The pharmacology of anxiolytics

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Abstract

Given that anxiety disorders are common and chronic and often co-morbid with both medical and psychiatric conditions, effective and safe anxiolytic drugs are in great demand. Serotonergic agents, in particular the selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors, have an established track record for the pharmacological treatment of a wide range of anxiety disorders. Despite their slow onset of therapeutic action, their initial exacerbation of anxiety and some of their long-term unwanted effects, they remain the drugs of first choice in primary care. They are relatively safe and exhibit both anxiolytic and antidepressant effects. Other antidepressants, such as mirtazapine, reboxetine and agomelatine, and the 5-HT$_{1A}$ agonist, buspirone, are alternative agents, although the evidence of their efficacy covers a narrower spectrum of anxiety disorders. Patients with anxiety disorders who are resistant to these drugs may benefit from second-line (tricyclic antidepressants or monoamine oxidase inhibitors) or even specialist initiated third-line (benzodiazepine, anticonvulsant or antipsychotic) therapy. None of the currently available drugs are ideal for every patient and the advantages and disadvantages of each are best considered when treatment is individualised.

Introduction

Anxiety symptoms are appropriate responses to stressful events or situations and often improve spontaneously, particularly if they are mild and of recent onset.

Anxiety disorders – panic disorder (PD), social-anxiety disorder (SAD), generalised anxiety disorder (GAD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) and specific disorder – are however, by nature, disabling, chronic or recurring conditions that require long-term treatment (Table I). Full symptomatic remission is uncommon and their individual, societal and economic impact is substantial.[1]

Anxiety disorders affect anywhere between 8% to 18% of the general population in any given year, with a lifetime prevalence exceeding 28%.[2,3] In South Africa, this figure, which excludes OCD and specific phobia, is estimated at 15.8%.[4] Less than 30% of individuals who suffer from anxiety disorders, however, actively seek treatment.

In addition, the diagnosis of an anxiety disorder is often obscured by the co-existence of depression (75%), other anxiety disorders, substance misuse and medical illness and is probably under-recognised in 15% to 36% of patients, leading some to advocate screening for these conditions with brief questionnaires.[5-7] The result is that only a small minority of anxious patients in primary care receive treatment targeting their anxiety and that, furthermore, roughly a quarter of these patients fail to respond to the available therapies.[8,9]

Pathophysiology

The amygdala, an almond-shaped mass of nuclei located deep within the medial temporal lobes of the brain, plays a pivotal role in threat processing. It is generally regarded as fundamental for the acquisition of conditioned fear and for the expression of innate and learned fear responses. Efferent neurons emerging from the amygdala activate the sympathetic nervous system, thus driving the classic fight-or-flight responses in end organs, such as increased heart rate and blood pressure, and pupillary and bronchodilation.[10]

Functional neuro-imaging studies have demonstrated excessive arousal of the amygdala in patients suffering a range of anxiety disorders and this hyperactivity has been

Table I: Summary of anxiety disorders defined by ICD-10* and DSM-IV-TR diagnostic criteria

Panic disorder (PD):
Recurrent discrete periods of intense fear or discomfort (panic attacks) that peak within 10 minutes and last, on average, 30 to 45 minutes. Accompanied by at least 4 (out of a possible 14) somatic and psychic symptoms. Many patients also suffer from agoraphobia, which is a fear of places or situations where escape or help in the event of a panic attack might be or is perceived to be difficult to access. Present for more than 6 months.

Generalised anxiety disorder (GAD):
Characterised by excessive worry and anxiety. Accompanied by restlessness, irritability, poor concentration, muscle tension, sleep disturbances and easy fatigability. Also accompanied by somatic-anxiety symptoms. Present for more than 6 months.

Social-anxiety disorder (SAD; social phobia):
Marked, persistent and unreasonable fear of being observed or evaluated negatively by others in social interactions or performance situations (fear of public speaking and possible scrutiny by others). Accompanied by somatic and cognitive symptoms. Present for more than 6 months.

