

# Overview and management of anxiety disorders

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## Abstract

Anxiety disorders are some of the most frequently occurring mental disorders in South Africa and can negatively impact on a patient's quality of life and disrupt important activities of daily living. They are a result of abnormal neurotransmitter function within the central nervous system. Abnormal functioning of neurochemicals as well as abnormal chemoreceptor activity lead to anxiety. There are various neurotransmitters that are involved in anxiety such as serotonin, glutamate, gamma-aminobutyric acid. Treatment options for anxiety disorders include lifestyle modifications, psychotherapy and pharmacotherapy. Several drug classes are indicated for the management of anxiety disorders with selective serotonin reuptake inhibitors considered as first-line therapy. Benzodiazepines are effective in reducing anxiety symptoms, but their use is often limited by the risk of abuse and adverse-effect profile. Pharmacists should be aware of adverse drug reactions and drug interaction for the various medications used in the treatment of anxiety disorders. Lifestyle modifications are as important as pharmacotherapy.

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## Introduction

Anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioural disturbances. Fear is the emotional response to real or perceived imminent threat, whereas anxiety is anticipation of future threat. Panic attacks feature prominently within the anxiety disorders as a particular type of fear response. Panic attacks are not limited to anxiety disorders but can be seen in other mental disorders as well. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) was released in May 2013.<sup>1</sup> The DSM-5 reclassifies obsessive-compulsive disorder (OCD) in the new obsessive-compulsive and other related disorders chapter, while post-traumatic stress disorder (PTSD) is included in the trauma- and stressor-related disorders chapter.<sup>1</sup> Selective mutism and separation anxiety disorder are both now considered as anxiety disorders (formerly in the disorders usually first diagnosed in infancy, childhood or adolescence category). Agoraphobia is decoupled from panic disorder and is no longer a requirement for individuals aged older than 18 years to recognise fear as excessive. The DSM-5 anxiety disorders include:

- Panic disorders (PD)
- Generalised anxiety disorder (GAD)
- Social anxiety disorder (SAD)
- Agoraphobia
- Specific phobia

- Separation anxiety disorder
- Selective mutism<sup>2</sup> (SM)

## Epidemiology

Anxiety disorders are the most common class of mental disorders. In the United States 31% of the population will experience anxiety.<sup>3</sup> The South African Stress and Health (SASH) study was the first large-scale population-based study of common mental disorders in South Africa. The lifetime prevalence for any psychiatric disorder was 30.3%, and the most prevalent 12-month and lifetime disorders were the anxiety disorders. Among the broad classes of disorders, anxiety disorders were the most prevalent (8.1%), followed by substance use disorders (5.8%) and mood disorders (4.5%). The anxiety disorder with the greatest proportion of severe cases was panic disorder (66%), followed by social phobia (43%) and post-traumatic stress disorder (36%). The Western Cape had the highest 12-month and lifetime prevalence rates, and the lowest rates were in the Northern Cape.<sup>4</sup>

## Pathophysiology

Various structures within the brain as well as the abnormal function of several neurotransmitters are associated with the development of anxiety disorders. The locus coeruleus, which is the primary norepinephrine (NE)-containing site within the brain, projects norepinephrine neurons to other areas of the brain in order to modulate mood, cognition, and sleep. Fear is processed

by the amygdala, which also stores emotional memories. The hippocampus is responsible for encoding memories and is involved in fear conditioning. Stress response is mediated by the hypothalamus.<sup>5</sup>

The emotional-processing brain structures historically are referred to as the “limbic system” which consists of the amygdala, hippocampus, thalamus, hypothalamus, basal ganglia, and cingulate gyrus.<sup>6</sup> Specific limbic structures, particularly the ventral medial prefrontal cortex and hippocampus (that play an important role in learning and memory of potential threat) as well as the anterior cingulate cortex and insular cortex (that respond to emotionally threatening stimuli including mediating the monitoring of internal body states) may also be hyperresponsive in anxiety-prone individuals (See Figure 1). Hippocampal volume and neurogenesis (growth of new cells) in this structure have been implicated in stress sensitivity and resiliency in relationship to mood and anxiety disorder.<sup>6</sup> The hyperactivation of the limbic-hypothalamus-pituitary-adrenal axis and secretion of stress hormones (corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol) are likely to be highly relevant to neuro-circulatory fear and anxiety (See Figure 1).<sup>7</sup>

