Chapter 8: The Pharmacologic Treatment of Anxiety

1 Contact Hour

By: Chris Paxos, PharmD, BCPP, BCPS, CGP is a psychiatric pharmacist.

Author Disclosure: Chris Paxos and Elite Professional Education do not have any actual or potential conflicts of interest in relation to this lesson.

Universal Activity Number (UAN): 0761-9999-17-036-H01-P
Activity Type: Knowledge-based
Initial Release Date: February 2, 2017
Expiration Date: February 2, 2019
Target Audience: Pharmacist in a community-based setting.

To Obtain Credit: A minimum test score of 70 percent is needed to obtain a credit. Please submit your answers either by mail, fax, or online at Pharmacy.EliteCME.com.

Learning objectives

- Describe common characteristics associated with specific anxiety disorders.
- Identify medications associated with causing or exacerbating symptoms of anxiety.
- List pharmacologic options available for the treatment of anxiety disorders.
- Compare and contrast pharmacologic options for the treatment of anxiety disorders with regard to pharmacologic properties and place in therapy.

Introduction

“Anxiety is a thin stream of fear trickling through the mind. If encouraged, it cuts a channel into which all other thoughts are drained.” – Arthur Somers Roche

According to the World Health Organization, anxiety disorders are the most common psychiatric disorders among the general population. Common anxiety disorders include generalized anxiety disorder (GAD), panic disorder (PD), posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and social anxiety disorder (SAD). The lifetime prevalence of any anxiety disorder was found to be approximately 16%, with the highest rates in western, industrialized nations.1 In the United States (U.S.), twelve month prevalence rates are as follows: 6.8% (SAD), 3.5% (PTSD), 3.1% (GAD), 2.7% (PD), and 1.0% (OCD).2-6 Women appear to have higher rates of anxiety disorders than men, particularly of GAD, PD, and PTSD.7

Anxiety disorders

The five principle anxiety disorders that will be discussed with regard to pharmacotherapy include GAD, PD, PTSD, OCD, and SAD. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) houses GAD, PD, and SAD under the anxiety disorders chapter. OCD and PTSD have been relocated to chapters entitled obsessive-compulsive and related disorders and trauma- and stressor-related disorders, respectively.8 In order to qualify for a diagnosis of an anxiety disorder, symptoms cannot be secondary to a general medical condition or caused by the effects of a medication; furthermore, symptoms generally interfere with the ability to function in important areas (e.g., work, school).9 A brief description of each disorder follows:

- **Generalized anxiety disorder:** The hallmark features of GAD include excessive anxiety about several events or activities that is difficult to control. Accompanying symptoms of fatigue, restlessness, irritability, trouble concentrating, muscle tension, or difficulty with sleep are also present. Signs of the disturbance are present for a minimum of six months.8,9
- **Panic disorder:** Recurring and unanticipated panic attacks characterize PD. Panic attacks are sudden bouts of intense anxiety accompanied by a sense of impending doom that peak within minutes. Symptoms include palpitations, sweating, chest pain, or even fear of dying. Anticipatory anxiety about future panic attacks may also occur. Agoraphobia, a fear of crowds and/or public places, may also be present.8,9
- **Posttraumatic stress disorder:** Following exposure to a traumatic event, PTSD manifests as symptoms of reexperiencing (e.g., flashbacks, distressing dreams), avoidance (e.g., avoiding people or places that trigger memories of the event), and hyperarousal (e.g., irritability, anger outbursts, sleep disturbances). Symptoms are present for a minimum of one month.8,9
- **Obsessive compulsive disorder:** Obsessions, compulsions, or both are present in OCD. Obsessions are repetitive and persistent thoughts or urges (e.g., contamination, pathological doubt, symmetry), whereas compulsions are marked by repetitive behaviors in response to an obsession (e.g., checking, counting, repeating). The obsessive-compulsive symptoms occupy a significant amount of time each day (e.g., greater than one hour).8,10
- **Social anxiety disorder:** Intense fear of social situations and fear of embarrassing oneself characterize SAD. Individuals either bear the situation with considerable anxiety or avoid it completely. The amount of anxiety or fear is disproportionate to the actual risk. Signs of the disturbance must be present for a minimum of six months.8,12

