Upon successful completion of this article, the pharmacist should be able to:
1. Explain the pathophysiology of post-traumatic stress disorder.
2. Describe the risk factors and symptoms of post-traumatic stress disorder.
4. Compare the advantages and disadvantages for the various treatment options used in post-traumatic stress disorder.
5. Design appropriate education for patients on the rationale, appropriate use and adverse effects of medications used for post-traumatic stress disorder.

Upon successful completion of this article, the pharmacy technician should be able to:
1. Explain the pathophysiology of post-traumatic stress disorder.
2. Describe the risk factors and symptoms of post-traumatic stress disorder.
3. Discuss lifestyle modifications and common drug treatment for post-traumatic stress disorder.
4. Identify patients at risk for, or exhibiting signs of, post-traumatic stress disorder and refer patients to the pharmacist for further assessment or referral.

Post-traumatic stress disorder (PTSD) is an anxiety disorder resulting from either the direct involvement with or the witnessing of a traumatic event. Similar to variations in exposure to traumatic events, the prevalence of PTSD also has been found to vary widely. It is estimated that the lifetime prevalence of PTSD in the general population is 5-6 percent for males and 10-14 percent for females. For populations exposed to interpersonal violence such as combat veterans, populations affected by genocide, survivors of rape, or those previously held captive, PTSD prevalence estimates are estimated to rise to 25-50 percent. With the increased availability of graphic videos and images available via media outlets and the internet, there is a concern of a potential rise in the prevalence of PTSD in the population of viewers of this material, but the expected prevalence of PTSD development after witnessing an event is thought to be lower than if actually confronted with the event. In addition to developing PTSD, those exposed to traumatic events are at increased risk for major depression, panic disorder, generalized anxiety disorder, substance abuse, hypertension, asthma and chronic pain syndromes.

PATHOPHYSIOLOGY
A number of biochemical processes are thought to be involved in the development and throughout the course of PTSD. The amygdala and hippocampus as well as the neurotransmitters serotonin, norepinephrine (NE) and dopamine are commonly cited. The amygdala is the portion of the brain responsible for fear response and is thought to signal the hippocampus which appears to assist in the development of memories. Imaging studies of PTSD patients have demonstrated altered activity in both areas. It is thought that at the time of the trauma a number of factors (such as previous traumas, ethnicity, support immediately following trauma) may influence the body’s response. If the body is unable to contain the biological stress, this may progress to the development of symptoms including intru-
sive recollection, re-experiencing, avoidance, numbness and hyperarousal. Changes in the body’s initial response to the trauma may be due to lower cortisol levels which may lead to greater availability of NE. In general, patients with PTSD tend to have higher levels of NE in their central nervous systems (CNS) and to a lesser extent in the periphery. In addition to elevations in NE, there appear to be alterations in the signaling of a number of CNS pathways that result in the symptoms experienced in PTSD that have not clearly been delineated at this time.

**CLINICAL PRESENTATION/DIAGNOSIS**
The diagnosis of PTSD is made if an individual has been personally exposed to or witnessed a traumatic event. This event inspires fear, hopelessness, or horror in the individual. Following the trauma, the individual often begins to re-experience the event and may attempt to avoid people or places associated with the event. Some individuals may become desensitized or numb to their surroundings while still experiencing increased symptoms of hyperarousal. Episodes are considered acute if the symptoms last for more than one month but less than three months, while episodes are considered chronic if the symptoms last more than three months. A third subset is delayed-onset PTSD, where six months or more have passed following the traumatic experience before the onset of symptoms. Symptoms may be present in patients of any age and the duration of the illness varies. Approximately half of patients have complete recovery within three months, but symptom reactivation may occur with exposure to reminders of the original trauma.