**Table I.** A summary of the neuronal changes in the brain during anxiety disorders (Adapted from Brook & Stein, 2016)<sup>9</sup>

Disorder	Neuronal Changes
<b>Anxiety disorders</b>	Hyperactivation of the “fear” network incorporating the thalamus, amygdala, hippocampus, anterior cingulate gyrus and striatum (not shown on diagram)
<b>Panic disorder</b>	Hyperactivation of the brain stem and hypothalamus, ineffective regulation of limbic activation by anterior cingulate gyrus
<b>General anxiety disorder</b>	Hypoactivation of the anterior cingulate gyrus and prefrontal cortex to perceived threat, hyperarousal to emotion via ineffective prefrontal cortex
<b>Social anxiety disorder</b>	Hyperactivation of the amygdala in response to social stimuli

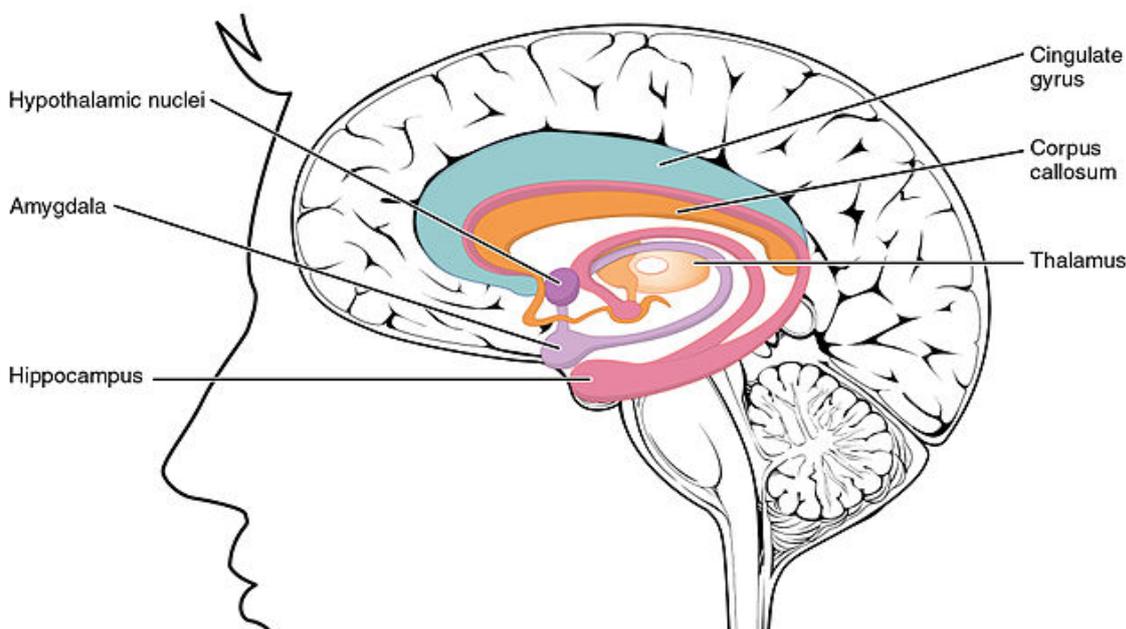
The neurotransmitters involved in the pathogenesis of anxiety disorders include:

- Norepinephrine (NE)
- Serotonin (5-HT<sub>1</sub>)
- Dopamine
- Glutamate, and gamma-aminobutyric acid (GABA)<sup>9</sup> (See Table II)

Compared to the general population, patients with anxiety disorders display increased NE and decreased 5-HT<sub>1</sub>, making these neurotransmitters the main targets for pharmacological therapy. Dopamine is also upregulated during states of anxiety, thus dopamine-D<sub>2</sub> blockade has exhibited anxiolytic effects. However, dopaminergic signalling may also produce feelings of confidence. Therefore, while some patients do respond well to prodopaminergic agents, others may report an increase in anxiety symptoms. The glutamate-NMDA (*N*-methyl-d-aspartate)-receptor substrate mediates learning and memory including fear consolidation. GABA is decreased in anxiety disorders. Therefore, drugs that increase GABA neurotransmission produce anxiolytic effects in these patients.<sup>10,11</sup>

