An update on the pharmacological treatment of anxiety and related disorders

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Abstract

The anxiety disorders, obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are common and debilitating, often coexist with medical and psychiatric conditions, and usually require long-term treatment. Effective anxiolytic drugs include the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs), which are the preferred agents in primary care. Patients who fail to respond adequately to these may benefit from second-line tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). Alternative antidepressants include agomelatine and mirtazapine. Benzodiazepines, the anti-epileptic agent, pregabalin, and atypical antipsychotics are generally reserved for specialist use. The 5-HT$_{1A}$ agonist, buspirone, and the antihistamine, hydroxyzine, may also be useful, although the evidence for their efficacy covers a very narrow spectrum. This review describes the pharmacology of these anxiolytics and provides updated evidence for their use in the anxiety and related disorders.

Keywords: anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, anxiolytics

Introduction

"Anxiety is the dizziness of freedom." (Søren Kierkegaard, 19th century existentialist philosopher)

Anxiety symptoms are appropriate responses to stressful events or situations and are usually self-limiting, particularly if they are mild and of recent onset. Conversely, in anxiety-dominated disorders, these symptoms may be severe and chronic, disabling and recurrent, causing significant personal distress, impaired function and reduced quality of life, and thus requiring long-term treatment.[1] In the past anxiety disorders specific disorder, generalised anxiety disorder, panic disorder, social anxiety disorder, obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). However, these are no longer grouped together, which is somewhat disorienting, particularly when seeking current treatment guidance. Rather, the latest DSM V classification has reassigned them to the following four main categories: anxiety disorders, obsessive-compulsive and related disorders, trauma and stressor-related disorders and somatic symptom and related disorders[2] (Table 1). The common thread for all of these conditions is excessive fear (and therefore avoidance and worry), often in response to specific objects or situations and in the absence of true danger.[3]

Collectively, these particular anxiety-related disorders affect approximately 15% of the general population in any given year, with a lifetime prevalence exceeding 20%.[4,7] In South Africa this figure, which excludes OCD and specific phobia, is estimated at 15.8%.[8] Under a third of individuals who suffer from chronic anxiety and related disorders actively seek treatment, and the diagnosis is often obscured by the co-existence of depression (75%), other anxiety disorders, substance misuse and medical illness, leading to under recognition in 15–35% of patients.[4,9,10] Only a small minority of chronically anxious patients in primary care receive treatment targeting their anxiety and roughly a quarter of these patients fail to respond to the available therapies.[11,12] Full symptomatic remission of these disorders is uncommon and their individual, societal and economic impact may be substantial.[13]

Pathophysiology

In chronic anxiety disorders, seemingly innocuous stimuli are seen as life-threatening events, and the brain and body respond vigorously to these perceived threats in order to survive. Patients with anxiety disorders are often on high alert, and act accordingly by worrying, becoming hyper-vigilant and avoiding potentially "dangerous" situations.

The amygdala, one of four basal ganglia located deep within the medial temporal lobes of the brain, forms an important part of the limbic system and is involved with experiencing emotions. It plays a pivotal role in threat processing and is generally regarded as fundamental for the acquisition of conditioned fear and for the expression of innate and learned fear responses. Efferent neurons projecting from the amygdala ultimately activate the sympathetic nervous system thus

Table I: Summary of the classification and main characteristics of the anxiety disorders, obsessive compulsive disorder and post-traumatic stress disorder[2,7]

