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Pharmacotherapy of Anxiety

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Abstract The pharmacological treatment of anxiety has a long and chequered history, and recent years have seen a rich development in the options available to prescribers. Most of the currently used anxiolytic agents act via monoaminergic (chiefly serotonin) or amino acid (GABA or glutamate) neurotransmitters, and this chapter describes the pharmacology of the major drug groups. Clinical applications are discussed with respect to the five major

anxiety disorders, as well as simple phobia and depression with concomitant anxiety. Prospective future developments in the field are considered.

Keywords Pharmacology · Anxiety · GABA · Serotonin · Benzodiazepines · Antidepressants

1 Introduction

These are exciting times for physicians involved in the treatment of anxiety disorders. Therapeutic options are increasing whilst the level of public interest in the field has never been greater. Patients can equip themselves to be active partners in the therapeutic process using the various available sources of medical information. Longstanding controversies, such as the relative merits of psychological therapies versus medication and the safety of long-term medical treatments of anxiety, are debated in the national media. Perversely, at a time when psychiatrists have more to offer their anxious patients than ever before, the validity of their role is challenged from some quarters. Nevertheless, medical practice is now based on a substantial volume of clinical experience and evidence from controlled trials, and we can justify with confidence many of the treatment options we put before our patients.

Since the publication of the work of Donald Klein (1964) that described the discrimination of panic disorder from other neuroses, the diagnostic classification of anxiety disorders has undergone a progressive evolution, with new diagnostic categories emerging. Discrepancies remain between different classifications, with the accepted gold standard being the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV 1994), but general agreement has been reached for the diagnostic validity of the main categories. This has allowed the quantitative measurement of anxiety disorders in epidemiological surveys (Kessler et al. 1994; Wittchen H-U et al. 1998), and the demonstration of the prevalence and economic burden of anxiety has been a key factor driving research into anxiolytic therapies.

The rapid development of the psychiatry of anxiety over the past 15 years has been accelerated by developments in a diversity of other disciplines, including cognitive and experimental psychology, preclinical and clinical pharmacology, and neuroscience (particularly neuroimaging). Research from areas such as genetics and molecular biology is only just beginning to have an impact. With the current pace of scientific discovery, physicians can anticipate an increasing range of effective and acceptable treatment options for anxiety disorders. This chapter describes the state of clinical psychopharmacology for anxiety in 2005, but may soon become out of date.

2
Clinical Management of Anxiety

Optimal treatment of an anxious patient involves far more than the prescription of medication (Fig. 1). The skill of the psychiatrist in establishing the

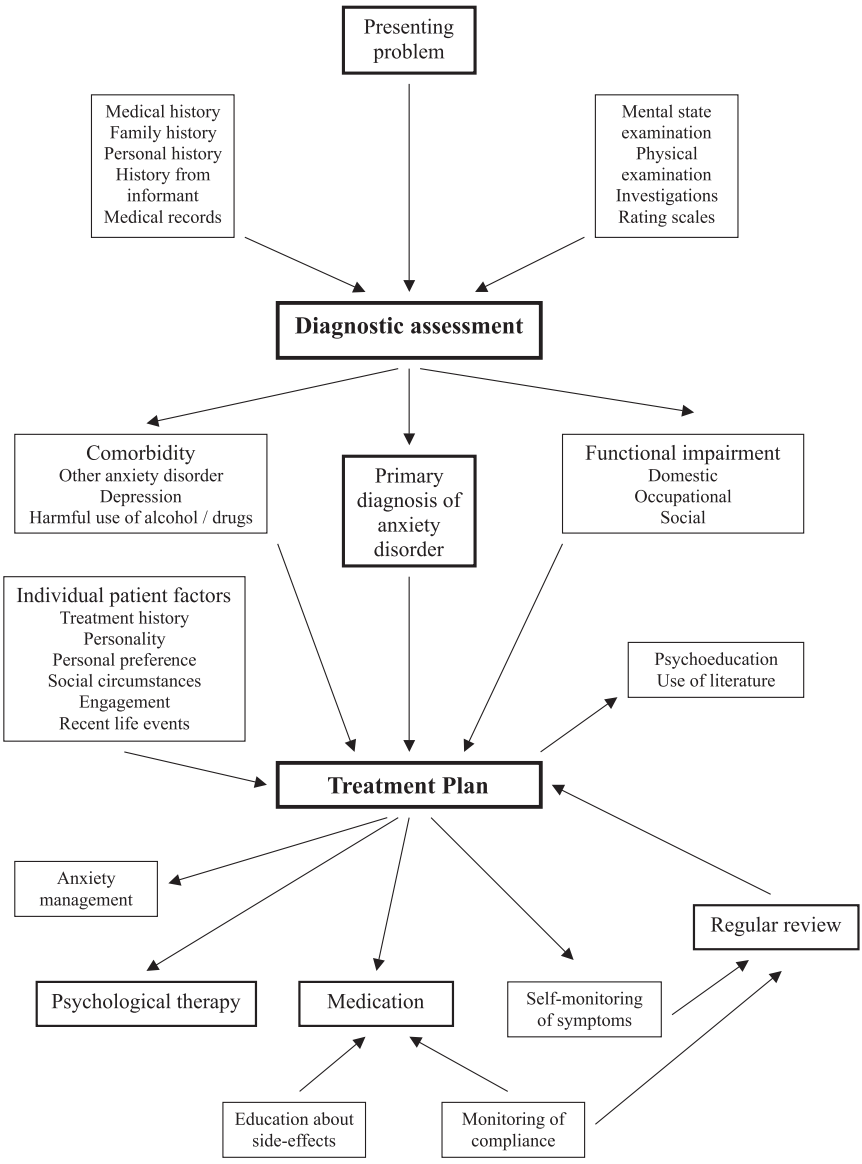

Fig. 1. Management of the anxious patient

diagnosis of a specific anxiety disorder is an invaluable part of the assessment process, as a correct diagnosis has a great influence on the treatment offered. Anxiety disorders frequently present with comorbid conditions, particularly depression, alcohol or substance use problems, and other anxiety disorders. These must be detected and managed appropriately.

Patients tend to present when their anxiety impairs their occupational, social or domestic functioning, and identification of the key complaints and motivations for seeking treatment is critical in drawing up an effective management plan. For example, a patient with generalized anxiety disorder (GAD) may present because her resulting insomnia is impairing her ability to work; management should include strategies to improve sleep efficiency as well as treatment of the anxiety.

Education about the nature of anxiety helps engagement and improves recovery. Models have been described for most anxiety disorders in both the biological and psychological dimensions, and patients benefit from an explanation, tailored to their level of understanding, in each dimension. This can be reinforced by the use of educative literature (Dannon et al. 2002). Patients should be encouraged to record and monitor their symptoms, as this can improve treatment efficacy (Febbraro and Clum 1998).