**Table II.** Summary of neurotransmitters, receptors and the physiological change in anxiety disorders<sup>10,12</sup>

Neurotransmitters	Receptors	Physiological change during anxiety
<b>Norepinephrine</b>	α <sub>1</sub> α <sub>2</sub>	Increased NE neurotransmitter release
<b>Serotonin</b>	5-HT <sub>1A</sub> 5-HT <sub>2C</sub>	Decreased serotonin neurotransmitters release
<b>Dopamine</b>	D <sub>2</sub>	Receptors upregulated during states of anxiety
<b>Glutamate</b>	Glutamate-NMDA ( <i>N</i> -methyl-d-aspartate)	Decreased release of neurotransmitters
<b>GABA</b>	GABA <sub>A</sub> with α subunits (α <sub>1</sub> , α <sub>2</sub> , α <sub>3</sub> , or α <sub>5</sub> ) and γ subunit	Increased GABA neurotransmission



**Figure 1.** A schematic diagram of the limbic system involved in anxiety<sup>8</sup>

## Management

Management options for anxiety disorders usually consist of a combination of psychotherapy (non-pharmacological management) and/or pharmacotherapy. Antidepressant agents are the drugs of choice in the treatment of anxiety disorders, particularly the newer agents, such as selective serotonin reuptake inhibitors (SSRIs) which have a safer adverse effect profile and higher ease of use than the older tricyclic antidepressants (TCAs).<sup>13</sup>

The outcome of treatment is determined by several factors, including the following:

- Specific type of anxiety
- Severity of diagnosis
- Level of functioning prior to onset of symptoms
- Degree of motivation for treatment
- Level of support (e.g. family, friends, work)
- Ability to adhere to medication and/or psychotherapeutic regimen<sup>13</sup>
- Acute anxiety

Patients with significant discomfort from their anxiety can benefit from emergency anxiolytic treatment, primarily with a benzodiazepine.<sup>13</sup> In addition to emergency treatment patients in an acute anxious state of such severity that they pose a danger to themselves or to others should be hospitalised in a psychiatric hospital.<sup>14</sup>

In the best circumstances, a calm environment and social support from family, friends and emergency staff are ideal. For patients with more severe anxiety, a short course of fast-acting anxiolytic agent is recommended. Chronic anxiety requires a comprehensive approach and the best pharmacotherapy varies for each individual.<sup>13</sup>

### **Panic disorder (PD)**

PD is characterised by episodic, unexpected panic attacks that occur without a clear trigger. Panic attacks are defined by the rapid onset of intense fear (typically peaking within about ten minutes) with at least four of the physical and psychological symptoms in the DSM-5 diagnostic criteria of palpitations, sweating, trembling, sensation of shortness of breath, feelings of choking, chest pain or discomfort, paresthesia (numbness or tingling sensation), fear of losing control and fear of dying.<sup>3</sup> Pharmacotherapy, cognitive and behavioural psychotherapy and other psychological treatment modalities are all used to treat panic disorder. Reassure and calm the patient. Untreated panic attacks can subside spontaneously within twenty to thirty minutes, especially with reassurance and a calming environment. The 2011 American Psychiatric Association practice guideline for treatment of patients with panic disorders strongly recommends SSRIs and cognitive behavioural therapy (CBT) as initial therapy.<sup>12</sup> The Standard Treatment Guidelines and Essential Medicine List (STG/EML) recommends benzodiazepines such as diazepam per mouth (po) or lorazepam intramuscular (IM)

as a single dose for an acute panic attack. If PD is diagnosed, long-term treatment may be required and patients should be referred to a specialist. Most patients can be treated as outpatients, but some may need to be admitted to hospital. Pharmacotherapy would include an SSRI at the lowest dose, titrating the dose to a therapeutically effective dose. Duration of treatment is variable but initially six months to a year.<sup>14</sup>

### **Generalised anxiety disorder (GAD)**

GAD is characterised by persistent and excessive anxiety and worry about various events and activities for more than six months. Physical symptoms such as muscle tension or tremulousness may be reported. According to the STG/EML, pharmacological management for acute cases includes a benzodiazepine e.g. diazepam. As maintenance therapy, an SSRI should be initiated and monitored by a specialist.<sup>14</sup> Although very few head-to-head clinical trials exist, all of the antidepressants in the various classes studied for GAD appear to have comparable efficacy. They are significantly more effective than placebo.<sup>15</sup>