Obsessive-compulsive disorder (OCD):
Recurrent obsessions or compulsions or both, causing distress and loss of functioning. Common obsessions involve concerns about cleanliness, harm, sex, hoarding and religion. Compulsions include washing, checking, repeating, ordering, counting and hoarding. Present for more than 6 months.

Post-traumatic stress disorder (PTSD):
Develops after terrifying ordeal involving physical harm or the threat thereof to the patient, a loved one or a stranger (if witnessed by the patient). Recurrent and intrusive distressing recollections of the event, nightmares, reliving of the event via illusions, delusions, hallucinations and flashbacks. Intense distress at subsequent exposure to cues resembling the traumatic event, avoidance of these stimuli, estrangement from others, sleep disturbances, hyper-vigilance and exaggerated startle response. Present for more than 1 month.

Specific phobia:
Excessive or unreasonable fear of single objects or situations (flying, heights, insects, spiders, open spaces etc). Not responsive to drug therapy.

*World Health Organization. International classification of diseases (ICD-10). Geneva: World Health Organization, 1991.
**American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association Press, 2000.

hypothesised as contributing to the hypervigilant monitoring of negative information reported in these disorders.[11,12] Other limbic structures, particularly the hippocampus, the medial prefrontal cortex and the locus coeruleus (which receives information directly from the sensory cortex and is largely under noradrenergic control) are also implicated in anxiety disorders.[10]

At a molecular level, there is evidence of an underlying dysfunction of the neuro-inhibitory γ-aminobutyric acid (GABA) and serotonin (5-HT) neurotransmitter systems. Anxiety may therefore be reduced, either by increasing the effects of GABA with anticonvulsants or by increasing serotonin with antidepressants. Both are effective strategies for anxiolysis, albeit through different pathways.[13]

Of note is that projections from the amygdala to the locus coeruleus form an intersection of many diverse neurochemicals, which have increasingly become the focus of research seeking rational targets for the pharmacological treatment of anxiety disorders.[10]

General treatment issues

Treatment is indicated for those patients who fulfil the diagnostic criteria (ICD-10 or DSM-IV-TR) for an anxiety disorder and is based on patient preference, severity, suicide risk and substance abuse, co-morbidity, history of prior treatment, availability of treatment and cost.[14] Anxiety severity may be measured by means of the generalised anxiety disorder scale, the GAD-7, where a score above 10 suggests that the severity is sufficient to warrant treatment. Patients with other anxiety disorders also score high on this particular scale.[2] Treatment options include either evidence-based psychotherapies, particularly disorder-specific cognitive behavioural therapy by trained and supervised staff, or pharmacological therapy to which all anxiety disorders, with the exception of specific phobias, respond.[8,13]

Both psychological and pharmacological approaches show similar efficacy for the acute treatment of anxiety disorders. Yet there is an apparent strong patient preference for psychological interventions, possibly because patients worry about starting psychopharmacological treatment, fearing unwanted sedation or the risk of becoming dependent on drugs.[1] Cognitive behavioural therapy is not universally available, however, and evidence of its long-term efficacy compared to pharmacotherapy is lacking. Drug treatment, however, is often more readily accessible. It remains unclear whether combining psychological and pharmacological treatments is associated with greater efficacy than either

Table II: Evidence-based drug treatment options for anxiety disorders (adapted from the World Federation of Societies of Biological Psychiatry guidelines[14] and the British Association for Psychopharmacology guidelines[15])

Class	Drug	Dose/day	PD	SAD	OCD	GAD	PTSD
SSRI	Paroxetine	20–60 mg	√	√	√	√	√
	Citalopram	20–60 mg	√	√	√		
	Escitalopram	10–20 mg	√	√	√	√	
	Fluoxetine	20–60 mg	√	√	√		√
	Sertraline	25–200 mg	√	√	√	√	√
	Fluvoxamine	50–300 mg	√	√	√		
SNRI	Venlafaxine	75–225 mg	√	√		√	√
	Duloxetine	60–120 mg				√	
TCA	Clomipramine	25–250 mg	√		√		
	Imipramine	25–250 mg	√			√	√
MAOI	Tranylcypromine	10–60 mg	√	√	√		
RIMA	Moclobemide	300–600 mg		√			
Benzodiazepine	Alprazolam	1.5–8 mg	√				
	Clonazepam	1–4 mg	√	√			
	Diazepam	5–20 mg	√			√	
	Lorazepam	2–8 mg	√			√	
Anticonvulsant	Gabapentin	300–2 400 mg		√			
	Pregabalin	150–600 mg				√	
	Lamotrigine	25–500 mg					√
Atypical antipsychotic	Quetiepine	50–300 mg				√	
	Risperidone	0.5–6 mg					√
	Olanzapine	2.5–20 mg					√
NRI	Reboxetine	4–10 mg	√				
NaSSA	Mirtazapine	30–60 mg			√		√
Azapirone	Buspirone	15–45 mg				√	
MASSA	Agomelatine	25–50 mg				√	