Questions regarding statements of credit and other customer service issues should be directed to 1-888-666-9053. This lesson is $4.00.
Pharmacologic treatments

A diverse group of medications are used for the treatment of anxiety disorders. Common anxiolytic medications include antidepressants, benzodiazepines, buspirone, anticonvulsants, antipsychotics, and other miscellaneous agents. The medications vary widely with regard to pharmacologic properties and indications for use with little in common other than their anxiety relieving properties. Some have wide spectrums of activity, while others have narrower indications. Antidepressants, for example, have been shown to be effective for GAD, PD, PTSD, OCD, and SAD. Buspirone, on the other hand, is predominantly used for the treatment of GAD.

Nonpharmacologic treatments

It is important to note the important role that nonpharmacologic treatments serve in the treatment of anxiety disorders. Nonpharmacologic therapies may be as effective as pharmacotherapy for treating anxiety. In fact, the combination of nonpharmacologic and pharmacologic approaches is often more effective than either approach alone.

Medication-induced anxiety

Symptoms of anxiety may arise secondary to the use of various medications and illicit substances. A thorough medication history should be taken for each patient. The use of over-the-counter medications, prescription medications, herbs and dietary supplements, and illicit substances should be investigated with new-onset symptoms or exacerbations of pre-existing anxiety. Treatment typically involves discontinuation of the causative agent. In the case of antidepressant-induced anxiety, symptoms are typically transient and a dose reduction or changing to an alternative agent may be necessary. Examples of agents causing drug-induced anxiety include:

- Antidepressants.
- Corticosteroids.
- Thyroid hormones.

Antidepressants

The selective serotonin reuptake inhibitors (SSRIs) are the cornerstone of anxiety disorder treatment. They possess a wide range of anxiolytic effects, including anti-panic and anti-obsessional properties. Treatment guidelines generally regard SSRIs as first-line therapy for the treatment of anxiety disorders and are effective as monotherapy for GAD, PD, PTSD, OCD, and SAD. In addition to their anxiolytic effects, antidepressants treat major depressive disorder (MDD) that may also be present, are non-habit forming, and have favorable adverse effect profiles. A number of SSRIs hold U.S. Food and Drug Administration (FDA) approvals for one or more anxiety disorders, but anxiolytic effects likely extend across the entire class of SSRIs. Unfortunately, SSRIs and other antidepressants take several weeks of continuous use to exert their maximal therapeutic effects; therefore, patient education regarding medication adherence is of the utmost importance.

The SSRIs inhibit the reuptake of serotonin into presynaptic neurons. They have little effect on histaminic, alpha adrenergic, and muscarinic receptors and are generally considered safer and more tolerable than the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Common adverse effects include gastrointestinal (GI) distress (e.g., nausea, vomiting) and activating effects (e.g., anxiety, jitteriness, restlessness). While GI distress and activation are usually transient in nature, antidepressant doses should be started low and slowly titrated to therapeutic doses in order to minimize both adverse effects. For example, dosing should be initiated at one-fourth to one-half of normal MDD starting doses, particularly for PD, in order to minimize activating adverse effects which can worsen a patient’s anxiety. Sleep disturbances may occur with SSRI use, and patients should be encouraged to take the medication in the morning to avoid exacerbating symptoms of anxiety. Some medications have a potential for abuse and dependence (e.g., benzodiazepines), while others are non-habit forming (e.g., antidepressants, hydroxyzine, buspirone). Benzodiazepines produce anxiolytic effects with the first dose of medication, but antidepressant therapy may take several weeks for maximal therapeutic effects. Finally, some medications are effective as monotherapy, whereas others are considered adjunctive treatments. For example, antidepressants are effective as monotherapy for the treatment of anxiety disorders; however, antipsychotics are typically used as adjuncts to antidepressant therapy.