### **Social anxiety disorder (SAD)**

Psychotherapy and pharmacotherapy are useful in treating SAD. SAD typically responds to either SSRI or monoamine oxidase inhibitors (MOAI). Treatment should be initiated with an SSRI and titrated to the minimum effective dose. The SSRI dose can be increased if response is partial or non-existent at six weeks. Doses can be increased every two weeks until the maximum dose is reached.<sup>13</sup>

Failing this, patients sometimes respond to high-potency benzodiazepines. Long-term data from clinical studies of clonazepam are limited but support the drug's efficacy.<sup>12</sup> Beta-blockers, clonidine and buspirone are usually not helpful for the long-term treatment, although a beta-blocker such as atenolol or propranolol may be useful for the situational/performance anxiety on an as-needed basis.<sup>13</sup> Tapering of medication can be considered slowly after six to twelve months of full response. If symptoms reoccur following tapering, therapy should be restarted and continued indefinitely.<sup>13</sup>

### **Agoraphobia**

Agoraphobia is characterised by fear or anxiety of multiple situations in which escape might be difficult or panic-like symptoms might develop. Onset is in childhood and has a lifetime prevalence rate of 2.5%–6.7%.<sup>16</sup> Agoraphobia most often responds to treatment with an SSRI. Treatment should be started at a low dose then titrated to the minimum effective dose controlling the patient's panic. Benzodiazepines are indicated for patients with frequent panic attacks until the SSRI takes effect.<sup>13</sup>

### **Specific phobia**

Specific phobias are manifested as excessive or unreasonable fear of (and restricted to) single people or objects or situations which are either avoided or endured with significant personal distress. Most patients respond to psychological approaches, such as CBT,

but some patients may benefit from pharmacological treatment. The findings of one small randomised placebo-controlled trial provide evidence for the efficacy of escitalopram and paroxetine.<sup>13</sup> Gradual desensitisation is the most commonly used treatment. To date, no controlled studies have demonstrated the efficacy of psychopharmacological intervention for specific phobias.<sup>13,17</sup>

### Separation anxiety disorder

Separation anxiety disorder is characterised by fear or anxiety concerning separation from those to whom an individual is attached. Common features include excessive distress when experiencing separation from home and persistent and excessive worry about potential harm to attachment figures or untoward events that might result in separation.<sup>13</sup>

### Selective mutism (SM)

SM is a disorder in which an individual is not able to speak aloud in specific situations when there is an expectation of conversational speech. SM can be accompanied by other anxiety disorders such as separation anxiety disorder, social anxiety disorder (formerly called social phobia), agoraphobia, and panic disorder, as well as by shyness and anxiety; however, it can also exist without other anxiety-related disorders (See Table III).<sup>1</sup>

Anxiety disorder	Characteristics
Panic disorder	Experiences recurrent unexpected panic attacks and is persistently anxious about having more attacks. May change behaviour in an effort to avoid panic attacks. May have a marker of a disease severity for other disorders.
Generalised anxiety disorder	Persistent and excessive anxiety and worry about various events and activities for more than six months. Physical symptoms include restlessness, feeling on edge, being easily fatigued, having difficulty concentrating, irritability, muscle tension and sleep disturbance. The disturbance is not better explained by another medical disorder.
Social anxiety disorder	Fear, anxiety, avoidance of social interactions or performance situations in which the person is exposed to unfamiliar people. Persistent, typically lasting six months or more.
Agoraphobia	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.
Specific phobia	Excessive or unreasonable fear of (and restricted to) single people or objects which are either avoided or endured with significant personal distress.
Separation anxiety disorder	Fear or anxiety concerning separation from those to whom an individual is attached.
Selective mutism	Individual is not able to speak aloud in specific situations when there is an expectation of conversational speech

## Non-pharmacological management

CBT is an integral part of the therapeutic plan for anxiety disorders. The purpose of CBT is to identify and correct dysfunctional cognitions. This therapy helps patients to control their emotional distress and decrease their use of maladaptive behaviour such as avoidance strategies.<sup>18</sup> The ideal treatment should be tailored to the individual and may involve a combination of both psychotherapy and pharmacotherapy.<sup>19</sup>

