994), Platelet paroxetine binding and fluoxetine pharmacotherapy in post-traumatic stress disorder. *Life Sciences, 54,* 39-44.

Fineberg, N.A., Bullock, T., Montgomery, D.B. & Montgomery S.A. (1992), Serotonin reuptake inhibitors are the treatment of choice in obsessive compulsive disorder. *International Clinical Psychopharmacology, 7,* (Suppl. 1), 43-47.

Fineberg, N. & Drummond, L.M. (1995), Anxiety disorders: drug treatment or behavioural cognitive psychotherapy? *CNS Drugs, 3,* 448-466.

Fontaine R., Chouinard G. and Annable L. (1984), Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment, *American Journal of Psychiatry, 141,* 848-852.

Frank, J.B., Giller, E.L. & Kosten, T. (1988), A randomised clinical trial of phenelzine and imipramine for post traumatic stress disorder. *American Journal of Psychiatry, 145,* 1289-1291.

Goa, K.L. & Ward, A. (1986) Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. *Drugs, 32,* 114-129.

Golombok S., Higgitt A., Funagy P., Dodds S., Saper J. and Lader M. (1987), A follow-up study of patients treated for benzodiazepine dependence, *British Journal of Medical Psychology, 60,* 141-149.

Greenblatt, D.J., Harmatz, J.D., Shapiro, L., Engelhardt, N., Gouthro, T.A. & Shader, R.I. (1991), Sensitivity to triazolam in the elderly. *New England Journal of Medicine, 324,* 1691-1698.

Hindmarch I. (1980), Human psychopharmacological differences between benzodiazepines, in *Benzodiazepines: Current Concepts,* ed. I. Hindmarch, G. Beaumont, S. Brandon and B.E. Leonard, Wiley, Chichester, 73-93.

Holden J. (1989), Benzodiazepine dependence, *The Practitioner, 233,* 1479-1483.

Hollister L., Motzenbecker F.P. & Degan R.O. (1961), Withdrawal reactions from chlordiazepoxide ("librium"), *Psychopharmacologia, 2,* 63-68.

Johnson, M.R., Lydiard, R.B. & Ballenger, J.C. (1995), Panic disorder: pathophysiology and drug treatment. *Drugs, 49,* 328-344.

Johnstone, E., Cunningham Owens, D.G., Frith, C.D., McPherson, K., Dowie, C., Riley, G. & Gold, A. (1980), Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychological Medicine, 10,* 321-328.

Kahn, R.J., McNair, D.M., Lipman, R.S., Covi, L., Rickels, K., Downing, R., Fisher, S. & Frankenthaler, L.M. (1986), Imipramine and chlordiazepoxide in depressive and anxiety disorders, II: Efficacy in anxious outpatients. *Archives of General Psychiatry, 43,* 79-85.

Klein, D. & Fink, M. (1962), Psychiatric reaction patterns to imipramine. *American Journal of Psychiatry, 119,* 432-438.

Lader, M.H. (1993), New pharmacological strategies for the treatment of anxiety disorders. In: Costa e Silva, J.A. & Nadelson, C.C.(Eds.) *International Review of Psychiatry, (Vol. 1)* (pp 263-302). Washington, D.C.: American Psychiatric Press.

Lader M. & File S. (1987), The biological basis of benzodiazepine dependence. *Psychological Medicine, 17,* 539-547.

Laughren T.P., Battey Y. and Greenblatt D.J. (1982), A controlled trial of diazepam withdrawal in chronically anxious outpatients, *Acta Psychiatrica Scandinavica, 65,* 171-179.

Liebowitz, M.R. (1989), Antidepressants in panic disorders. *British Journal of Psychiatry, 155,* (Suppl. 6), 46-52.

Liebowitz, M.R., Schneier, F. & Campeas, R. (1992), Phenelzine vs atenolol in social phobia: a placebo-controlled comparison.

Archives of General Psychiatry, 49, 290-300.

Lister R.G. (1991), The effects of benzodiazepines and 5-HT1A agonists on learning and memory, In: Rodgers, R.J. & Cooper, S.J. (Eds.) *5-HT1A Agonists, 5-HT3 Antagonists and Benzodiazepines,*(pp267-280), Chichester, John Wiley.

Lockwood, A. & Berbatis, C.G. (1990) Psychotropic drugs in Australia: consumption patterns. *Medical Journal of Australia, 15,* 604-611.

Mellinger G.D., Balter M.B. and Uhlenhuth E.H. (1984), Prevalence and correlates of the long-term regular use of anxiolytics, *Journal of the American Medical Association, 251,* 375-379.

Montgomery, S.A. (1993). Obsessive compulsive disorder is not an anxiety disorder. *International Clinical Psychopharmacology, 8* (Suppl. 1), 57-62.