PD: panic disorder; SAD: social-anxiety disorder; GAD: generalised anxiety disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder;
SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant; MAOI: monoamine oxidase inhibitor; RIMA: reversible inhibitor of monoamine oxidase A; NRI: noradrenaline reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressant; MASSA: melatonin agonist and specific serotonin antagonist

√: Licensed indication in South Africa
√: European and Food and Drug Administration-approved and/or extensive randomised controlled clinical trials

treatment given alone. It is for this reason that it may be best to plan sequential steps in patient management.

The current pharmacopoeia for anxiety disorders includes the selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs), the monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs), the benzodiazepines, some anticonvulsants and antipsychotics, and some miscellaneous agents, including the 5-HT$_{1A}$ partial agonist,

buspirone[14] (Table II). It is unfortunately not possible to predict who will respond well to pharmacological therapy and response rates to initial treatment can be unsatisfactory.[1]

Antidepressants, particularly the SSRIs, are generally used first-line, mainly because of the high association of anxiety disorders with depression but also because they lack the potential for dependence and abuse. Antidepressants (and buspirone), however, have a slow onset of therapeutic action, often taking weeks to months to work. In addition, most

of these agents actually exacerbate anxiety at the start of therapy. These drugs therefore need to be initiated at lower doses than are usually used in depression and increased gradually to their therapeutic dose. The short-term ad hoc use of benzodiazepines during initiation of antidepressant therapy is an alternative option for the alleviation of this early increased anxiety, as benzodiazepines, unlike antidepressants, have a fast onset of action, usually showing therapeutic effects within hours or days.[13]

The optimal duration for prescribing after a satisfactory response to acute treatment remains uncertain, although there is broad consensus amongst clinical experts that drug treatment should be continued at full therapeutic dose for at least a year after the symptoms have abated.[1]

First-line drug options[15]

SSRIs and SNRIs

SSRIs (paroxetine, citalopram, escitalopram, fluoxetine, sertraline or flovoxamine) are recommended first-line for patients who have never received medication for anxiety disorders. SNRIs (venlafaxine or duloxetine) are alternative first-line agents. All available compounds have shown good evidence of efficacy in one or more of the anxiety disorders and most have regulatory approval for these conditions. If there is a previous non-response to an SSRI, a different SSRI is recommended. If there is a prior response to benzodiazepines, an SSRI is still preferred. If, however, a patient has a history of responding to a different class of antidepressant, that particular antidepressant should be tried first.[2]

SSRIs act by inhibiting the reuptake of serotonin, which results in an overall increase of the neurotransmitter in the synapse. SNRIs also increase serotonin in this manner but, at higher doses, block the reuptake of noradrenaline and dopamine as well.

The therapeutic effects of these drugs are thought to be related to serotonergic stimulation of 5-HT_1 receptor subtypes, which ultimately leads to their down-regulation in the neurons projecting to the locus coeruleus.[16]

Adverse effects may be due to stimulation of postsynaptic 5-HT_2 (initial increased anxiety, akathisia, agitation, sexual dysfunction) and 5-HT_3 receptor subtypes (nausea, headaches, gastrointestinal disturbances). These effects are generally transient, resolving after a few weeks. Persistent effects include the development of sexual dysfunction, an increase in weight by as much as 6 kg to 10 kg after 6 to 12 months of treatment, disturbed sleep (including initial, middle and late insomnia) and the potential for experiencing discontinuation reactions on cessation of treatment.[13]