Anxiety disorders
Specific phobia Excessive or unreasonable fear of (and restricted to) single people, animals, objects, or situations (for example, dentists, spiders, lifts, flying, seeing blood) which are either avoided or are endured with significant personal distress.
Separation anxiety disorder Fear or anxiety concerning separation from those to whom an individual is attached: common features include excessive distress when experiencing or anticipating separation from home, and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation.
Social anxiety disorder A marked, persistent and unreasonable fear of being observed or evaluated negatively by other people, in social or performance situations, which is associated with physical and psychological anxiety symptoms. Feared situations (such as speaking to unfamiliar people or eating in public) are either avoided or are endured with significant distress.
Panic disorder (with or without agoraphobia) Recurrent unexpected surges of severe anxiety ('panic attacks'), with varying degrees of anticipatory anxiety between attacks. Panic attacks are discrete periods of intense fear or discomfort, accompanied by multiple physical or psychological anxiety symptoms. Panic attacks typically reach their peak within 10 minutes and last around 30–45 minutes. Most develop a fear of having further panic attacks. Around two-thirds of patients with panic disorder develop agoraphobia, defined as fear in places or situations from which escape might be difficult or in which help might not be available, in the event of having a panic attack. These situations include being in a crowd, being outside the home, or using public transport: they are either avoided or endured with significant personal distress.
Agoraphobia Many patients with panic disorder 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.
Generalised anxiety disorder Excessive and inappropriate worrying that is persistent (lasting more than a few months) and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension and disturbed sleep). Is often co-morbid with major depression, panic disorder, phobic anxiety disorders, health anxiety and obsessive-compulsive disorder.
Obsessive-compulsive related disorders
Obsessive compulsive disorder (OCD) Recurrent obsessive ruminations, images or impulses, and/or recurrent physical or mental rituals, which are distressing, time-consuming and cause interference with social and occupational function. Common obsessions relate to contamination, accidents, and religious or sexual matters; common rituals include washing, checking, cleaning, counting and touching.
Trauma and stressor related disorders
Post-traumatic stress disorder (PTSD) A history of exposure to trauma (actual or threatened death, serious injury, or threats to the physical integrity of the self or others) with a response of intense fear, helplessness or horror; with the later development of intrusive symptoms (such as recollections, flashbacks or dreams), avoidance symptoms (for example, efforts to avoid activities or thoughts associated with the trauma), negative alterations in cognitions and mood, and hyper-arousal symptoms (including disturbed sleep, hyper-vigilance and an exaggerated startle response).
Somatic symptom and related disorders
Illness anxiety disorder Excessive or disproportionate preoccupations with having or acquiring a serious illness, with excessive health-related behaviours and high levels of alarm about personal health status.

driving the classic fight-flight responses in end organs, such as increased heart rate and blood pressure, pupillary- and bronchodilation.[14] Functional neuro-imaging studies have demonstrated excessive activation of the amygdala in patients suffering a range of anxiety disorders and this hyperactivity has been hypothesised to contribute significantly to the hyper-vigilant monitoring of negative information reported in these disorders[3,15,16] (Figure 1).

Other limbic structures, particularly the ventral medial prefrontal cortex and hippocampus (that play prominent roles in learning and remembering that stimuli that used to predict threat no longer do so) as well as the anterior cingulate cortex and insular cortex (that respond to emotional or threatening stimuli including mediating the monitoring of internal body states) may also be hyper-responsive in anxiety-prone individuals.[3] Thus, hyper-activation of limbic–hypothalamic–

pituitary–adrenal axis and secretion of stress hormones like corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol are likely to be highly relevant to the neuro-circuitry of fear and anxiety.[3]

At a molecular level, there is evidence for 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 serotonin with antidepressants or by diminishing neuronal excitation with anticonvulsants. Both are effective strategies for anxiolysis, albeit through different pathways.[17]