Once a diagnosis has been made and explained to the patient, a treatment plan should be negotiated. A range of biological and psychological treatments may be suitable and should be put to the patient, who is offered an element of choice alongside the recommendations of the physician. A combination of drug and psychological therapies can be more effective than either alone (Barlow et al. 2000). The patient may have preconceptions about specific therapies, often as a result of their anxiety, e.g. a patient with panic disorder fears the effects of drugs and a patient with social anxiety baulks at the suggestion of group therapy. An open discussion of benefits and adverse effects, including long-term side-effects, is likely to improve compliance. Although medications are generally well-tolerated, some side-effects commonly occur, and anxious patients experience more than others (Davies et al. 2003). Progress with treatment should be encouraged by regular review, particularly in the early stages.

3 Anxiolytic Drugs

The use of substances for their anxiolytic properties dates to the beginning of recorded human history. The twentieth century saw a substantial development of their use for medical purposes, and major progress was made in the 1990s, “the decade of anxiety”, as advances in neuroscience provided a basis for the targeted design of new treatments. There is now a greater range of drugs available that are better tolerated, although not necessarily more effective, than their predecessors. However, despite increased knowledge of the

complex physiology of the brain, the actions of current pharmacotherapeutic agents are moderated via a relatively small number of neurotransmitter systems, with the most important being the amino acid neurotransmitters (chiefly γ-aminobutyric acid, GABA, but also glutamate) and the monoaminergic neurotransmitters (serotonin, noradrenaline and to a lesser extent dopamine).

3.1 Drugs Acting via Amino Acid Neurotransmission

Glutamate is the major excitatory amino acid in the brain. It has a key role in learning and memory and is involved in the mediation of the response to stress. Glutamate receptors are present throughout the central nervous system but differ widely according to their localisation and function (Kent et al. 2002), and as a result have not been easy to identify as targets for pharmacological manipulation.

GABA is formed by the decarboxylation of glutamate, and is the major inhibitory neurotransmitter. In recent years the $GABA_A$ receptor has been identified as the mediator of the anxiolytic and sedative effects of drugs such as alcohol and the benzodiazepines. Abnormalities of this receptor have been identified in humans with anxiety disorders (Nutt and Malizia 2001).

For much of the second half of the twentieth century the benzodiazepines were the mainstay of the treatment of anxiety. Despite well-publicised concerns about their long-term safety, they remain an important therapeutic option. The anticonvulsants contain a number of drugs that act via GABA or glutamate neurotransmission and have a limited but interesting role in the treatment of particular anxiety disorders.

3.1.1 Benzodiazepines

The efficacy of benzodiazepines in most anxiety disorders has been proved through extensive clinical experience and controlled trials (Faravelli et al. 2003), although it is important to note that they are not effective at treating post-traumatic stress disorder or comorbid depression, and there is less evidence to support their use in obsessive–compulsive disorder (OCD). Their anxiolytic effects have an immediate onset and in contrast to many other drugs, they do not cause a worsening of anxiety when therapy is initiated.

3.1.1.1 Tolerability and Safety

Benzodiazepines are generally well-tolerated (Table 1), although side-effects such as sedation, loss of balance and impaired psychomotor performance may be problematic for some patients. There are reported associations with road

Table 1 Benzodiazepines in anxiety

Efficacy	Panic disorder Generalised anxiety disorder Social anxiety disorder Specific phobias	
Side-effects	**Common**	**Uncommon**
	Depressed CNS functioning (sedation, muscle weakness, light-headedness, confusion, ataxia, impaired psychomotor performance)	Paradoxical aggression Headache Hypotension Weight gain Sexual dysfunction
	Discontinuation effects (see Table 2)	Respiratory depression (in respiratory disease)
Toxic effects	Coma Aspiration of gastric contents Respiratory depression	

traffic accidents (Barbone et al. 1998) and with falls and fractures in the elderly (Wang et al. 2001). They are relatively safe in overdose (Buckley et al. 1995), although the risk is increased if taken in combination with alcohol or other sedative drugs.

3.1.1.2 Discontinuation Problems

The major controversy surrounding the use of benzodiazepines has concerned the risks of long-term treatment, specifically tolerance, abuse, dependence and withdrawal effects. From being the most widely prescribed psychotropic drug they suffered a major backlash, but a more balanced view of their place in treatment is emerging (Williams and McBride 1998). After 40 years of clinical experience there is little evidence of tolerance to the anxiolytic effects of benzodiazepines (Rickels and Schweizer 1998). Abuse (taking in excess of the prescribed dose) is uncommon except in individuals with a history of abuse of other drugs, who may not be suitable for benzodiazepine therapy (Task Force Report of the American Psychiatric Association 1990). There is, however, a consensus that adverse effects on discontinuation are more common than with other anxiolytics (Schweizer and Rickels 1998). A careful clinical assessment is indicated in this situation, as these effects may be caused by recurrence or rebound (recurrence with increased intensity) of the original anxiety symptoms.

Table 2 Benzodiazepine withdrawal syndrome

Symptoms	Hyperarousal: anxiety, irritability, insomnia, restlessness	Autonomic lability: sweating, tachycardia, hypertension, tremor, dizziness
	Neuropsychological effects: dysphoria, perceptual sensitisation, tinnitus, confusion, psychosis	Seizures
Risk factors	**Treatment factors:** treatment duration > 6 months; high dose; short-acting drug; abrupt cessation	**Patient factors:** severe premorbid anxiety; alcohol/substance use disorder; female; dysfunctional personality; panic disorder
Therapeutic strategies	Gradual tapering: Switch to long-acting drug, e.g. diazepam Cover with secondary agent (anticonvulsant, antidepressant) Cognitive behavioural therapy	

A benzodiazepine withdrawal syndrome has been described in some patients discontinuing therapy (Table 2). Although potentially serious, it is generally mild and self-limiting (up to 6 weeks), but may accompany or provoke a recurrence of anxiety symptoms and cause great concern to the patient. As with any other treatment, the risks and benefits of benzodiazepine therapy should be carefully assessed and discussed with the patient. Monotherapy will not be first-line treatment for the majority of patients, but benzodiazepines offer a valuable option that should not be discounted.

3.1.1.3 Drug Interactions

The potential for interaction with other medications comes largely from two sources: (1) the exacerbation of sedation and impaired psychomotor performance by other drugs also causing these effects, and (2) alterations in the hepatic metabolism of benzodiazepines by drugs that are either inducers or inhibitors of cytochrome P450 (CYP450) enzymes. The increased toxicity in combination with alcohol is mostly pharmacodynamic but may partly be due to the inhibition of metabolism of some benzodiazepines by high alcohol concentrations. Other drugs that may have additive effects on sedation include tricyclic antidepressants, antihistamines, opioid analgesics and the α_2-adrenoceptor agonists clonidine and lofexidine.

Most benzodiazepines undergo oxidative metabolism in the liver that may be enhanced by enzyme inducers (e.g. carbamazepine, phenytoin) or slowed by inhibitors (sodium valproate, fluoxetine, fluvoxamine). Oxazepam, lorazepam and temazepam are directly conjugated and are not subject to these interactions.