Various cognitive and behavioral therapies have been studied extensively. Examples include exposure and response prevention for OCD and cognitive behavioral therapy for GAD or PD. Nonpharmacologic approaches should be considered for all patients, especially in patients not responding to pharmacotherapy.

Antidepressants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>PD Starting Doses (mg/day)</th>
<th>MDD Starting Doses (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac®</td>
<td>5-10</td>
<td>20</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro®</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox®</td>
<td>25-50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 1: SSRI Starting Doses
Several differences exist between individual SSRIs with regard to adverse effects and pharmacokinetics. Citalopram (Celexa®) dosing is limited by dose-related QT prolongation, with a 40 mg/day maximum dose or a 20 mg/day maximum dose in patients greater than 60 years of age or with hepatic impairment.23 Fluoxetine (Prozac®) is considered the most activating SSRI, whereas fluvoxamine (Luvox®) is the most sedating.18, 20, 25 Sertraline (Zoloft®) may cause slightly more GI distress, including diarrhea, than other SSRIs.22 Paroxetine (Paxil®) has mild anticholinergic effects and may cause more sexual dysfunction than other SSRIs.19, 21 In addition, paroxetine is most likely to cause antidepressant discontinuation syndrome upon abrupt discontinuation. Symptoms include nausea, insomnia, dizziness, paresthesias or shock-like sensations, increased anxiety, and flu-like symptoms. Patients should be counseled to avoid discontinuing antidepressants abruptly, and prescribers should gradual taper antidepressants when discontinuing therapy.26, 27 Significant pharmacokinetic interactions may occur with SSRI therapy. Fluoxetine and paroxetine possess strong cytochrome P450 (CYP) 2D6 inhibition while fluvoxamine possesses strong CYP1A2 inhibition.20, 25 Citalopram and escitalopram are the least likely to contribute to pharmacokinetic interactions because both are only mild inhibitors of CYP2D6.20, 24

**Drug alert!** The treatment of OCD can require very high doses to achieve symptom improvement. For example, the sertraline off-label dose of 400 mg/day demonstrated significantly greater symptom improvement than its FDA approved maximum dose of 200 mg/day.28

**Drug alert!** SSRIs may require 4-6 weeks to achieve maximal therapeutic effects. Substantial benefits for the treatment of OCD may require as long as 10-12 weeks in some patients.16

**Drug alert!** Successful treatment of anxiety disorders with antidepressant therapy should be continued for at least 1-2 years before discontinuing pharmacotherapy in order to reduce the risk of recurrence.16, 17

**Drug alert!** Fluvoxamine is a strong CYP1A2 inhibitor. It is contraindicated with ramelteon (Rozerem®), a melatonin receptor agonist for the treatment of insomnia, which is a CYP1A2 substrate.25

A number of serotonin/norepinephrine reuptake inhibitors (SNRIs) are currently available, however, only specific SNRIs have evidence for use in the treatment of anxiety. The SNRIs inhibit the reuptake of serotonin and norepinephrine to varying degrees.18 Similar to SSRIs, GI distress, activating adverse effects, sleep disturbances, and sexual dysfunction are common.20-23 Discontinuation syndrome is most common with the abrupt discontinuation of venlafaxine therapy.26, 27 Diaphoresis may also occur during SNRI use as can dose-related increases in blood pressure. Blood pressure monitoring is recommended for all agents.20-23 Of all of the SNRIs, venlafaxine (Effexor®) has the most data for use in anxiety disorders. While it is currently FDA approved for the treatment of GAD, PD, and SAD, off-label venlafaxine use is also considered a first-line option for the treatment of PTSD due to positive results in multiple trials.29, 30, 31 Duloxetine (Cymbalta®) is FDA approved for the treatment of GAD. Because duloxetine is also approved for fibromyalgia, chronic musculoskeletal pain, and diabetic nerve pain, it may be particularly useful in patients with concurrent pain.32 Rarely, duloxetine has been associated with liver injury and is best avoided in patients with liver impairment or cirrhosis.30, 31 Desvenlafaxine (Pristiq®), the major active metabolite of venlafaxine, milnacipran (Savella®), and levomilnacipran (Fetzima®) are not FDA approved for the treatment of any anxiety disorder and have little to no data supporting their use.31, 32