**DESIZED GOALS/OUTCOMES**
Goals for the treatment of PTSD involve the resolution of all PTSD symptoms experienced by the patient as well as any co-morbid conditions such as other anxiety disorders, depression or substance abuse. To achieve this goal, combination psychotherapy and pharmacotherapy are often utilized as approximately 40 percent of patients will not respond to pharmacotherapy alone. Engagement of families and supportive individuals is also recommended as involving them in treatment may assist in achieving optimal outcomes. Once the patient’s symptoms are controlled, treatment should focus on attempting to work with the patient’s ability to cope with situations. This may assist in preventing future relapses or exacerbations from other potentially traumatic events so the patient is able to maintain a sense of safety and trust. To prevent relapse, medication therapy often needs to be continued long-term.

**NON-PHARMACOLOGIC THERAPIES/PSYCHOTHERAPY**
There are a number of different approaches recommended for the treatment of PTSD. Cognitive behavioral therapy is recommended to commence two to three weeks following exposure to the trauma to prevent the development of PTSD or to accelerate recovery. This therapy focuses on desensitizing the patient to trauma-related triggers. Eye movement desensitization and reprocessing (EMDR) requires the patient to recall traumatic material while simultaneously focusing on an external stimulus. The efficacy of EMDR is thought to be similar to that of other non-pharmacologic options. Individual and group therapy focus on educating patients about the condition as well as restructuring the patient’s thoughts and automatic responses to thoughts, images or experiences. Learning a variety of coping skills may assist in managing anxiety during these experiences. Support groups are also available for family and friends to provide education and skills to help these important individuals play an active role in facilitating the recovery of their loved one. Not all of the non-pharmacologic therapies are ap-
propriate for all PTSD patients. Similar to other mental illnesses, treatment should be tailored to the needs of the individual, including the recognition that these needs often change over time.

PHARMACOLOGIC TREATMENT

Antidepressants

Currently, paroxetine and sertraline are the only two medications approved for PTSD by the Food and Drug Administration (FDA). Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are first-line pharmacotherapeutic options for the treatment of PTSD due to their safety, efficacy, and tolerability. Nevertheless, antidepressants have not consistently demonstrated benefit across all patient types (such as civilian versus combat-related PTSD) and symptom clusters (such as re-experiencing, avoiding/numbing, and hyperarousal). Various medications have been investigated as adjunctive therapy to enhance antidepressant response or for use in treatment-refractory patients with varying degrees of success. Antidepressant doses for sertraline and paroxetine are similar to dosing for other indications and should be titrated from a starting dose to that which is clinically effective and tolerated. Sertraline dose should start at 50 mg once daily, up to 200 mg daily and paroxetine dose should start at 20 mg once daily, up to 60 mg. The same approach to dosing could be applied to off-label use of other drugs as illustrated in the following table. Patients responding to pharmacotherapy should continue treatment for at least one year.

All antidepressants carry a black box warning for suicidal thinking and behavior (http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm) in children, adolescents and young adults (up to age 24 years). Families and friends should be engaged to communicate signs of suicidal thinking and behavior to the prescriber.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs are first-line options for the treatment of PTSD. They

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Starting Dose (mg/day)</th>
<th>Usual Dosage Range (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>10–20</td>
<td>20–80</td>
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<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>10–20</td>
<td>20–50</td>
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<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>25–50</td>
<td>50–200</td>
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<tr>
<td>Venlafaxine</td>
<td>Effexor</td>
<td>37.5–75</td>
<td>75–300</td>
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<tr>
<td><strong>Sympatholytic Agent</strong></td>
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<tr>
<td>Prazosin</td>
<td>Minipress</td>
<td>1</td>
<td>1–20</td>
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<tr>
<td><strong>Antiepileptic Drugs</strong></td>
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<tr>
<td>Divalproex</td>
<td>Depakote</td>
<td>500</td>
<td>Serum levels</td>
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<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
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<td>100–400</td>
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<tr>
<td>Topiramate</td>
<td>Topamax</td>
<td>25–50</td>
<td>50–400</td>
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<tr>
<td><strong>Second Generation Antipsychotics</strong></td>
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<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
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<td>5–20</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>25–50</td>
<td>300–800</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>0.5</td>
<td>0.5–8</td>
</tr>
</tbody>
</table>

*a* Paroxetine and sertraline are FDA-approved for the treatment of PTSD.