3.1.1.4 Clinical Usage

The specific clinical use of the numerous available benzodiazepines depends on their individual pharmacokinetic and pharmacodynamic properties. Drugs with a high affinity for the $GABA_A$ receptor (alprazolam, clonazepam, lorazepam) have high anxiolytic efficacy; drugs with a short duration of action (temazepam) are used as hypnotics to minimise daytime sedative effects. Diazepam has a long half-life and duration of action and may be favoured for long-term use or when there is a history of withdrawal problems; oxazepam has a slow onset of action and may be less susceptible to abuse.

Guidance on the clinical indications for benzodiazepine therapy is available from various sources (Task Force Report of the American Psychiatric Association 1990; Ballenger et al. 1998a; Bandelow et al. 2002). Long-term therapy is most likely to present problems with discontinuation and is usually reserved for cases that have proved resistant to treatment with antidepressants alone. Patients may benefit from a 2–4 week course of a benzodiazepine whilst antidepressant therapy is initiated, as this counteracts the increased anxiety caused by some drugs (Goddard et al. 2001). A benzodiazepine may be useful as a hypnotic in some cases of anxiety disorder, and can be used by phobic patients on an occasional basis before exposure to a feared situation.

3.1.2 Anticonvulsants

There is some overlap between the clinical syndromes of anxiety and epilepsy: panic disorder and post-traumatic stress disorder can present with symptoms similar to temporal lobe seizures; alcohol and drug withdrawal states can cause both anxiety and seizures; and some drugs (e.g. barbiturates and benzodiazepines) act as both anticonvulsants and anxiolytics. Most anticonvulsant drugs act via the neurotransmission of GABA or glutamate, and in recent years have offered a promising field for the development of novel anxiolytic therapies (Kent et al. 2002). Although there is solid preclinical research demonstrating their anxiolytic properties, the evidence base in humans is less impressive and they tend to be reserved for second-line or adjunctive therapy. Drug interactions mediated via hepatic enzymes are a significant feature of these drugs.

3.1.2.1 Carbamazepine

No satisfactory randomised controlled trials have been published demonstrating the efficacy of carbamazepine in anxiety disorders, although it has a history of use as an anxiolytic in panic disorder and PTSD. It has an unfavourable side-effect profile (nausea, dizziness, ataxia) and multiple drug interactions due to induction of liver enzymes.

3.1.2.2 Gabapentin and Pregabalin

Gabapentin acts by increasing GABA activity, although its exact mechanism of action is unclear. It causes dose-related sedation and dizziness. It has been shown in randomised controlled trials to be effective in social anxiety disorder (Pande et al. 1999) and to benefit some patients with panic disorder (Pande et al. 2000). Pregabalin is a related compound that has recently demonstrated efficacy in GAD in a phase III study (Pande et al. 2003).

3.1.2.3 Lamotrigine

This anticonvulsant drug blocks voltage-gated sodium channels and inhibits release of glutamate. A controlled study found efficacy in PTSD (Hertzberg et al. 1999). Important side-effects include fever and skin reactions.

3.1.2.4 Sodium Valproate

As with carbamazepine, the historical use of valproate for anxiety is not supported by robust clinical trials. A randomised study showed efficacy in panic disorder (Lum et al. 1991) and benefit has been reported in open studies in OCD and PTSD. The major side-effects are tremor, nausea, ataxia and weight gain and there is the potential for drug interactions via inhibition of hepatic enzymes.

3.1.2.5 Other Drugs

Tiagabine blocks neuronal uptake of GABA and has reported benefits in panic disorder and PTSD (Lydiard 2003). Topiramate has complex actions on GABA and glutamate and was found to be helpful for some symptoms of PTSD (Berlant and van Kammen 2002). Vigabatrin inhibits GABA metabolism and has been shown to block induced panic attacks in healthy volunteers (Zwanzger et al. 2001).

3.2 Drugs Acting via Monoaminergic Neurotransmission

Aside from the $GABA_A$ receptor, most research into the neurochemistry of anxiety has explored the role of the monoamine transmitters serotonin (5-HT), noradrenaline and dopamine. This interest originated with the serendipitous discovery of drugs that were later found to exert their anxiolytic effects by actions on monoamine function. Advances in neuroscience research techniques have, rather than clarifying the role of these neurotransmitters, tended to present an increasingly complex picture (Argyropoulos and Nutt 2003). Nevertheless these advances have led to the development of "designer drugs" with selective effects on neurotransmitter function that have been successfully tested as anxiolytics. These drugs do not exceed their predecessors in terms of efficacy, but better tolerability has led to their adoption as first-line treatments for anxiety disorders.

The biology of the monoamines is described in detail elsewhere. In simple terms, they facilitate transmission in neural pathways that originate in nuclei of the brainstem and have descending projections to the autonomic nervous system and widespread ascending projections to sites in the limbic system and cortex. These pathways modulate many aspects of behavioural function as well as anxiety responses. Of the three monoamines, the role of serotonin in anxiety is best understood, but the picture is complex as increased serotonergic activity may be anxiogenic or anxiolytic depending on the site of action (Bell and Nutt 1998).

Anxiolytic drugs alter monoaminergic neurotransmission by increasing synaptic availability or by direct action on postsynaptic receptors. Mechanisms for increasing monoamine availability include increasing release by blocking inhibitory autoreceptors, decreasing reuptake by blocking transporters, and decreasing metabolism by inhibiting oxidative enzymes. Monoamines are also implicated in the pathophysiology of depression, and drugs that increase their synaptic availability tend to have antidepressant effects. These drugs have been traditionally classified as antidepressants, although they have a primary role as anxiolytics. Other anxiolytic drugs acting via monoamine neurotransmission are the postsynaptic serotonin receptor partial agonist buspirone, the β-adrenoceptor blockers and drugs classed as antipsychotics.

3.2.1 Antidepressants

The growth during the 1990s in the use of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), for the treatment of anxiety disorders represented a major advance in the pharmacotherapy of anxiety. The efficacy of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) had been established alongside their antidepressantw actions several decades

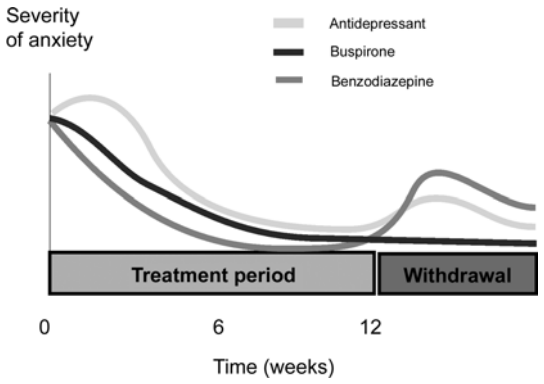

Fig. 2. Treatment response to anxiolytic drugs

previously, but the launch of new, better-tolerated medications coincided with the backlash against benzodiazepines and an increase in the profile of anxiety disorders.