A number of other antidepressants are commercially available, including mirtazapine (Remeron®), bupropion (Wellbutrin®), trazodone (Desyrel®), nefazodone (Serzone®), vortioxetine (Brintellix®), and vilazodone (Viibryd®); however, none of the aforementioned agents are FDA approved for the treatment of any anxiety disorder. Bupropion is a norepinephrine and dopamine reuptake inhibitor.18 It is an activating medication, causing a significant amount of insomnia, agitation, and irritability, and caution should be used during initiation for the treatment of anxiety. Bupropion use is associated with dose-related seizures and is contraindicated in patients with seizure disorders, eating disorders, or with the abrupt discontinuation of alcohol or sedatives.8 Bupropion has failed to show benefit for the treatment of PTSD in placebo-controlled trials.37, 38 Mirtazapine, on the other hand, has been shown to be effective for the treatment of PTSD in placebo-controlled and open-label trials.10, 40 Mirtazapine is an alpha-2 receptor antagonist and commonly causes sedation, appetite stimulation, and weight gain.18, 41 Rarely, agranulocytosis has been reported with its use.41 Nefazodone and trazodone are both serotonin reuptake inhibitors and serotonin-2A receptor antagonists.16 Nefazodone is rarely used secondary to the risk of hepatotoxicity.15, 42 Furthermore, its strong inhibition of CYP3A4 contraindicates its use with a number of medications.42 Trazodone is predominantly used as a hypnotic secondary to its sedating effects. It is uncommonly used as the primary treatment for anxiety.16 Vortioxetine and vilazodone, serotonin reuptake inhibitors with various effects at serotonergic receptors, have limited to no data for the treatment of anxiety disorders.43, 44

**Drug alert!** Bupropion can cause dose-related seizures and is contraindicated in patients with seizure disorders, eating disorders, and with the abrupt discontinuation of alcohol or sedatives. Head trauma, CNS tumor, CNS infection, and severe stroke also increase the risk of seizure and pose a substantial risk with bupropion therapy.16

**Drug alert!** Trazodone has been associated with rare cases of priapism in 1/1,000 to 1/10,000 men. Patients must be counseled on this rare, yet serious, adverse reaction.16

Older antidepressants have a wealth of data for treating anxiety disorders, however, adverse effects and drug interactions often limit their utility. The TCAs inhibit the reuptake of serotonin and norepinephrine to varying degrees.18 They have demonstrated efficacy in a variety of anxiety disorders; however, adverse effects and the greater risk of lethality in overdose limit their use. In general, TCAs are reserved until after other antidepressants have failed.16, 17 The TCAs cause multiple adverse effects including sedation, orthostatic hypotension, and anticholinergic effects secondary to their antagonism of histamine-1, alpha-1 adrenergic, and muscarinic receptors, respectively.18 Similar to the TCAs, the MAOIs are not considered first-line anxiety disorder treatments. The MAOI phenelzine, for example, has demonstrated therapeutic benefits in various anxiety disorders. Its use, however, has been relegated to last line therapy, only after other treatment options have failed, due to drug interactions and dietary restrictions.17 The use of MAOIs with other pro-serotonergic medications should be avoided due to the risk of serotonin syndrome.45 Furthermore, the use of MAOIs and sympathomimetic medications (e.g., pseudoephedrine, methylphenidate) is contraindicated due to the risk of hypertensive crisis. Finally, patients receiving MAOIs must be counseled to follow a tyramine-free diet.17

**Drug alert!** Patients receiving MAOI therapy should be instructed to follow a tyramine-free diet. The combination of a diet high in tyramine and MAOI therapy may precipitate a hypertensive crisis. Various aged and fermented foods (e.g., certain meats, cheeses, wines) contain high amounts of tyramine.17