Lifestyle modifications may also be effective in decreasing anxiety symptoms. These lifestyle modifications include limiting the consumption of caffeine, drugs of abuse, and stimulants. Caffeine in high doses has been shown to exacerbate anxiety, and patients with anxiety disorders may be more sensitive and reactive to the effects of caffeine compared to the general population.<sup>18</sup> Exercise, both aerobic and anaerobic, has shown benefit in decreasing anxiety disorder symptoms.<sup>20</sup>

## Pharmacological management

Table IV provides an overview of the registered drug treatments for the main types of anxiety disorders. Antidepressants are considered first-line treatment in anxiety disorders, either alone or in combination with CBT. The response rate to antidepressants in anxiety is often lower and takes longer than that seen in depression. Up to twelve weeks may be needed to assess the response to an antidepressant.<sup>19</sup> There is a misconception that patients with anxiety disorders respond to lower doses of antidepressants than patients with depression. The average doses for treating anxiety disorders are as high as or higher than for depression.<sup>2</sup>

In GAD, if no response is seen within four weeks, any further improvement with the same treatment and dose is unlikely.<sup>17</sup>

### Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs have a broad anxiolytic effect and are considered the first drug options in all anxiety disorders.<sup>17</sup> These agents selectively inhibit the presynaptic reuptake of serotonin by the serotonin transporter, which increases the concentration available to bind to postsynaptic receptors.<sup>9</sup> SSRIs are as effective as TCAs in the management of anxiety disorders and have the advantage of fewer anticholinergic adverse effects. They generally do not cause weight gain to the same extent as the TCAs.<sup>20</sup> Individual SSRIs have varying registered indications across the anxiety disorders but this does not necessarily mean others have no supporting evidence.<sup>19</sup> The SSRIs also differ in their interaction potential, side-effect profile and ease of discontinuation.<sup>19</sup> Studies have shown comparable efficacy between SSRIs.<sup>23</sup> When initiating therapy, SSRIs should be started at a low dose and titrated up to achieve a therapeutic dose. The anxiolytic effect may take two weeks or up to eight weeks to manifest.<sup>19</sup>

- **Citalopram** is a weak inhibitor of cytochrome P450 (CYP) enzymes and has reduced potential for drug interactions and may be considered where multiple drugs are being used. A dose higher than 40 mg per day carries a risk of QT prolongation and

**Table IV.** Overview of the registered drug treatment for the main types of anxiety disorders.<sup>5,21,22</sup>

Drug	Indication	Dosage	Major adverse effects
<b>Selective serotonin reuptake inhibitors (SSRIs)</b>			
Citalopram	Panic disorder	20–40 mg po daily	Risk of dose-dependent (40 mg/day) QT prolongation and contraindicated in patients with heart failure and bradyarrhythmia.
Escitalopram	GAD Panic disorder SAD	10–20 mg po daily 5–20 mg po daily 5–20 mg po daily	Nausea, ejaculation disorder, insomnia and decreased libido, anticholinergic effects. Gradual dose reduction upon discontinuation. Serotonin syndrome in conjunction with other serotonergic agents.
Fluoxetine	Panic disorder GAD	20–60 mg po daily 20–40 mg po daily	Initial agitation, hypoglycaemia in diabetic patients, sedation, inhibitor of cP450. Sexual dysfunction.
Paroxetine	GAD  Panic disorder  SAD	20–50 mg po daily 12.5–62.5 mg po daily Controlled release (CR) 40–60 mg po daily 12.5–75 mg po daily (CR) 20–40 mg po daily 12.5–37.5 mg po daily (CR)	Compared to other SSRIs, it has a lower incidence of diarrhoea, a higher incidence of anticholinergic effects, sedation/somnolence/drowsiness, sexual side-effects, and weight gain.
Sertraline	Panic disorder	25–50 mg po daily	No sedation, weak inhibitor of cP450, little anticholinergic adverse effects. Well tolerated.
<b>Serotonin-norepinephrine reuptake inhibitors (SNRIs)</b>			
Duloxetine	GAD	60 po daily	Hepatotoxicity, especially in patients with underlying liver disease or substantial alcohol use.
Trazodone	GAD	100–600 mg po daily	Drowsiness at therapeutic doses. Minimal anticholinergic adverse effects.
Venlafaxine XR	GAD, panic disorder SAD	75–225 mg po daily	Increase in blood pressure at high doses. Avoid abrupt withdrawal.
Desvenlafaxine	GAD, panic disorder SAD	50–100 mg po daily	Anticholinergic adverse effects.