Considerations when choosing between the different SSRIs and SNRIs are cost and generic availability, the risk of symptoms when a dose is inadvertently missed (paroxetine and venlafaxine have the shortest half-lives and therefore produce more immediate discontinuation reactions, whereas fluoxetine has the longest half-life and therefore carries very little risk of breakthrough symptoms), the ease of titration (venlafaxine requires careful titration, whereas the others generally do not), the potential for CYP450-mediated drug interactions with other medication (citalopram, escitalopram and venlafaxine have no inhibiting or inducing properties) and the risk of adverse effects (such as venlafaxine causing hypertension).[2]

Practical issues include starting at a low dose, titrating up to average doses after two to three weeks, as tolerated, and thereafter increasing to the maximum tolerated dose by six weeks, unless substantial response has already occurred at the lower dose. Four to six weeks of treatment (eight to twelve weeks for OCD and PTSD) at adequate doses (either the maximum suggested by the manufacturer or the maximum tolerated dose, whichever occurs first) constitutes a proper trial of drug therapy. Treatment may be monitored by means of questionnaires, such as the GAD-7 (for GAD) and the overall anxiety severity and impairment scale (OASIS), in order to gauge whether there has been partial response, response or remission.[17,18]

If there has been partial response, expert guidelines suggest reconfirming the diagnosis, ensuring patient compliance with therapeutic doses and excluding concomitant medication (enzyme-inducing drugs) that may be causing sub-therapeutic levels. Maintaining the full therapeutic dose for a further four to six weeks is plausible in this scenario, as there is still a chance that treatment may work. This is also true for the elderly, where therapeutic action may be delayed.[13]

If, however, a patient fails to respond to treatment altogether after a proper trial of therapy, medication should be switched, usually to a drug of a different class.[14]

Once a patient has benefited from acute therapy, treatment should be continued at the full therapeutic dose for 12 to 24 months or perhaps even longer if there is a high risk of relapse. Thereafter, treatment discontinuation should be planned and medication gradually tapered.[2]

Second-line strategies[15]

TCAs

TCAs have proved themselves in anxiety disorders: imipramine is a useful drug for PD and GAD, clomipramine for PD and OCD and amitriptyline for PTSD. There is no evidence of TCA efficacy in SAD.

The use of TCAs in clinical practice is somewhat limited by their less favourable side effect and safety profiles compared to the newer antidepressant agents. Their therapeutic effects are considered to be related to increasing synaptic serotonin and noradrenaline by blocking the reuptake of these neurotransmitters. Side effects, which may compromise compliance, are related to the multipotent blocking nature of this class of antidepressants. These comprise anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation and confusion in the elderly), alpha-1 blocking effects (postural hypotension and reflex tachycardia) and antihistamine effects (accounting for drowsiness and weight gain). These effects, including an initial increase in anxiety, generally improve after a few weeks.[13] The TCAs, however, are proconvulsant and cardiotoxic and carry a high potential for fatality in overdose. They should thus be avoided in patients with cardiovascular disorders, with epilepsy or in those considered at risk for suicide.

TCAs should be initiated at low doses and increased every three to five days. If low or medium doses fail, the dose should be increased to the highest recommended dose. OCD usually requires medium to high doses.[14]

MAOIs

MAOIs have shown good efficacy in anxiety disorders but their use is restricted by patients needing to maintain a low tyramine diet. The classical MAOIs, such as phenelzine (no longer available in South Africa) and tranylcypromine, bind irreversibly to the serotonin, noradrenaline and dopamine metabolising enzymes, thereby increasing the availability of these neurotransmitters. They have been used successfully in PD, PTSD and SAD. Side effects include drowsiness or insomnia, headache, weight gain and toxicity in overdose. These agents are usually reserved as second-line agents and a washout period of at least two weeks (the time taken to synthesise new enzymes) is required when switching from a MAOI to another antidepressant drug.[13]