Taken together, the efficacy of antidepressants covers the spectrum of anxiety disorders, although there are important differences between drugs in the group (Table 3). Several new antidepressants have been marketed since the SSRIs: venlafaxine and mirtazapine are discussed later (Sects. 3.2.1.2 and 3.2.1.4); nefazodone, a serotonin reuptake inhibitor and postsynaptic 5-HT_2 blocker showed promise in early studies but was recently withdrawn by its manufacturers; reboxetine, a noradrenaline reuptake inhibitor (NARI) showed benefits in panic disorder in one published study (Versiani et al. 2002) and further evidence of its anxiolytic efficacy is awaited.

Antidepressants differ from benzodiazepines in the onset and course of their actions (Fig. 2). Most cause an increase in anxiety on initiation of therapy, and anxiolytic effects occur later. In comparative studies, improvement matches that on benzodiazepines after 4 weeks (Rocca et al. 1997). Withdrawal effects, particularly rebound, are less problematic with antidepressants, although stopping treatment is associated with a significant rate of relapse, and a withdrawal syndrome has been described for most of the shorter-acting drugs.

3.2.1.1 SSRIs

These drugs increase synaptic serotonin by selectively blocking the serotonin reuptake transporter. In preclinical and human studies acute doses tend to be anxiogenic (Bell and Nutt 1998) but chronic administration has anxiolytic effects, possibly due to downregulation of presynaptic autoreceptors (Blier et al. 1990). There are five SSRIs widely available: citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. Escitalopram, the *S*-enantiomer of citalopram,

Table 3 Antidepressants in anxiety disorders

Antidepressant	Efficacy[a]	Tolerability	Safety	Discontinuation syndrome
MAOI/RIMA	Panic disorder	Significant short- and long-term side-effects; special dietary requirements; moclobemide better tolerated	Significant overdose toxicity (less with moclobemide)	Reported
	Social anxiety disorder PTSD			
Mirtazapine	(Panic disorder, PTSD)	Few side-effects on initiation; few long-term side-effects	Relatively safe in overdose	Not reported
TCA	Panic disorder	Onset worsening; side-effects on initiation; some long-term effects	Significant overdose toxicity	Well-described
	OCD (GAD, PTSD)			
SSRI/SNRI	GAD	Onset worsening; side-effects on initiation; few long-term effects	Relatively safe in overdose (venlafaxine possibly less safe)	Well-described; more common with paroxetine; uncommon with fluoxetine
	OCD			
	Panic disorder			
	PTSD			
	Social anxiety disorder			

[a] Parentheses indicate where evidence is less strong.

was recently licensed in the UK for the treatment of panic disorder and is likely to have the same spectrum of efficacy as citalopram (Waugh and Goa 2003).

The SSRIs as a class are now widely considered to be appropriate first-line anxiolytic drugs; in particular paroxetine, the most potent 5-HT reuptake blocker, has been licensed in the UK for the treatment of each of the major anxiety disorders. Short-term efficacy has been clearly demonstrated in randomised controlled trials, but in common with other antidepressants, research evidence is lacking for long-term efficacy and necessary duration of treatment.

Tolerability and Safety An advantage of the SSRIs has been their improved tolerability relative to their predecessors, the tricyclic antidepressants and benzodiazepines. This has been demonstrated in comparative studies of drugs from these classes (e.g. Zohar and Judge 1996). Nevertheless they are not without side-effects: on initiation nausea, anxiety, jitteriness and insomnia are related to the starting dose; later sedation, asthenia, headache, sweating and sexual dysfunction may occur. Hyponatraemia occurs mostly in the elderly. Some effects are particular to individual drugs within the class; for example paroxetine has anticholinergic properties and can cause dry mouth, constipation and urinary hesitancy; sertraline is more likely to cause dyspepsia and diarrhoea; fluoxetine has agonist activity at 5-HT_{2c} receptors causing headache, agitation and loss of appetite (Goodnick and Goldstein 1998).

Although SSRI overdose can cause seizures, coma and cardiac abnormalities (Barbey and Roose 1998), these toxic effects occur only in large overdoses or in combination with other drugs. Fatality rates are substantially lower than with TCA overdose (Mason et al. 2000). Public attention has been drawn to reports of suicidal and aggressive thoughts and behaviour associated with initiating SSRIs (Healy 2003). The scientific basis for this assertion is disputed and continues to be debated, but it does not appear that SSRI treatment is associated with increased suicidality on a population level (Carlsten et al. 2001; Khan et al. 2003).

Discontinuation Problems Further controversy has surrounded misleading claims in the lay media that SSRIs have "addictive" properties. These centre around reports of patients suffering symptoms when trying to discontinue medication. As with the benzodiazepines, these symptoms may be a recurrence of the premorbid anxiety, although rebound anxiety has not been clearly demonstrated. Self-limiting symptoms associated with SSRI withdrawal have been widely reported (Haddad 1998), and are generally described as the "SSRI discontinuation syndrome" (Table 4). The most frequently occurring symptoms are dizziness, nausea and headache.

The syndrome is more common with paroxetine, possibly due to its anticholinergic activity, and is very uncommon with fluoxetine due to the long half-life of its metabolites (Michelson et al. 2000). It can start 48 h after the

final dose, and although most cases resolve within 2–3 weeks, symptoms may rarely last longer than this.

Drug Interactions SSRIs interact with other drugs that have effects on 5-HT neurotransmission, including TCAs, buspirone, sumatriptan and tryptophan, but particularly important is the interaction with MAOIs that can lead to a synergistic increase in synaptic serotonin. This can result in the serotonin syndrome, comprising restlessness, irritability, tremor, sweating and hyperreflexia. The syndrome can be lethal (Sternbach 1991). In general clinical practice, there should be a washout of 2 weeks between discontinuing MAOI therapy and starting SSRI; a washout of 1–2 weeks should follow SSRI discontinuation (5 weeks for fluoxetine).

The drugs have variable potential for drug interactions via hepatic CYP450 enzymes (Table 5). Escitalopram has the lowest potential for interactions.

Clinical Usage Expert sources recommend SSRIs as first-line treatments of anxiety disorders (American Psychiatric Association 1998; Ballenger et al. 1998a; Bandelow et al. 2002). In preparation for treatment, a full discussion of potential benefits and anticipated side-effects (including discontinuation effects) should be held with the patient (Bull et al. 2002). Some patients have difficulty initiating treatment because of anxiety about side-effects. In these cases the drug may be increased slowly from a low starting dose, if necessary using the

Table 4 SSRI discontinuation syndrome

Symptoms	Neurological symptoms: dizziness, tremor, vertigo, paraesthesia/shooting pains	Somatic distress: nausea, headache, lethargy
	Psychological symptoms: anxiety, confusion, memory problems	Hyperarousal: agitation, restlessness, insomnia, irritability
Risk factors	**Treatment factors:** longer duration of treatment; rapid discontinuation; short half-life drug; possibly increased dose	**Patient factors:** possibly younger age; any psychiatric diagnosis
Therapeutic strategies	Careful assessment: Reassurance Reinstitute therapy if necessary Taper slowly (over 1 month) Switch to fluoxetine	

Table 5 SSRIs and hepatic cytochrome P450 enzymes

SSRI	Inhibitor of enzymes
Citalopram	–
Fluoxetine	2D6 (potent) 3A4 (potent)
Fluvoxamine	1A2 (potent) 3A4 (potent) 2D6 (moderate)
Paroxetine	2D6 (potent) 3A4 (moderate)
Sertraline	2D6 (moderate)

–, No significant enzyme inhibition.

syrup form of fluoxetine or paroxetine, or a benzodiazepine may be used to cover the initiation period.