potential fatal changes in heart rhythm. Because of the risk of QT prolongation, citalopram is contraindicated in patients with congestive heart failure, bradyarrhythmias and congenital long QT syndrome.<sup>21</sup>

- **Escitalopram** is the pure S-enantiomer (single isomer) of the racemic derivative citalopramis. It is a weak inhibitor of CYP<sub>2D6</sub> and likely to cause fewer hepatic enzyme interactions and may be an appropriate choice for patients with complicated medical regimens and may have a reduced risk of drug interactions.<sup>13</sup> Escitalopram, like other SSRIs, has been shown to affect sexual functions causing side-effects such as decreased libido, delayed ejaculation, genital anaesthesia and anorgasmia. Escitalopram seems to be less dangerous than citalopram in overdose and comparable to other SSRIs.<sup>24</sup> If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms of dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania.<sup>5</sup>
- **Fluoxetine** is used off-label for anxiety disorders, especially panic disorders and general anxiety disorders. Patients with anxiety are prone to developing agitation, which may affect adherence. Initiation at lower doses may reduce these effects. Fluoxetine is an inhibitor of cytochrome P450<sub>2D6</sub> enzymes

and has potential interactions with drugs metabolised by this system (e.g. nifedipine, omeprazole, haloperidol). It has a long half-life, making it a better choice in patients with marginal adherence to their medication. Patients with suicidal tendencies should be carefully monitored, especially during the early weeks of therapy. Glycaemic control may be altered in diabetic patients causing hypoglycaemia and dosage adjustment may be required. Fluoxetine commonly causes change in appetite and sleep disorders as adverse effects.<sup>21,13</sup>

- **Paroxetine** has a short half-life and is formulated as a controlled release preparation which will increase patient adherence. Paroxetine causes somnolence as adverse effect and should be prescribed only at night before bedtime.<sup>13</sup>
- **Sertraline** has a favourable adverse effect profile with little anticholinergic adverse effect, does not impair psychomotor performance, has a low probability of adverse central nervous and cardiovascular effects and is a weak inducer of hepatic microsomal enzyme activity. Study reviews show that sertraline is an effective and well-tolerated treatment of all of anxiety disorders. A comparison of sertraline with other pharmacotherapeutic options shows it to be at least equivalent to other medications for anxiety disorders. A systematic review on the efficacy of drug treatments for GAD found the SSRI fluoxetine ranked first for response and remission (probability of 62.9% and 60.6%, respectively) and sertraline ranked first for tolerability (49.3%).<sup>17</sup>

### Serotonin-norepinephrine reuptake inhibitors (SNRIs)

SNRIs are often initiated after treatment failure of, or inadequate response to, an SSRI. SNRI agents inhibit both serotonin and norepinephrine reuptake. Some patients experience an increase in physiological anxiety symptoms due to the increased norepinephrine-mediated signalling. As with SSRIs, SNRIs carry an increased risk of suicidal thoughts and behaviour in children and young adults who should be closely monitored for the first two months of treatment. The most common adverse effects are gastrointestinal-related.<sup>5</sup>