The reversible inhibitor of monoamine oxidase type A (RIMA), moclobemide, has demonstrated some efficacy in PD, GAD and SAD. At high doses (> 900 mg/day), selectivity is lost and dietary restrictions need to be observed. Doses are usually given in the morning and at midday to avoid over-stimulating effects, including insomnia.[13]

Third-line and augmenting strategies[15]

Role of benzodiazepines

The benzodiazepines have demonstrated efficacy in most anxiety disorders, although evidence is less compelling in OCD and they are probably ineffective in PTSD.[13]

Benzodiazepines have potent and rapid anxiolytic effects but are controversial agents, firstly because of their inability to treat co-morbid depression and, secondly, because they are associated with sedation, memory problems and dependence. Benzodiazepine withdrawal syndrome, characterised by hyper-arousal, autonomic over-activity, dysphoria and, rarely, seizures or psychosis, occurs most frequently after long-term treatment or when a drug with a short half-life is abruptly discontinued.

Benzodiazepine use is therefore generally confined to the first two to four weeks of treatment with SSRIs, SNRIs or TCAs to mitigate the onset worsening of these agents and sometimes on an occasional basis before exposure to a feared situation. Long-term augmentation or monotherapy is usually reserved for cases that are resistant to treatment with antidepressants alone and may prove highly successful in selected cases within the specialist arena.[13] They are thus recommended third-line, after patients have failed to respond to at least two treatments.[15]

Benzodiazepines act by binding to the GABA$_A$ receptor complex, facilitating the opening of ligand-gated chloride channels and thereby enhancing the effects of the inhibitory neurotransmitter, GABA. Interestingly, GABA$_A$ receptors containing the alpha-2 subunit are hypothesised to mediate anxiolysis, whilst those containing the alpha-1 subunit mediate sedation (sleepiness, incoordination, amnesia). The benzodiazepines may potentiate or be potentiated by alcohol, which also binds to the GABA receptor complex. This possibly contributes to their potential for abuse.[16]

Individual benzodiazepines vary with respect to their potency, half-life and onset of action. Some have the potential for pharmacokinetic interactions, as they utilise the hepatic CYP-450 for oxidative metabolism. Oxazepam, lorazepam and temazepam are directly conjugated and are the preferred agents in liver disease and when multiple drugs are used. Other benzodiazepines with demonstrated efficacy in anxiety disorders include alprazolam, clonazepam and diazepam.[13] Doses should be kept as low as possible but as high as necessary.[14]

When withdrawing benzodiazepines, the dose should be gradually reduced by 10% to 20% at two to four-week intervals. Alternatively, substituting a short-acting drug for one with a long half-life (clonazepam) may prove helpful for some patients when cessation of treatment is planned.[2]

Anticonvulsants

Anticonvulsants work along the broad principles of, firstly, prolonging the inactivated state of voltage-gated ion channels (carbamazepine, valproate, lamotrigine,

topiramate, gabapentin), secondly, inhibiting the excitatory neurotransmitter glutamate and its effects on the *N*-methyl *D*-aspartate (NMDA) ligand-gated channels (topiramate) and, thirdly, enhancing the neuroinhibitory effects of GABA by inhibiting its reuptake (tiagabine), preventing its metabolism (vigabatrin), providing GABA analogues (pregabalin, gabapentin) or stimulating the $GABA_A$ receptor complex directly (benzodiazepines, barbiturates, alcohol).[15] Many of the anticonvulsants have been used as augmenting agents in PD (tiagabine, topiramate, vigabatrin, carbamazepine, sodium valproate, gabapentin), PTSD (carbamazepine, sodium valproate, lamotrigine), GAD (pregabalin) and SAD (gabapentin). Pregabalin has been used as monotherapy for both GAD and SAD.[16] The side effects of these anticonvulsants are varied and beyond the scope of this article.