General treatment issues

Treatment is indicated for those patients who fulfil the diagnostic criteria (DSM V) for an anxiety disorder, OCD or PTSD, and is based on patient preference, severity, suicide risk
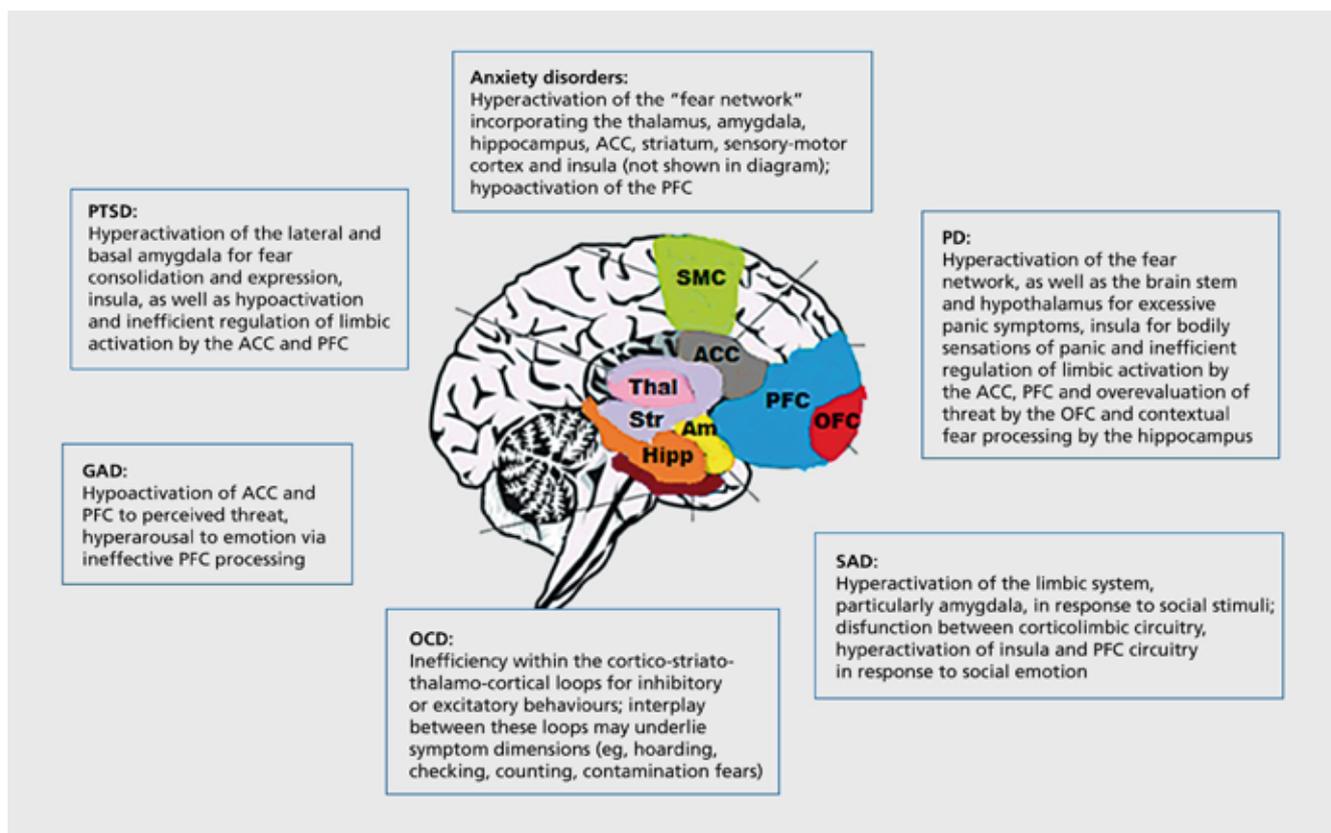
Figure 1: Postulated neural correlates of anxiety and related disorders. PTSD, post-traumatic stress disorder; PD, panic disorder; GAD, generalised anxiety disorder; SAD, social anxiety disorder; OCD, obsessive-compulsive disorder; SMC, sensory-motor cortex; ACC, anterior cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex; Thal, thalamus; Str, striatum; Am, amygdala; Hipp, hippocampus[18]

and substance abuse, co-morbidity, history of prior treatment, availability of treatment and cost.[19] Options include evidence-based psychotherapies, particularly disorder-specific cognitive behavioural therapy, or pharmacotherapy.[11,17] Although psychological and pharmacological approaches show similar efficacy for the acute treatment, there is an apparent strong patient preference for psychological interventions possibly because patients worry about starting drug treatment, fearing unwanted sedation or the risk of becoming dependent on drugs.[13] Cognitive behavioural therapy is not universally available, however, whereas drug treatment is more readily accessible. It remains unclear whether combining psychological and pharmacological treatments is associated with greater efficacy than either treatment given alone.[7]