- **Duloxetine** causes hepatotoxicity in those vulnerable to liver disease.<sup>5</sup>
- **Trazodone** is a triazolopyridine, which does not appear to influence the peripheral reuptake of norepinephrine, although it may indirectly facilitate neuronal release. It blocks the reuptake of serotonin at presynaptic neurons and also has action at 5HT<sub>1</sub> receptors. Trazodone blocks central  $\alpha_1$  adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant anticholinergic activity but has marked sedative action.<sup>21</sup> In South Africa it is registered for the treatment of mixed anxiety disorder.<sup>21</sup>
- **Venlafaxine**, extended release, is effective and well-tolerated for GAD and PD.<sup>3</sup> The dose of venlafaxine should be adjusted in patients with existing hepatic impairment. Venlafaxine is noted to have the most effect on sustained blood pressure elevations. Abrupt discontinuation of treatment should be avoided, medication should be tapered to prevent discontinuation symptoms of headache, dizziness, nausea, irritability and sleep disturbances.<sup>5</sup> These symptoms can be experienced after missing a single dose.<sup>19</sup> The higher risk and increased severity of discontinuation syndrome symptoms relative to other antidepressants may be related to the short half-life of venlafaxine and its active metabolite.<sup>25</sup>
- The newer SNRI **desvenlafaxine** is a synthetic form of the major active metabolite of venlafaxine and is only registered in South Africa for major depressive disorders and not anxiety disorders.<sup>21</sup>
- **Vortioxetine** is a novel antidepressant for the treatment of major depressive disorders (MDD). It is a 5HT<sub>3A</sub>, 5HT<sub>7</sub> and 5HT<sub>1D</sub> receptor antagonist, a 5HT<sub>1B</sub> receptor partial agonist, a 5HT<sub>1A</sub> receptor agonist and a serotonin transporter inhibitor (SERT). The combination effects result in regional increases in norepinephrine, dopamine and glutamatergic transmission.<sup>21</sup> In the review article Sobnosky indicated that vortioxetine is registered for GAD, however in South Africa vortioxetine is only registered for the treatment of MDD.<sup>5</sup>
- **Agomelatine** has a novel mode of action with an agonist effect at melatonin 1 and 2 receptors and an antagonist effect at 5-HT<sub>2C</sub> receptors. The blockade of these receptors increases norepinephrine and dopamine release, improving circadian rhythm and sleep quality.<sup>19</sup> Agomelatine has proven efficacy in acute treatment and prevention of relapse in GAD. Sexual dysfunction is less likely to occur with agomelatine than with SSRI and SNRI antidepressants, as are discontinuation

symptoms.<sup>17</sup> Agomelatine is not registered for the treatment of anxiety disorders in South Africa.<sup>21</sup>

### Older antidepressants

- Certain **tricyclic antidepressants (TCAs)**, clomipramine, lofepramine and amitriptyline, are effective in some anxiety disorders. They are however associated with a greater burden of adverse reactions such as anticholinergic effects (dry mouth, blurred vision, urinary retention and confusion),  $\alpha_1$  adrenergic blocking effects (hypotension and reflex tachycardia) and antihistamine effects (sedation and weight gain). TCAs are cardiotoxic in overdose and have a lower seizure threshold. These agents should therefore be avoided in patients with cardiovascular disorders, epilepsy or those considered at risk of suicide. Doses should be initiated at a low dose and increased every three to five days.<sup>19,26</sup>
- The **monoamine-oxidase inhibitors (MOAIs)** are rarely used in practice because of their potentially life-threatening interactions with other serotonergic medicines and tyramine in the diet. Phenelzine and moclobemide are occasionally used by specialists in the management of social anxiety disorder following failure of an SSRI.<sup>19</sup>

### Benzodiazepines

Benzodiazepines act by binding to the GABA<sub>A</sub> receptor complex and enhance the effects of the inhibitory neurotransmitter, GABA, by facilitating the opening of ligand-gated chloride channels. GABA<sub>A</sub> receptors containing the alpha-2 subunit are hypothesised to mediate anxiolysis, while those containing the alpha-1 subunit mediate sedation.<sup>27</sup>

Individual benzodiazepines vary with respect to their potency, half-life and onset of action. Benzodiazepines with demonstrated efficacy in anxiety disorders include alprazolam, clonazepam and diazepam. Alprazolam has a short half-life, which makes it particularly prone to rebound anxiety and psychological dependence.<sup>13</sup> Clonazepam and diazepam have high lipophilicity and are rapidly absorbed and distributed into the central nervous system.<sup>10</sup>

Benzodiazepines act quickly and can be reasonably used as an initial adjunct while SSRIs are titrated to an effective dose, and they can then be tapered over four to twelve weeks while the SSRI is continued. Prescription of use as necessary (prn) benzodiazepines for unpredictable anxieties (e.g. panic disorder) or chronic anxiety disorder (e.g. GAD) is not recommended. Benzodiazepines should generally be prescribed for anxiety on a regular schedule.<sup>2</sup> Long-term benzodiazepines for chronic anxiety disorders should be avoided. Abrupt discontinuation should be avoided and doses should be gradually reduced by 25% over a two to three week period. Alternatively substituting a short-acting drug for a drug with a long half-life (lorazepam) may limit withdrawal symptoms.<sup>10</sup> Benzodiazepines can cause troublesome sedation and cognitive impairment in both short-term and long-term treatment and tolerance and dependence can occur with prolonged use.<sup>17</sup>