Atypical antipsychotics

The atypical antipsychotics are antagonists at both the dopamine and the serotonin receptors. Olanzapine has demonstrated efficacy as monotherapy in SAD, whilst others have been employed as augmenting agents for SSRIs in OCD and PTSD. Side effects include postural hypotension, metabolic syndrome, extrapyramidal effects and sexual dysfunction.[13]

Antihistamines

Hydroxyzine has been used to treat GAD but experience in long-term treatment is lacking.[14]

Other anxiolytic drugs

Buspirone is a $5-HT_{1A}$ receptor partial agonist that has shown efficacy for GAD only. It has a desultory onset of action, taking several weeks for therapeutic effects to emerge. Response is less favourable if a patient has recently taken a benzodiazepine. Buspirone is generally safe and well tolerated but may cause initial nausea and dizziness, restlessness and fatigue.[13]

Mirtazapine increases synaptic serotonin and noradrenaline by blocking auto-inhibitory alpha-2 receptors and preferentially blocking postsynaptic $5-HT_2$ and $5-HT_3$ receptors. Unlike the SSRIs and SNRIs, it does not cause initial deterioration of anxiety symptoms and is able to promote sleep by blocking histamine receptors. Other antihistamine effects include increased appetite and weight gain. Pharmacokinetic interactions are rare.[13]

Reboxetine, the noradrenaline reuptake inhibitor (NRI), has demonstrated efficacy in the acute treatment of PD but efficacy in other disorders has not been demonstrated in randomised controlled trials.[16]

Agomelatine (not yet licensed in South Africa) is a melatonergic MT_1 and MT_2 agonist with $5-HT_{2c}$ antagonist properties. It has shown efficacy in the acute treatment of GAD. The most commonly reported side effects are nausea, diarrhoea and headache, which, incidentally, occur at the same frequency as with placebo.[19]

Beta blockers, having no intrinsic or central anxiolytic properties, play only a superficial role in anxiety disorders. They are occasionally used to control the physical manifestations of performance anxiety, such as tremor, palpitations and sweating, when these peripheral sympathetic effects are disabling, such as in concert musicians.[14]

Special considerations

Pregnancy

In pregnancy, the risks of pharmacological therapy need to be carefully weighed against the potential benefits. Drugs with demonstrated teratogenic or neuro-behavioural effects include anticonvulsants, benzodiazepines and the SSRI paroxetine. TCAs and fluoxetine have the longest safety records and remain the drugs of choice.[14]

Breastfeeding

Although TCAs have been detected in breast milk, their presence does not necessarily preclude breastfeeding. Antidepressant drugs that are sedating should, however, be used with caution by breastfeeding mothers.[16] Benzodiazepines may cause sedation, lethargy, poor suckling and weight loss in infants and, if high doses need to be used long-term, breastfeeding should probably be stopped. There have been reports of fluoxetine causing behavioural changes in breast-fed infants but the other SSRIs, citalopram, fluvoxamine, paroxetine and sertraline, appear to be compatible with breastfeeding.[14]

Children and adolescents

Pharmacological treatment is usually reserved for children who have failed to respond to psychological approaches. There is good evidence that the SSRIs and the TCA, clomipramine, are effective in OCD and paroxetine in SAD. The SSRIs are the agents of choice. However, a clear diagnosis should be established first and the risks of treatment highlighted. Depression, co-morbid or otherwise, needs to be excluded because of the potential increased risk at the start of treatment for suicidal ideation, and patients require careful monitoring for the duration of their treatment.[15]

Elderly patients and co-morbid medical conditions

The elderly are more susceptible to adverse drug effects (particularly anticholinergic and extrapyramidal), drug-drug interactions and paradoxical pharmacodynamic effects (benzodiazepines causing aggression, depression and suicidal tendencies).

There are few randomised controlled trials in patients over the age of 65 years. There is, however, demonstrated efficacy for venlafaxine for GAD and citalopram for a range of anxiety disorders. SSRIs that have a low propensity for drug interactions are the preferred agents for the elderly. Treatment should be started at half the recommended dose or less in order to minimise initial side effects. Benzodiazepines and TCAs should be avoided if possible.[15]

In patients with cardiac disease, TCAs and venlafaxine should be used with extreme caution because of their potential for cardiotoxicity. Once again, the SSRIs are preferred.[14]