The current pharmacopoeia for anxiety and related disorders includes the antidepressants (SSRIs, SNRIs, TCAs, MAOIs), the benzodiazepines, some anticonvulsants and antipsychotics, and a variety of miscellaneous agents including the $5-HT_{1A}$ partial agonist, buspirone.[7,19] (Table 2) Unfortunately, it is not possible to predict who will respond to pharmacological therapy and response rates to initial treatment may be disappointing.[13]

Antidepressants, particularly the SSRIs and SNRIs, are generally used first line, mainly because of the high association between anxiety disorders and depression, but also because they lack the potential for dependence and abuse. However, the antidepressants 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. For this reason, these drugs 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 when initiating antidepressant therapy is an alternative option for alleviating this early increased anxiety. Benzodiazepines, unlike antidepressants, have a fast onset of action, usually showing therapeutic effects within hours or days.[17]

The optimal duration for prescribing after a satisfactory response to acute treatment remains uncertain, although there is broad consensus that drug treatment should be continued at full therapeutic dose for at least a year after symptoms have abated.[13]

Antidepressants

SSRIs and SNRIs

For patients who have never received medication for an anxiety disorder, a selective serotonin reuptake inhibitor (SSRI) is recommended. Serotonin and noradrenaline reuptake inhibitors (SNRIs) are alternative first line agents. All available agents have shown efficacy in one or more of the anxiety disorders, OCD and PTSD, and most have regulatory approval for these conditions. For previous non-response to an SSRI, a different SSRI is recommended, while if there has been prior response to benzodiazepines, an SSRI is still preferred. Conversely, if the patient has a history of responding to a

Table II: Drug treatment options for the anxiety disorders, OCD and PTSD
(Adapted from World Federation of Societies of Biological Psychiatry Guidelines[14])

Class	Drug	Dose/day	PD	SAD	OCD	GAD	PTSD
SSRI	Paroxetine	20–60 mg	x	x	x	x	x
	Citalopram	20–60 mg	x	x	x		
	Escitalopram	10–20 mg	x	x	x	x	
	Fluoxetine	20–60 mg	x	x	x		x
	Sertraline	25–200 mg	x	x	x	x	x
	Fluvoxamine	50–300 mg	x	x	x		
SNRI	Venlafaxine	75–225 mg	x	x		x	x
	Duloxetine	60–120 mg				x	
TCA	Clomipramine	25–250 mg	x		x		
	Imipramine	25–250 mg	x			x	x
MAOI	Phenelzine	45–90 mg	x	x	x		
MASSA	Agomelatine	25–50 mg				x	
NaSSA	Mirtazapine	30–60 mg			x		x
Benzodiazepine	Alprazolam	1.5–8 mg	x				
	Clonazepam	1–4 mg	x	x			
	Diazepam	5–20 mg	x			x	
	Lorazepam	2–8 mg	x			x	
Anticonvulsant	Pregabalin	150–600 mg				x	
Antipsychotic	Quetiapine	50–300 mg				x	
Azapirone	Buspirone	15–45 mg				x	

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; NaSSA: noradrenergic and specific serotonergic antidepressant; MASSA: melatonin agonist and specific serotonin antagonist

different class of antidepressant, that particular antidepressant should be tried first.[6]

SSRIs act by inhibiting the re-uptake 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 re-uptake of noradrenaline and dopamine as well.