### Other agents

- **Pregabalin** is a GABA derivative but does not appear to alter GABA levels in the brain, so its pharmacological activity is presumed to be unrelated to GABA. If the SSRIs and SNRIs are not tolerated, the NICE guidelines recommend turning to pregabalin (Lyrica), which is approved for GAD in the United Kingdom but not in South Africa. The clinical trials evidence shows pregabalin works as fast as alprazolam or lorazepam while achieving symptom improvement scores comparable with antidepressants, making it a particularly attractive back-up option in antidepressant nonresponders.<sup>15</sup>
- **Antihistamines** such as hydroxyzine have been used in the acute treatment of GAD in adults at a dose of 50–100 mg four times daily. The clinical evidence only supports its use for acute treatment of GAD if sedation is required.<sup>19</sup>
- **Buspirone** is a 5HT<sub>1A</sub> receptor partial agonist that has shown efficacy in the acute treatment of GAD only.<sup>17</sup> A Cochrane review on GAD found buspirone to be superior to placebo in short term studies (four to nine weeks), but less effective or acceptable than benzodiazepines.<sup>19</sup>
- **Propranolol**, a non-selective  $\beta$ -adrenergic antagonist, is sometimes used for anxiety symptoms of palpitations, tremor and sweating. There is no evidence supporting their use in the acute or long-term treatment of anxiety disorders.<sup>19</sup>

### Complementary and alternative medicine therapies

Botanicals and supplements sometimes used in GAD and PD include:

#### • Botanicals

Lavender oil (*Lavendula angustifolia*)

Passionflower (*Passiflora incarnata*)

St John's wort (*Hypericum perforatum*)

Valerian (*Valeriana officinalis*)

#### • Supplements

5-Hydroxytryptophan

Inositol

L-theanine

L-tryptophan

S-adenosyl-L-methionine<sup>3</sup>

A number of complementary and alternative products have evidence for treating depression, but lack sufficient evidence for the treatment of anxiety. Most common adverse effects with these agents are headache and gastrointestinal upset. St John's wort, tryptophan, 5-hydroxytryptophan, and S-adenosyl-L-methionine should be used with caution in combination with SSRIs because of the increased risk of serotonin syndrome.<sup>3</sup>

### Patient education

Patient education itself can help reduce anxiety, particularly in PD. Compassionate listening and education are an important foundation in the treatment of anxiety disorders.

- Counselling begins by rejecting our stigmatising cultural attitude that anxiety is a character flaw and that the individual should "just deal with it".<sup>28</sup>

Remind patients that it may take two or three weeks before they notice improvement; encourage adherence.<sup>3</sup>

Inform patients of side-effects that are temporary or enduring. If a patient cannot tolerate the side-effects, encourage them to call their physician to consider an alternative drug.<sup>3</sup>

- Be especially encouraging to patients who may have already failed on one treatment agent.<sup>3</sup>
- Warn patients not to discontinue medication abruptly and that symptoms may reappear if they stop medication.<sup>3</sup>
- Lifestyle recommendations that may reduce anxiety-related symptoms include identifying and removing possible triggers (e.g. stress stimulants caffeine, nicotine, dietary triggers), as well as improving sleep quality/quantity and physical activity.<sup>3</sup>
- Encourage moderate exercising for twenty minutes three times weekly that has shown to decrease anxiety.<sup>3</sup>
- Magnesium, zinc and omega-3-containing foods help reduce anxiety.<sup>29</sup> Foods with a high sugar content can become habit forming.<sup>30</sup>

### Conclusion

The treatment of anxiety disorders can be challenging. Pharmacists can help prepare patients during pharmacotherapy initiation by counselling them on therapeutic onset, possible adverse drug reactions and drug interactions. Adherence should be monitored and pharmacists should work collaboratively with physicians to ensure the patient receives individualised effective and safe therapy.

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