Epileptic patients should be made aware that most antidepressants lower the seizure threshold. The SSRI, fluoxetine, is an enzyme inhibitor and may affect plasma levels of co-administered anticonvulsant drugs. In addition, traditional anti-epileptic drugs have strong enzyme-inducing properties, which may necessitate adjusting the dose of the anxiolytic drug.[15]

Conclusion

Treating patients with chronic anxiety disorders may be challenging and sometimes frustrating. The potential for good treatment outcomes may be maximised by employing prescribing decisions and algorithms that are evidence based. In this context, the SSRIs and SNRIs are solid first-line choices. Benzodiazepines continue to court controversy and, in primary care, their use should be limited to short-term use as adjuvants to initial pharmacological therapy. The TCAs and MAOIs show more toxicity than the newer antidepressants, yet their efficacy in anxiety disorders is undisputed. Specialist treatment options include benzodiazepines and other anticonvulsants as well as the atypical antipsychotics, either alone or as augmenting agents. There is a reassuringly robust armamentarium of anxiolytic drugs, but in order to optimise compliance and treatment responses, these agents should be prescribed judiciously after due consideration of their individual pharmacological advantages and disadvantages.

References

1. Baldwin DS. Room for improvement in the pharmacological treatment of anxiety disorders. Current Pharmaceutical Design 2008;14:4382–3491.

2. Roy-Byrne P, Veitengruber JP, Bytritsky A, et al. Brief intervention for anxiety in primary care. J Am Board Fam Med 2009;22(2):175–86.

3. Strine TW, Mokdad AH, Balluz LS, et al. Depression and anxiety in the United States: Findings from the 2006 behavioural risk factor surveillance system. Psychiatr Serv 2008;59:1383–90.

4. Herman AA, Stein DJ, Seedat S, Heeringa SG, Moornal H, Williams DR. The South African stress and health (SASH) study: 12-month and lifetime prevalence of common mental disorders. SAMJ 2009;99(5):339–44.

5. Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJG, Kubzansky L, Lydiard RB. Anxiety disorders and co-morbid medical illness. General Hospital Psychiatry 2008;30:208–25.

6. Kessler D, Lloyd K, Lewis G, Gray DP. Cross sectional study of symptom attribution and recognition of depression and anxiety in primary care. BMJ 1999;318:436–90.

7. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: Prevalence, impairment, co-morbidity and detection. Ann Intern Med 2007;146:317–25.

8. Stein MB, Sherbourne CD, Craske MG, et al. Quality of care for primary care patients with anxiety disorders. Am J Psychiatry 2004;161:2230–7.

9. Liebowitz MR, DeMartinis NA, Weihs K, et al. Efficacy of sertraline in severe generalised social anxiety disorder; Results of a double blind placebo controlled study. J Clin Psychiatry 2003;64:785–92.

10. Bandelow B. Future perspectives: New compounds with putative anxiolytic effects. Program and abstracts of the International Congress of Biological Psychiatry; 2004; Sydney, Australia. Workshop 56.

11. Drevets WC. Neuroimaging abnormalities in the amygdala in mood disorders. Ann N Y Acad Sci 2003;985:420–44.

12. Whalen PJ, Shin LM, Somerville LH, McLean AA, Kim H. Functional neuroimaging studies of the amygdala in depression. Semin Clin Neuropsychiatry 2002;7:234–42.

13. Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. CNS Spectr 2005;10(1):49–56.

14. Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, WFSBP task force. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. World J Biol Psychiatry 2008;9(4):248–312.

15. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005;19(6):567–96.

16. Garner M, Mohler H, Stein DJ, Mueggler T, Baldwin DS. Research in anxiety disorders: From the bench to the bedside. Eur Neuropsychopharmacol 2009;19:381–90.

17. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalised anxiety disorder: The GAD-7. Arch Intern Med 2006;166:1092–7.

18. Norman SB, Cissell SH, Means-Christensen AJ. Development and validation of an overall anxiety severity and impairment scale (OASIS). Depres Anxiety 2006;23:245–9.

19. Stein DJ, Ahokas A, Fabiano A. Agomelatine in generalised anxiety disorder: A randomised placebo controlled study. Eur Neuropsychopharmacol 2007;17(4): S509–S510.