**Drug alert!** The TCA clomipramine (Anafranil®) is FDA approved for the treatment of OCD. Treatment guidelines continue to recommend SSRIs over clomipramine due to SSRIs having a more favorable adverse effect profile.16
Benzodiazepines encompass a large group of structurally related compounds with anxiolytic, hypnotic, amnestic, anticonvulsant, and myorelaxant properties. Benzodiazepines enhance the effects of gamma-aminobutyric acid (GABA), the major inhibitor neurotransmitter of the central nervous system (CNS), by binding to the GABA-A receptor. Benzodiazepine use is associated with a number of adverse effects, including sedation, motor incoordination, and memory impairment. Rarely, paradoxical disinhibition, the increase in anxiety, excitement, and hyperactivity, occurs with benzodiazepine use. Benzodiazepines are schedule IV controlled substances and pose a risk for dependence and withdrawal. Clinicians should consider alternative, non-habit forming options for patients with substance use disorders. Long-term benzodiazepine therapy requires taper upon discontinuation in order to avoid withdrawal symptoms. Withdrawal symptoms can include anxiety, insomnia, muscle tension, increased heart rate, diaphoresis, and seizures. While benzodiazepines share similar pharmacodynamic properties, they differ predominantly by pharmacokinetic profiles. All benzodiazepines have a rapid onset of action within 30-60 minutes of administration; however, half-lives vary considerably. Alprazolam (Xanax®) has a half-life of approximately 12 hours, while a metabolite of diazepam (Valium®) has a half-life of over 100 hours.

### Benzodiazepines

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>GAD</th>
<th>PD</th>
<th>PTSD</th>
<th>OCD</th>
<th>SAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro®</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Serotonin/Norepinephrine Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>GAD</th>
<th>PD</th>
<th>PTSD</th>
<th>OCD</th>
<th>SAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>Effexor®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Prialt®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta®</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Savella®</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>Fetzima®</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Miscellaneous Agents

- Mirtazapine | Remeron®
- Bupropion | Wellbutrin®
- Nefazodone | Serzone®
- Trazodone | Desyrel®
- Vilazodone | Viibryd®
- Vortioxetine | Brintellix®

### Table 2: FDA Approved Anxiety Disorder Indications

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>GAD</th>
<th>PD</th>
<th>PTSD</th>
<th>OCD</th>
<th>SAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro®</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drug alert!** Paradoxical disinhibition with benzodiazepine therapy most commonly occurs in children, the elderly, and patients with developmental disabilities.

**Drug alert!** Withdrawal symptoms can occur within two days of stopping a benzodiazepine with a short half-life or after 4-7 days when stopping a benzodiazepine with a long half-life.

In general, antidepressants are first-line agents for the treatment of anxiety disorders, and benzodiazepines are regarded as second-line agents. Benzodiazepines, however, are not supported by the literature in all types of anxiety. They have demonstrated efficacy with the short-term treatment of GAD, SAD, and PD; however, they are poorly supported by the literature for the treatment of OCD and PTSD.

Advantages of benzodiazepine therapy include a rapid onset of action and short-term efficacy for GAD and PD. Disadvantages include lack of efficacy for comorbid MDD, abuse potential, and paucity of data supporting long-term use.

**Drug alert!** Benzodiazepines can be combined with antidepressants to provide rapid anxiolytic effects and to attenuate antidepressant-induced activation. Benzodiazepines can be discontinued after a couple of weeks with the onset of antidepressant therapeutic effects.

### Buspirone (BuSpar®)

Buspirone is an anxiolytic that is FDA approved for the treatment of GAD. It acts as a serotonin-1A receptor partial agonist which results in anxiolytic effects. Similar to antidepressants, buspirone must be taken every day and requires weeks of continuous administration to exert its therapeutic effects. Buspirone is generally well tolerated, with common adverse effects of dizziness, drowsiness, nausea, and headache. The major pathway involved in the metabolism of buspirone is CYP34A; therefore, caution is warranted with CYP34A4 inducers and inhibitors. The half-life of buspirone is approximately 2-3 hours, necessitating twice a day or three times a day dosing. Buspirone differs from benzodiazepines in three fundamental ways: buspirone is serotoninergic (versus GABAergic), has a delayed onset of action (versus quick onset of action), and is non-habit forming (versus dependence and abuse potential).
Treatment guidelines regard buspirone as a second-line option for GAD. Two limitations to buspirone therapy are noteworthy. First, buspirone does not effectively treat comorbid MDD in patients with GAD. Second, data supporting buspirone for the treatment of anxiety disorders other than GAD are mixed. As a result, antidepressant therapy continues to be first-line for patients with GAD secondary to their ability to treat both MDD and other anxiety disorders that may also be present.