There is little research evidence to guide a decision on duration of treatment. Some studies have shown continued improvement for up to 12 months, and for most disorders there is a significant relapse rate when treatment is stopped (Lecrubier and Judge 1997; Michelson et al. 1999). Guidelines suggest a duration of 12–24 months if treatment is successful, but if there are risk factors for relapse treatment may be required for much longer. Treatment discontinuation should be carefully planned and medication tapered.

3.2.1.2 Venlafaxine

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI). It shares these properties with the TCAs amitriptyline, clomipramine and imipramine, but it is the first selective SNRI, with low affinity for muscarinic, histaminic and α-adrenergic receptors. At low doses serotonergic effects predominate, but at higher doses the reuptake of noradrenaline is significantly blocked (Melichar et al. 2001). It is available as immediate and extended release (XR) preparations.

There is a large evidence base for the antidepressant efficacy of venlafaxine, but fewer studies have been carried out in anxiety disorders. The best evidence is for GAD (Allgulander et al. 2001) and anxiety symptoms associated with depression (Silverstone and Ravindran 1999). Side-effects on initiation of therapy are similar to those of SSRIs, with nausea being the most common. Higher doses can cause raised blood pressure. A discontinuation syndrome similar to that seen with SSRIs has been reported. Toxicity causes cardiac conduction problems, seizures and coma, and venlafax-

ine overdose is associated with a higher mortality than that of the SSRIs (Buckley and McManus 2002). Although metabolised by CYP2D6, venlafaxine does not inhibit this enzyme and has a low potential for drug interactions.

3.2.1.3 Tricyclic Antidepressants

This group includes compounds with actions on a range of neurotransmitter systems. Their antidepressant efficacy is mediated by reuptake inhibition of serotonin and noradrenaline, although side-effects such as sedation may also be useful. Their use in anxiety disorders is supported by a long history of clinical experience and a reasonable evidence base from controlled trials. Studies support the use of clomipramine (a potent serotonin reuptake inhibitor) in panic disorder and OCD (Lecrubier et al. 1997; Clomipramine Collaborative Study Group 1991), of imipramine in panic disorder and GAD (Cross-National Collaborative Panic Study 1992; Rickels et al. 1993), and of amitriptyline in PTSD (Davidson et al. 1993a). No controlled studies support the use of TCAs in social anxiety disorder.

A meta-analysis of controlled studies suggested superior efficacy of clomipramine over SSRIs in OCD (Kobak et al. 1998), but this has not been demonstrated in direct comparisons and the use of SSRIs has superseded that of TCAs because of advantages in safety and tolerability (Zohar and Judge 1996). Side-effects of TCAs include anticholinergic effects (drowsiness, dry mouth, blurred vision and constipation), antihistaminergic effects (drowsiness and weight gain) and postural hypotension caused by α_1-adrenoceptor blockade, as well as the side-effects common to SSRIs. Some effects are dose-related, and usual practice is to titrate the dose slowly upwards. A discontinuation syndrome similar to that with SSRIs is well-described, and withdrawal should be tapered. Overdose causes hypotension, cardiac arrhythmias, metabolic acidosis, seizures and coma and is associated with a significant mortality. Interactions can occur with other drugs with CNS effects (particularly MAOIs), and with drugs that affect hepatic metabolism.

3.2.1.4 Mirtazapine

Mirtazapine has a novel mechanism of action that in theory should promote anxiolytic effects, although evidence from studies of anxiety disorders is awaited. It increases synaptic release of serotonin and noradrenaline via blockade of presynaptic inhibitory α_2-adrenoceptors, as well as blocking postsynaptic 5-HT_2 and 5-HT_3 serotonin receptors and H_1 histamine receptors. Mirtazapine has good efficacy for anxiety symptoms associated with depression (Fawcett and Barkin 1998), and in controlled studies was superior to

placebo in PTSD (Davidson et al. 2003) and equivalent to fluoxetine in panic disorder (Ribeiro et al. 2001).

The actions of mirtazapine lead to a unique side-effect profile. Important effects are sedation, drowsiness, dry mouth, increased appetite and weight gain. It does not cause initial worsening of anxiety. Tolerance to the sedative properties occurs after a few weeks and paradoxically higher doses tend to be less sedating. The main effect of overdose is sedation. It has the potential for interaction with drugs that inhibit the CYP450 2D6 and 3A4 isoenzymes, although reports of interactions are rare. Discontinuation symptoms have not yet been reported.

3.2.1.5 Inhibitors of Monoamine Oxidase

MAOIs increase synaptic availability of serotonin, noradrenaline and dopamine by inhibiting their intracellular metabolism. The classical MAOIs phenelzine and tranylcypromine bind irreversibly to monoamine oxidase, whilst the newer drug moclobemide is a reversible inhibitor of monoamine oxidase A (RIMA). The long history of use of MAOIs in panic disorder, PTSD and social anxiety disorder is supported by controlled trials (Sheehan et al. 1980; Frank et al. 1988; Versiani et al. 1992). The evidence for moclobemide is less conclusive, with both positive and negative studies in panic disorder and social anxiety disorder, and meta-analysis suggests a lower response rate in social anxiety disorder than with SSRIs (van der Linden et al. 2000). Brofaromine, a RIMA, was effective in a controlled trial in social anxiety disorder but is no longer marketed.

MAOIs have a significant side-effect profile, including dizziness, drowsiness, insomnia, headache, postural hypotension and anticholinergic effects. Asthenia, weight gain and sexual dysfunction can occur during long-term use. A hypertensive reaction (cheese reaction) may follow the ingestion of foods containing tyramine, which must therefore be removed from the diet. Overdose can be fatal due to seizures, cardiac arrhythmias and hypotension. Interactions can occur with sympathomimetics, antihypertensives and most psychoactive drugs, and a washout of 2 weeks is advised when switching from an MAOI to another antidepressant. Moclobemide is better tolerated than MAOIs, although at high doses (>900 mg daily) dietary restrictions should be observed. The main side-effects are dizziness and insomnia. Overdose toxicity is less, although fatalities have been reported.

3.2.2 Buspirone

Buspirone differs from the antidepressants in that its effects are mediated solely via 5-HT_{1A} receptors. It is a partial agonist at postsynaptic 5-HT_{1A} re-

ceptors in the limbic system but a full agonist at autoreceptors in the raphé (Blier and Ward 2003). Acute dosage inhibits serotonin release, but this recovers with continued administration. Anxiolytic effects take several weeks to emerge (Fig. 2). Buspirone is effective in the treatment of GAD (Enkelmann 1991) and for anxiety symptoms in depression (Rickels et al. 1991), either as monotherapy or combined with an SSRI. Response is less favourable if the patient has recently taken a benzodiazepine (DeMartinis et al. 2000). In comparison with benzodiazepines for the treatment of GAD, the onset of the anxiolytic effects are slower but equate to benzodiazepines at 4–6 weeks (Enkelmann 1991). Evidence is lacking to support the use of buspirone in other anxiety disorders.