The therapeutic effects of these drugs are thought to be related to serotonergic stimulation of serotonin $5\text{-}HT_1$ and $5\text{-}HT_2$ receptor subtypes in the dorsal periaqueductal grey matter of the midbrain (as shown in panic disorder), or alternatively to desensitisation of $5\text{-}HT_{2c}$ receptors and increased stimulation of $5\text{-}HT_{1A}$ receptors in forebrain structures, including the amygdala and medial prefrontal cortex (as shown in generalised anxiety disorder) resulting in reduced activation of the amygdala, medial prefrontal cortex and insula.[20]

Adverse effects are possibly due to stimulation of postsynaptic $5\text{-}HT_2$ (initial increased anxiety, akathisia, agitation, sexual dysfunction) and $5\text{-}HT_3$ receptor subtypes (nausea, headache, 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 6–10 kg after six to twelve months of treatment, disturbed sleep including initial, middle and late insomnia, and

the potential for experiencing discontinuation reactions on cessation of treatment.[17]

Considerations when choosing between the different SSRIs and SNRIs are: cost and generic availability, the risk for symptoms when a dose is inadvertently missed (paroxetine and venlafaxine have the shortest half-lives and therefore produce more immediate discontinuation reactions; fluoxetine has the longest half-life and therefore carries very little risk for 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 (fluoxetine and paroxetine inhibit CYP450 enzymes, while citalopram, escitalopram and venlafaxine have no inhibiting or inducing properties) and the risk of adverse effects such as venlafaxine potentially causing hypertension at higher doses or duloxetine causing hepatotoxicity in those vulnerable to liver disease.[6,21,22]

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 with questionnaires such as the GAD-7 (generalised anxiety disorder) or OASIS (overall anxiety severity and impairment scale) in order to gauge whether there has been partial response, response or remission.[6]

If there has been a partial response, guidelines suggest reconfirming the diagnosis, ensuring patient compliance with therapeutic doses and excluding concomitant medication (enzyme inducing drugs) which may be causing sub-therapeutic levels. Maintaining the full therapeutic dose for a further 4–6 weeks is plausible in this scenario as there is still a chance that treatment will work. This is also true for the elderly where therapeutic action may be delayed.[17]

However, if 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 is continued at the full therapeutic dose for 12–24 months or perhaps even longer if there is a high risk of relapse. Thereafter, treatment discontinuation is planned, and medication gradually tapered.[6]

Tricyclic antidepressants (TCAs)

TCAs are effective in a variety of anxiety disorders; for instance imipramine is useful for panic disorder and generalised anxiety disorder, clomipramine for panic disorder and OCD, and amitriptyline for PTSD. However, 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 related to increasing synaptic serotonin and noradrenaline by blocking the reuptake of these neurotransmitters.[17]

Side-effects, which may compromise compliance, are mainly due to the multipotent blocking nature of this class of antidepressants: 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.[17] However, the TCAs are proconvulsant and cardiotoxic and carry a high potential for fatality in overdose. They are therefore avoided in patients with cardiovascular disorders, epilepsy or in those considered at risk for suicide. TCAs are initiated at low doses and increased every 3–5 days. If low or medium doses fail, the dose is increased to the highest recommended dose. Patients with OCD usually require higher doses.[14,23]

Monoamine oxidase inhibitors (MAOIs)

Irreversible MAOIs have shown good efficacy in the anxiety disorders, but their use is restricted by patients needing to maintain a low tyramine diet. The classical MAOIs such as phenelzine 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 panic disorder, PTSD and social anxiety disorder. 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 any other antidepressant drug.[17]

The reversible inhibitor of monoamine oxidase type A, moclobemide, has demonstrated some efficacy in panic disorder and social anxiety disorder. 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 the over-stimulating effects including insomnia.[17]

Other antidepressants

Agomelatine is a melatonergic MT_1 and MT_2 agonist with serotonin $5\text{-}HT_{2c}$ antagonist properties. It has shown good efficacy in the acute treatment as well as the prevention of relapse of generalised anxiety disorder.[24] The most commonly reported side-effects are nausea, diarrhoea and headache, which incidentally occur at the same frequency as with placebo.[24,25] However, elevations of hepatic enzymes may occur and regular monitoring of liver function tests is required in the early months of treatment.[26]