**Anticonvulsants**

The anticonvulsants, gabapentin (Neurontin®) and pregabalin (Lyrica®), have been investigated for the treatment of anxiety disorders. Neither medication affects GABA. Rather, both bind to the alpha-2 delta subunit of calcium channels, inhibiting excitatory neurotransmission. While neither medication is FDA approved for the treatment of an anxiety disorder, both have demonstrated efficacy for the treatment of SAD. Pregabalin has also been studied extensively and is currently recommended as a first-line treatment option for GAD. Pregabalin offers several advantages over antidepresant therapy for the treatment of GAD, including faster onset of action and decreased likelihood of sexual dysfunction.

**Antipsychotics**

Second generation antipsychotics (SGAs), also known as atypical antipsychotics, have been increasingly studied for the treatment of anxiety disorders. While each SGA has a unique receptor profile, all SGAs antagonize the dopamine-2 and serotonin-2A receptors. The mechanism responsible for providing anxiolysis is not completely understood. Ten SGAs are commercially available, but none are FDA approved for the treatment of anxiety disorders. The most commonly studied agents for the treatment of anxiety are risperidone (Risperdal®), quetiapine (Seroquel®), and olanzapine (Zyprexa®). The SGAs have been predominately studied in GAD, PTSD, and OCD as adjunctive therapy, augmenting first-line antidepressant therapy. Some literature, such as quetiapine for GAD, has examined antipsychotic monotherapy. The SGAs are associated with a considerable adverse effect profile, but the risk for varies between agents. Adverse effects include cardiometabolic disturbances (e.g., weight gain, hyperlipidemia, hyperglycemia), extrapyramidal symptoms (e.g., pseudoparkinsonism, akathisia, tardive dyskinesia), sedation, orthostatic hypotension, anticholinergic effects, and QT prolongation. Period monitoring for cardiometabolic disturbances throughout therapy is required and includes patient weight, waist circumference, blood pressure, fasting plasma lipids, and fasting plasma glucose. Continuous monitoring for the development of extrapyramidal symptoms is also required with SGA treatment. The Abnormal Involuntary Movement Scale or AIMS is commonly used to assess for signs of tardive dyskinesia. Overall, the role of antipsychotic therapy appears to be in augmenting antidepressant therapy in treatment-refractory disease. The considerable adverse effect profile of SGAs warrants judicious use and careful weighing of risks versus benefits.

**Comparison of Cardiometabolic Disturbances among SGAs**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Weight Gain</th>
<th>Hyperlipidemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril®</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa®</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel®</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal®</td>
<td>moderate</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt®</td>
<td>moderate</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega®</td>
<td>low</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify®</td>
<td>low/absent</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon®</td>
<td>low/absent</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda®</td>
<td>low/absent</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris®</td>
<td>low/absent</td>
<td>low/absent</td>
<td>low/absent</td>
</tr>
</tbody>
</table>

*Table 3: Comparison of Cardiometabolic Disturbances among SGAs*
Antihistamines

The antihistamine hydroxyzine (Atarax®, Vistaril®) is commonly utilized for the treatment of GAD. Hydroxyzine is a histamine-1 receptor antagonist. Common adverse effects include sedation and anticholinergic effects. An advantage of hydroxyzine therapy includes its lack of addiction potential, making it potentially useful for patients with substance use disorder. Another advantage includes its flexibility with regard to scheduled or as needed dosing. Disadvantages include lack of antidepressant activity as well as lack of activity for other types of anxiety, including panic symptoms. Hydroxyzine is commonly given as monotherapy or in combination with other anxioitics.17