Buspirone is well-tolerated, with the main side-effects being dizziness, anxiety, nausea and headache. It is tolerated by the elderly (Bohm et al. 1990). It does not cause sexual dysfunction and does not appear to be associated with a discontinuation syndrome. Overdose causes drowsiness but there are no reports of serious toxic effects. A potential for interaction with drugs that inhibit the CYP450 3A4 isoenzyme is not a significant problem in clinical practice. GAD is usually a chronic condition and buspirone is suitable for long-term treatment. Patients should be advised to expect a slow onset of benefits and be reviewed regularly in the early stages of treatment.

3.2.3 β-Blockers

The rationale for using β-adrenoceptor blockers for the treatment of anxiety is twofold: first for the control of symptoms caused by autonomic arousal (e.g. palpitations, tremor) and second because there is a postulated but poorly understood involvement of central noradrenergic activity in anxiety pathways. There is a history of clinical use of these drugs in each of the five major anxiety disorders, but evidence is lacking from controlled clinical trials, and positive findings have often been superseded by later negative studies. Early trials were carried out with propranolol and the more cardioselective atenolol, which has mainly peripheral effects. The efficacy of atenolol in performance anxiety suggests that not all of the effects are centrally mediated (Gorman et al. 1985). Recently there has been interest in pindolol, a β-blocker that also blocks 5-HT_{1A} autoreceptors and may promote serotonergic neurotransmission. Studies using pindolol to augment SSRI treatment of anxiety disorders have had mixed results (Hirschmann et al. 2000; Dannon et al. 2000).

β-Blockers commonly cause side-effects including bradycardia, hypotension, fatigue and bronchospasm. Overdose can cause fatal cardiogenic shock. Because of the doubtful evidence for efficacy and poor tolerability and safety, their use in anxiety disorders is limited. They may have a circumscribed role in the prevention of performance anxiety (Elman et al. 1998).

3.2.4 Antipsychotics

This category contains various drugs that are licensed for the treatment of psychotic disorders. Their effects are mediated via antagonism of D_2 dopamine receptors in the limbic system and cortex. They are loosely divided into two groups: older "classical" drugs such as haloperidol and chlorpromazine that are potent D_2 blockers; and "atypical" antipsychotics that have a lower affinity for D_2 receptors but also block 5-HT_2 receptors. The history of clinical use of classical antipsychotics as "major tranquillisers" has little support from controlled trials (El-Khayat and Baldwin 1998). Evidence is greatest in OCD for the augmentation of SSRI treatment with haloperidol (McDougle et al. 1994) and the atypical drugs risperidone (McDougle et al. 2000) and quetiapine (Atmaca et al. 2002). Recent controlled trials have reported benefits for the atypical drug olanzapine in social anxiety disorder (Barnett et al. 2002) and in addition to SSRIs in PTSD (Stein et al. 2002). Open studies are reporting efficacy for atypical antipsychotics in anxiety disorders and it may be that their clinical use expands in the future.

Atypical antipsychotics have advantages in tolerability and safety over the older drugs. They have a lower incidence of extrapyramidal movement disorders, but may cause sedation and weight gain. Their metabolism by CYP450 enzymes leads to a potential for interaction with many co-prescribed drugs.

3.3 Drugs with Other Mechanisms of Action

3.3.1 Antihistamines

The longstanding use in some countries of hydroxyzine, a centrally-acting H_1-histamine receptor antagonist, is supported by positive findings in controlled trials in GAD (Ferreri and Hantouche 1998; Lader and Scotto 1998). Hydroxyzine promotes sleep and its anxiolytic effects have an early onset. Although it causes sedation, tolerance to this effect often occurs and effects on psychomotor performance are smaller than with benzodiazepines (de Brabander and Deberdt 1990). It is well-tolerated and withdrawal effects have not been reported. Although the evidence for its efficacy is not large, hydroxyzine provides an option for some patients with GAD for whom standard treatments are unsuitable.

3.3.2 Lithium

Lithium is effective in the treatment of mood disorders. Its mechanism of action is unclear but is likely to be via modification of intracellular second

messenger systems. There are no controlled trials demonstrating the efficacy of lithium in anxiety disorders, but there have been case reports of its use as an augmenting agent in panic disorder and OCD. The high toxicity and poor tolerability of lithium limit its use in anxiety in the absence of a stronger evidence base.

4 Diagnostic Aspects

Although every method for categorising anxiety disorders has its shortcomings, in current clinical practice the diagnostic criteria of the American Psychiatric Association (DSM-IV 1994) is most commonly used. "Anxiety disorder" is broken down into sub-syndromes with clear operational criteria. In particular, the criteria are clearly stated for a symptomatic individual to become a case, and this diagnostic threshold is usually defined in terms of impairment of occupational, social or domestic functioning. Although many patients will have symptoms from more than one diagnostic category, it is important to elicit the primary diagnosis, as this will influence the recommended treatment. Comorbid disorders, usually a second anxiety disorder, mood disorder or substance use disorder are common and should be detected. The key diagnostic criteria for the major anxiety disorders are given in Table 6.

5 Pharmacotherapy of Anxiety Disorders

5.1 Generalised Anxiety Disorder

GAD is a prevalent, chronic, disabling anxiety disorder. It is comorbid with other anxiety or mood disorders in the majority of cases (Ballenger et al. 2001). Whilst it is a relatively new diagnostic concept, longitudinal studies have reinforced its validity (Kessler et al. 1999). The core symptoms are chronic worry and tension, and GAD frequently presents with somatic complaints such as headache, myalgia or insomnia (Lydiard 2000). The diagnosis requires symptoms to be present for at least 6 months, although the duration of illness at presentation is usually much longer than this. The presence of comorbidity leads to a worse prognosis (Yonkers et al. 1996). Cognitive behavioural therapy (CBT) has been shown to be effective in GAD and should be considered if available (Durham et al. 1994).

Recommended drugs for GAD are antidepressants, benzodiazepines, buspirone and hydroxyzine (Ballenger et al. 2001). The use of antipsychotics is not supported by controlled trials and is discouraged due to their poor long-term

Table 6 DSM-IV classification of anxiety disorders

Generalised anxiety disorder	Excessive worry/anxiety about various matters for at least 6 months Difficulty in controlling worry Accompanying somatic symptoms (effects of chronic tension) Clinically important distress or impairment of functioning
Obsessive–compulsive disorder	Presence of obsessions (thoughts) or compulsions (behaviours) Symptoms are felt by patient to be unreasonable or excessive Clinically important distress or impairment of functioning
Panic disorder (± agoraphobia)	Severe fear or discomfort peaking within 10 minutes Characteristic physical/psychological symptoms Episodes are recurrent and some are unexpected Anxiety about further attacks or consequences of attacks (Agoraphobia: anxiety about place/situation where panic attack is distressing or escape difficult; situation is avoided, endured with distress or companion is required)
Post-traumatic stress disorder	Severe traumatic event that threatened death or serious harm Felt intense fear, horror or helplessness Repeated reliving experiences Phobic avoidance of trauma-related stimuli Hyperarousal Symptoms last >1 month and cause clinically important distress or impairment of functioning
Social anxiety disorder	Recurrent fears of social or performance situations Situations avoided or endured with distress Clinically important distress or impairment of functioning
Specific phobia	Persistent fear/avoidance of specific object or situation Phobic stimulus immediately provokes anxiety response Clinically important distress or impairment of functioning

tolerability. Pregabalin (related to the anticonvulsant gabapentin) was effective in preliminary trials and may be a future treatment option (Pande et al. 2003).