Murphy S., Owen R. and Tyrer P. (1984), Withdrawal symptoms after 6 weeks'treatment with diazepam, *Lancet, ii,* 1389.

Onyett S. (1989), The benzodiazepine withdrawal syndrome and its management, *Journal of the Royal College of General Practitioners, 39,* 160-163.

Oster G., Huse D., Adams S., Imbimbo J. and Russell M.W. (1990), benzodiazepine tranquillizers and the risk of accidental injury, *American Journal of Public Health, 80,* 1467-1470.

Owen R.T. & Tyrer P. (1983), Benzodiazepine dependence: a review of the evidence, *Drugs, 25,* 385-398.

Peet, M. & Ali, S. (1986), Propanolol and atenolol in the treatment of anxiety. *International Clinical Psychopharmacology, 1,* 314-319.

Petursson H. & Lader M.H. (1981), Withdrawal from long-term benzodiazepine treatment, *British Medical Journal, 283,* 643-645.

Rasmussen. S.A., Eisen, J.L. & Pato, M.T. (1993) Current issues in the management of obsessive-compulsive disorder. *Journal of Clinical Psychiatry, 54,* (Suppl. 6), 4-9.

Rickels K., Case W.G., Downing R. W. & Winokur A. (1983), Long-term diazepam therapy and clinical outcome, *Journal of the American Medical Association, 250,* 767-771.

Rickels K., Case W.G., Schweizer E., Swenson S. & Fridman R. (1986), Low dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients, *Psychopharmacology Bulletin, 22,* 407-415.

Rickels, K., Downing, R., Schweitzer, E. & Hassman, H. (1993) Antidepressants for the treatment of general anxiety disorder. *Archives of General Psychiatry, 50,* 884-895.

Rickels K., Schweizer E., Case W.G. and Greenblatt D.J. (1990), Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation, *Archives of General Psychiatry, 47,* 899-907.

Royal Australian and New Zealand College of Psychiatrists (1991), *College guidelines for use of benzodiazepines.* Melbourne. RANZCP.

Royal College of Psychiatrists, (1988), Benzodiazepines and dependence: a College statement, *Bulletin of the Royal College of Psychiatrists, 12,* 107-109.

Roy-Byrne P.P. (1991), Benzodiazepines: dependence and withdrawal. In: Roy-Byrne, P.P. & Cowley, D.S. (Eds.), *Benzodiazepines in Clinical Practice,* (pp. 133-153) Washington D.C., American Psychiatric Press.

Schweizer E., Rickels K., Case W.G. and Greenblatt D.J. (1990), Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. *Archives of General Psychiatry, 47,* 908-915.

Sheehan, D.V., Ballenger, J. & Jacobsen, G. (1980), Treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Archives of General Psychiatry, 37,* 51-59.

Sheehan, D.V., Raj, B.A., Trehan, R.R. & Knapp, E.L. (1993) Serotonin in panic disorder and social phobia. *International Clinical Psychopharmacology, 8,* (Suppl. 2), 63-77.

Silverstone T. (1988), The influence of psychiatric disease and its treatment on driving performance. *International Clinical Psychopharmacology, 3,* (Suppl. 1), 59-66

Silverstone T. and Turner P. (1995), *Drug Treatment in Psychiatry,* (5th Edition), London, Routledge.

Skegg D.C.G., Richards S.M. and Doll R. (1979), Minor tranquillizers and road accidents, *British Medical Journal, 1,* 117-191.

Tyrer P., Seivewright, N., Murphy, S., Kingdon, D., Brothwell, J., Gregory, S., Ferguson, B., Barczak, P., Darling, C. & Johnson, A.L. (1988), The Nottingham Study of neurotic disorder: comparison of drug and psychological treatments. *Lancet, ii,*235-240

Tyrer P. (1989), Choice of treatment in anxiety. In: Tyrer, P. (Ed.) *Psychopharmacology of Anxiety,* (pp255-282), Oxford, Oxford University Press.

Tyrer P., Rutherford D. & Huggett T. (1981), Benzodiazepine withdrawal symptoms and propanolol, *Lancet, i,* 520-522.

Versiani, M., Mundim, F.P. & Nardi, A.E. (1988), Tranylcypramine in social phobia. *Journal of Clinical Psychopharmacology, 8,* 279-283.

Versiani, M., Nardi, A.E., & Mundim, F.D. (1992) Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *British Journal of Psychiatry, 161,* 353-360.

Weissman M.M. & Merikangas K.R. (1986), The epidemiology of anxiety and panic disorders: an update, *Journal of Clinical Psychiatry, 47,* (Suppl.), 11-17.

Woods, J.H., Katz, J.L. & Winger, G. (1992) Benzodiazepines: use, abuse and consequences. *Pharmacological Reviews, 44,* 151-347.

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