Beta-blockers

Beta-blockers such as propranolol (Inderal®) have been examined for anxiety disorders. The predominant role of beta-blockers may be in nongeneralized or performance-related SAD. Beta-blockers may alleviate manifestations of anxiety caused by the autonomic nervous system, including tachycardia, blushing, and tremor. While prazosin is not formally FDA approved for PTSD, a wealth of data support its adjunctive role in PTSD treatment.39,46-49 Blood pressure should be monitored, particularly during dose titration, and patients should be counseled on the possible adverse effect of orthostatic hypotension.59

Drug alert! Blood pressure should be monitored, particularly during dose titration, due to the vasodilating properties of prazosin. Patients should be counseled regarding the risk of orthostatic hypotension.59

References

22. Chirino M. Blood pressure should be monitored, particularly during dose titration, due to the vasodilating properties of prazosin. Patients should be counseled regarding the risk of orthostatic hypotension.59

Prazosin (Minipress®)

Prazosin, an alpha-1 adrenergic receptor antagonist, plays a specific role in the treatment of PTSD. Increased adrenergic activity in the CNS is involved in the pathophysiology of PTSD.59 Prazosin, given at bedtime, alleviates symptoms such as PTSD-related nightmares and sleep disturbance. It is thought to exert its effects by antagonizing alpha-1 receptors found in the hippocampus, amygdala, and other areas of the brain.59 While prazosin is not formally FDA approved for PTSD, a wealth of data support its adjunctive role in PTSD treatment.39,46-49 Blood pressure should be monitored, particularly during dose titration, and patients should be counseled on the possible adverse effect of orthostatic hypotension.59

Drug alert! Blood pressure should be monitored, particularly during dose titration, due to the vasodilating properties of prazosin. Patients should be counseled regarding the risk of orthostatic hypotension.59

Pharmacy.EliteCME.com  Page 94
1. A patient stops by the community pharmacy with a question regarding new-onset symptoms of anxiety, tachycardia, and insomnia. The patient is diagnosed with panic disorder and worries the new symptoms may trigger a panic attack. The patient states that she has recently started a new over-the-counter cough and cold medication. Which of the following in the patient’s cough and cold product is most likely causing her new symptoms?
   a. Acetaminophen.
   b. Dextromethorphan.
   c. Diphenhydramine.
   d. Pseudoephedrine.

2. A patient is diagnosed with generalized anxiety disorder by his primary care physician. The patient has never tried a medication and is unwilling to try psychotherapy at this time. Which of the following medications is the best initial choice for the treatment of generalized anxiety disorder?
   a. Alprazolam.
   b. Buspirone.
   c. Escitalopram.
   d. Imipramine.

3. A patient’s anxiety disorder is in remission after treatment with sertraline therapy. Following this successful treatment, how long should sertraline be continued in order to reduce the risk of recurrence?
   a. 1-2 weeks.
   b. 1-2 months.
   c. 1-2 years.
   d. 3-5 years.

4. A patient with posttraumatic stress disorder agrees to a trial of pharmacotherapy. The patient currently has uncontrolled blood pressure with a reading this morning of 160/95 mmHg. Until the blood pressure is controlled, the prescriber would like to avoid medications that may further increase the patient’s blood pressure. Which of the following antidepressants should be avoided at this time secondary to its ability to cause dose-related increases in blood pressure?
   a. Mirtazapine.
   b. Paroxetine.
   c. Sertraline.
   d. Venlafaxine.

5. A patient is diagnosed with treatment-refractory obsessive-compulsive disorder. The patient has tried nonpharmacologic and pharmacologic treatment strategies in the past. Past trials of medications include paroxetine, fluvoxamine, and clomipramine. The patient is currently prescribed sertraline 200 mg once daily. The prescriber would like to augment sertraline therapy with a second generation antipsychotic. Which of the following antipsychotics is the most appropriate choice?
   a. Asenapine.
   b. Iloperidone.
   c. Lurasidone.
   d. Risperidone.