Recent evidence has brought about a shift in prescribing in GAD and now the usual choice for first-line treatment will be an antidepressant. These are effective, well-tolerated, suitable for long-term use and will treat comorbid mood and anxiety disorders. Suitable drugs include venlafaxine (Allgulander et al. 2001) and the SSRI paroxetine (Stocchi et al. 2003). A non-sedating TCA such as imipramine could also be used if tolerated and where the risk of suicide is deemed to be low (Rickels et al. 1993). Little research is available to guide a decision on treatment duration. The recommendation for panic disorder is to continue therapy for at least 12 months following clinical improvement and this seems a reasonable practice to follow in other anxiety disorders (American Psychiatric Association 1998). Buspirone is also appropriate for long-term therapy in the absence of comorbid depression (Rakel 1990).

Benzodiazepines are effective as monotherapy (Rickels et al. 1993) but are rarely used as first-line in this context because of their side-effect profile. They have a useful short-term role for the rapid control of anxiety symptoms or for the control of somatic symptoms such as muscle tension and insomnia, particularly in the early stages of antidepressant therapy. Hydroxyzine has a limited role but can be considered if other treatments are unsuitable (Lader and Scotto 1998).

5.2 Obsessive–Compulsive Disorder

OCD is a disabling disorder that tends to run a chronic or recurrent course (Sasson et al. 1997). It is diagnosed by the presence of obsessions (recurrent, intrusive thoughts, images or impulses that are experienced as irrational and unpleasant) or compulsions (repetitive behaviours that are performed to reduce a feeling of unease). The symptoms are present for at least 1 h every day and cause impairment of important functions. Prevalence has been measured in various populations and is generally 1%–2%. Symptoms start as early as the first decade and have often been present in excess of 10 years at presentation (Hollander et al. 1996). Depression occurs in more than 50% of cases and there is significant comorbidity with other anxiety disorders, eating disorders and tic disorders. Although classified with the anxiety disorders, OCD is distinct from the rest of this group in its epidemiological profile and neurobiology. In clinical terms, OCD symptoms respond to drugs that enhance serotonergic neurotransmission but not to noradrenergic drugs, and they respond poorly to benzodiazepines.

The recommended first-line drugs for OCD are SSRIs and the TCA clomipramine (Pigott and Seay 1999). The required dose is generally higher than that required for other disorders (e.g. clomipramine 150–250 mg, paroxetine 40–60 mg) and SSRIs have advantages in safety and tolerability. Long-term treatment may be required. There is a good evidence base for the efficacy of CBT, and there may be added benefits from combining psychological and pharmacological therapies (Hohagen et al. 1998). In cases poorly responsive to SSRI treatment, augmentation with the antipsychotics haloperidol, risperidone or quetiapine has support from clinical trials, and addition of buspirone, lithium and the serotonin precursor L-tryptophan have also been tried. In severe treatment-resistant cases the neurosurgical procedure stereotactic cingulotomy should be considered (Jenike et al. 1991).

5.3 Panic Disorder and Agoraphobia

Panic disorder is also a common, chronic and disabling disorder with its peak incidence in young adulthood (Ballenger et al. 1998a). A panic attack is defined

as the sudden onset of anxiety symptoms, rising to a peak within 10 min. DSM-IV requires 4 of 13 defined symptoms to be present. The symptoms are physical symptoms corresponding to those caused by autonomic arousal and psychological symptoms (fear and depersonalisation/derealisation, an altered perception of oneself or the world around). Panic disorder occurs when there are recurrent panic attacks, some of which are uncued or unexpected, and there is fear of having further attacks. Agoraphobia is present in around half of cases (Wittchen et al. 1998) and is a poor prognostic indicator. For some patients the anticipatory anxiety or agoraphobia may be considerably more disabling than the panic attacks themselves.

Panic disorder is comorbid with episodes of depression at some stage in the majority of cases (Stein et al. 1990), with social anxiety disorder and to a lesser extent GAD and PTSD, and with alcohol dependence and personality disorder. Comorbidity results in increased severity and poor response to treatment. Panic disorder is associated with a significantly increased risk of suicide, and this is increased further by the presence of comorbid depression (Lepine et al. 1993).

There is solid evidence for pharmacotherapy of panic disorder with SSRIs (Boyer 1995), the TCAs clomipramine and imipramine (Lecrubier et al. 1997; Cross-National Collaborative Panic Study 1992) and the benzodiazepines alprazolam, clonazepam, lorazepam and diazepam (Ballenger et al. 1988; Beauclair et al. 1994; Charney and Woods 1989; Noyes et al. 1996). Therapy is likely to be required for a minimum of 12 months, and the favourable tolerability of SSRIs will usually lead to their choice as first-line therapy. Patients with panic disorder are sensitive to drug side-effects, so a low initial dose should be used and titrated up to the recommended treatment dose (e.g. paroxetine 10 mg titrated up to 40 mg). Coadministration of a benzodiazepine with an SSRI for the first 2–4 weeks may reduce initial agitation and hasten clinical improvement (Goddard et al. 2001). Once improvement has been achieved, the dose may be slowly reduced to a lower maintenance level. Stopping treatment is associated with discontinuation effects and an increased risk of relapse and should be approached with caution. CBT is an effective treatment for panic disorder and additional benefits may be gained from combination therapy (Oehrberg et al. 1995). Other drugs effective in controlled studies include the antidepressants phenelzine (Sheehan et al. 1980), moclobemide (Tiller et al. 1999), venlafaxine (Pollack et al. 1996), mirtazapine (Ribeiro et al. 2001) and reboxetine (Versiani et al. 2002), and the anticonvulsants sodium valproate (Lum et al. 1991) and gabapentin (Pande et al. 2000).

5.4
Post-traumatic Stress Disorder

This is another anxiety disorder that is common although underdiagnosed, frequently chronic and usually severely disabling (Ballenger et al. 2000). The

diagnosis is given when specific psychological and physical symptoms follow exposure to a traumatising event that invokes fear, horror and helplessness. Symptoms fall into three categories: re-experiencing phenomena (flashbacks, nightmares, distress when memories of trauma are triggered); persistent avoidance of triggers to memory of the trauma and general numbing; hyperarousal (insomnia, irritability, poor concentration, hypervigilance, increased startle response). Symptoms must persist for more than 1 month after the trauma.