Mirtazapine increases synaptic serotonin and noradrenaline by antagonising auto-inhibitory alpha-2 receptors and preferentially blocking postsynaptic $5\text{-}HT_2$ and $5\text{-}HT_3$ 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.[17,27]

Anticonvulsants

Benzodiazepines

The benzodiazepines have demonstrated efficacy in most anxiety disorders, although the evidence is less compelling in OCD and they are probably ineffective in PTSD.[17] 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, most frequently occurs after long-term treatment or when a drug with a short half-life is abruptly discontinued. Sporadic benzodiazepine use is therefore generally confined to the first two to four weeks of treatment with the SSRIs, SNRIs or TCAs in order to mitigate the additional anxiety associated with commencing 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.[7,17,27,28] They are thus recommended in patients who have failed to respond to at least three treatments, including psychotherapy.[7]

Benzodiazepines act by binding to the GABA$_A$ receptor complex and enhance the effects of the inhibitory neurotransmitter, GABA, by facilitating the opening of ligand-gated chloride channels. 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.[29]

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 CYP450 enzymes 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.[17] Doses should be kept as low as possible, but as high as necessary.[14]

When withdrawing benzodiazepines the dose should be gradually reduced by 10–20% 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.[4]

Pregabalin

Pregabalin is an anticonvulsant that has proven efficacy in both the acute treatment and prevention of relapse in generalised anxiety disorder and social anxiety disorder. In generalised anxiety disorder, it also relieves depressive symptoms of mild to moderate intensity and reduces the severity of sleep disturbance.[30] Although structurally related to the neuro-inhibitory GABA, its postulated mechanism of action is via high-affinity binding to the alpha-2-delta subunit of the P/Q type voltage-gated calcium channel in overexcited presynaptic neurons, thereby reducing the release of excitatory neurotransmitters such as glutamate.[31] Common adverse effects include drowsiness and dizziness, while long-term treatment is accompanied by weight gain in approximately a fifth of patients.[7] It is potentially disadvantageous in patients with renal disease as it is cleared via this route. Discontinuation symptoms after abrupt withdrawal have been reported, as has its abuse, generally in those with a history of other substance abuse.

Other agents

Atypical antipsychotics are antagonists at both the dopamine and serotonin receptors. While olanzapine has demonstrated efficacy as monotherapy in social anxiety disorder, the strongest evidence for benefit is restricted to acute treatment and prevention of relapse with quetiapine in generalised anxiety disorder. Other atypical antipsychotics may be used as augmenting agents for SSRIs in OCD.[7] Side-effects include postural hypotension, metabolic syndrome, extrapyramidal

effects and sexual dysfunction, and they are therefore reserved for use after failed therapies.[17]

Antihistamines, such as hydroxyzine, have been used in the acute treatment of generalised anxiety disorder, but experience in long-term treatment is lacking.[14]

Buspirone is a 5-HT$_{1A}$ receptor partial agonist that has shown efficacy in the acute treatment of generalised anxiety disorder only. It has a desultory onset of action, taking several weeks for therapeutic effects to emerge. Response is less favourable in patients who have recently taken a benzodiazepine. Buspirone is generally safe and well tolerated, but may cause initial nausea and dizziness, restlessness and fatigue.[17]

Conclusion

Treating patients with a chronic anxiety disorder, OCD or PTSD may be challenging. 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 agents that dampen neuronal excitability, including benzodiazepines and other anticonvulsants in particular pregabalin, as well as atypical antipsychotics used either alone or as augmenting agents. Although there is a reassuringly robust arsenal of anxiolytics, none of the currently available drugs is ideal for every patient. These agents should therefore be prescribed judiciously after due consideration of their individual pharmacological advantages and disadvantages in order to optimise patient compliance and treatment response.

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