PTSD is highly comorbid with depression (Kessler et al. 1995) and substance use disorders, and is associated with a previous exposure to trauma and a previous history of anxiety disorders. PTSD probably carries the highest risk of suicide among the anxiety disorders (Davidson et al. 1991). Without effective treatment the disorder generally runs a chronic, unremitting course.

The evidence base for pharmacotherapy is shallow although improving. Efficacy is established for the SSRIs, particularly paroxetine (Tucker et al. 2001), fluoxetine (Connor et al. 1999) and sertraline (Brady et al. 2000) and the TCA amitriptyline (Davidson et al. 1993a). Treatment is started at standard dose but may be required to be titrated upwards (e.g. paroxetine 20–50 mg). Results from long-term studies are awaited but treatment should be continued for a minimum of 12 months. Medication is given alongside psychotherapy, usually cognitive and exposure therapies (Foa 2000). Other treatments include the antidepressants phenelzine and mirtazapine, the anticonvulsants lamotrigine, sodium valproate, carbamazepine and tiagabine, and augmentation with the atypical antipsychotic olanzapine. The use of benzodiazepines is not advised, as their efficacy is not established and withdrawal symptoms may be particularly distressing. If insomnia is problematic then a non-benzodiazepine hypnotic may be prescribed.

5.5 Social Anxiety Disorder

This disorder is characterised by anxiety symptoms in social or performance situations, accompanied by a fear of embarrassment or humiliation. Situations are avoided or endured with distress. There may be a specific fear of one or two situations (most commonly public speaking), or of three or more situations in the generalized subtype. Epidemiological studies find this to be the most prevalent anxiety disorder among the general population (Magee et al. 1996). Its peak onset is around the time of adolescence, and the resulting impairments can have a profound effect on social and occupational development. If untreated it tends to follow a chronic, unremitting course. Social anxiety disorder is frequently comorbid with depression, other anxiety disorders, alcohol problems and eating disorders. It is associated with an increased rate of suicide that is significantly higher in the presence of comorbidity (Schneier et al. 1992).

Drug studies have focussed on the generalized subtype (Ballenger et al. 1998b). The largest evidence base is for the SSRIs, which are accepted to be the

drug treatment of choice. Treatment is started at standard dose and increased as necessary (e.g. paroxetine 20–50 mg). Duration of treatment is usually for at least 12 months, and there is benefit from combination with CBT (Blomhoff et al. 2001). The other class of antidepressant to be considered is the MAOIs, as phenelzine and moclobemide have controlled trial data to support their use (Versiani et al. 1992). TCAs have no proven efficacy and evidence for venlafaxine and mirtazapine is awaited. Among the benzodiazepines only clonazepam has been shown to be effective as monotherapy, possibly due to its effects on $5HT_{1A}$ receptors (Davidson et al. 1993b). Benzodiazepines may also be used to augment SSRI treatment. Other drugs to consider are the anticonvulsant gabapentin and the antipsychotic olanzapine. β-Blockers are not effective in generalized social anxiety disorder but have a role in symptomatic control in specific performance anxiety.

5.6
Specific Phobia

In specific phobia disorder the patient has an inappropriate or excessive fear of a particular stimulus or situation, such as animals, heights or thunder. An anxiety reaction is consistently and rapidly evoked on exposure to the stimulus, and there is anticipatory anxiety. Population studies have found a surprisingly high prevalence and associated disability, for example a lifetime prevalence of 12% in the National Comorbidity Survey (Magee et al. 1996). The standard treatment for specific phobia is behavioural therapy, and patients rarely present for pharmacological treatment. Nevertheless, there are clinical and pharmacological similarities between patients with specific phobias and those with other anxiety disorders (Verburg et al. 1994), and it might be predicted that anxiolytic medications would have beneficial effects. A small controlled study found an improvement in measures of fear and avoidance after a 4-week trial of the SSRI paroxetine (Benjamin et al. 2000), and there is also a role for the use of a short-acting benzodiazepine to control anxiety prior to exposure to the feared stimulus.

5.7
Depression with Concomitant Anxiety

The prevalence of depression in patients with anxiety disorders is high, as is the prevalence of anxiety in patients with depression (Tylee et al. 1999; Kessler et al. 1998). Among patients presenting for treatment of anxiety symptoms, a large proportion will have a primary diagnosis of depression. In these situations it is critical to offer a treatment plan that will prove effective against both anxiety and depression (Nutt 2000). The presence of both disorders together causes an increase in disability, increased severity of symptoms, a higher likelihood of suicidal thoughts and a poor response to treatment (Lepine et al. 1997).

Antidepressants would be the obvious drug class to select in this patient group, and a number of controlled studies have demonstrated their efficacy. Both SSRIs and TCAs are effective, with the most evidence being for the SSRI paroxetine and the TCAs clomipramine and amitriptyline (Feighner et al. 1993; Ravindran et al. 1997; Stott et al. 1993). Comparative studies favour the SSRIs because of their better tolerability, and safety is also a factor in a group at high risk of suicide. Recent studies have demonstrated the efficacy of the new antidepressants venlafaxine (Silverstone and Ravindran 1999) and mirtazapine (Fawcett and Barkin 1998) in this group, and as their tolerability matches that of the SSRIs they should also be considered as first-line treatment. Benzodiazepines produce a rapid improvement in anxiety but are ineffective at treating depression (Lenox et al. 1984) and are not suitable for long-term treatment in this context. They have a short-term role on initiation of antidepressant therapy in selected patients.

6 Conclusions and Future Directions

It has been shown that the recent shift in clinical practice towards the use of antidepressants, particularly SSRIs, for the first-line treatment of anxiety disorders is supported by research evidence from randomised controlled trials. The use of these drugs is likely to be refined in future years as important gaps in the current knowledge base are filled. These include the optimal duration of treatment, the identification of patients at particular risk of relapse, the benefits of combining drugs with psychotherapy and suitable options for patients resistant to first-line treatments. New drugs available for the treatment of depression may also prove to be effective for anxiety disorders. The prime position of the SSRIs has been reinforced by evidence for the role of serotonin in anxiety; the newer antidepressants tend to have a dual action on serotonergic and noradrenergic neurotransmission, and clarification of the role of noradrenaline in anxiety is likely to occur.

It is only in recent years that drugs acting via GABA neurotransmission have been supplanted as first-line treatments, and new drugs in this class with improved tolerability compared to the benzodiazepines are likely to be marketed in the near future (Ashton and Young 2003). Further down the line, agonists that are selective for specific subunits of the $GABA_A$ receptor offer the prospect of drugs that are anxiolytic but with fewer sedative properties (Nutt and Malizia 2001). Overall it is remarkable that current pharmacological strategies are centred around such a small number of brain mechanisms. Future strategies may involve glutamate neurotransmission (Kent et al. 2002) and neuropeptides such as corticotrophin releasing factor antagonists (Gutman et al. 2001) and substance P antagonists (Argyropoulos and Nutt 2000), and a continued expansion in the range of anxiolytic therapies should be anticipated.

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