*b* The dosage should be increased according to the patient’s response and tolerability. Usual serum concentrations range from 50–125 g/mL.

*c* Lamotrigine dosing is influenced by concomitant medications. Initiate lamotrigine at half the regular starting dose (i.e., 25mg every other day) with concurrent divalproex therapy or twice the regular starting dose (i.e., 50mg once daily) with concurrent metabolic inducers (e.g., carbamazepine).

References: 3, 7, 31
are considered effective treatment for all three PTSD symp-
tom clusters: re-experiencing, avoidance/numbing, and
hyperarousal. Furthermore, they also treat co-morbidities that
frequently accompany PTSD, including depression, suicidial-
ity, and impulsivity. Finally, SSRIs have a favorable side effect
profile relative to many other psychotropic medications.
SSRIs are specific for inhibiting the presynaptic reup-
take of serotonin via blockade of the serotonin transporter
carrier. They display relatively weak effects on the reuptake
of other neurotransmitters, notably norepinephrine and
catecholamines; therefore, they are considerably more tolerable than the tricyclic antidepres-
sants (TCAs). Despite similarities across SSRIs, individual
agents vary with regard to other properties, such as phar-
macokinetic parameters and side effect profiles.
Side effects are generally mild and more tolerable
than other psychotropic medications. Common side
effects include gastrointestinal disturbances (nausea, diar-
rhea), sexual dysfunction, headache, insomnia, somno-
lence, restlessness and anxiety. While side effects such as
gastrointestinal disturbances are transient, resolving within
the first few days to weeks of therapy, sexual dysfunction
may often persist. It has been estimated that upwards of
60 percent of patients report signs of treatment-related
sexual dysfunction during SSRI therapy, including symp-
toms of decreased libido, erectile dysfunction, and de-
layed or absent orgasm or ejaculation.
Other potential side effects include hyponatremia,
abnormal bleeding, and discontinuation symptoms. The
mechanism of SSRI-induced hyponatremia has not been
fully elucidated; however, risk factors for its development
include older age, female gender, concurrent diuretic use,
and a lower serum sodium concentration at baseline.
Abnormal bleeding has been observed with SSRI therapy.
It has been suggested that the risk of abnormal bleeding
secondary to SSRIs is caused by the inhibition of serotonin
uptake into platelets. Gastrointestinal bleeding is most
often observed; nevertheless, the overall risk appears low.
The risk appears to be increased with concurrent antico-
agulant, antiplatelet, or nonsteroidal anti-inflammatory drug
use. Discontinuation syndrome is manifested by the abrupt
discontinuation of therapy. Flu-like symptoms, insomnia,
nausea, dizziness, anxiety, and sensory disturbances (par-
esthesias) are common features. Discontinuation syndrome
occurs more commonly with the shorter half-life antide-
pressants, such as paroxetine, than those with
longer half-lives and active metabolites, such as
fluoxetine and its active metabolite, norfluoxetine.
The FDA has approved six SSRIs: citalopram
(Celexa), escitalopram (Lexapro), fluoxetine (Pro-
zac), fluvoxamine (Luvox), paroxetine (Paxil), and
sertraline (Zoloft). SSRIs are FDA-approved for
a number of conditions, including major depres-
sive disorder, generalized anxiety disorder, panic
disorder, obsessive-compulsive disorder, and
bulimia nervosa. While sertraline and paroxetine
are the only medications approved for PTSD,
many clinicians regard all SSRIs as having similar
efficacy in its treatment. Unfortunately, head-to-
head trials among SSRIs for PTSD are lacking.
Sertraline, paroxetine, and fluoxetine currently
have the most evidence for use in PTSD.
Sertraline is one of two FDA-approved
medications for the treatment of PTSD. Two ran-
donized, placebo-controlled, 12-week trials in
civilian-related PTSD found sertraline superior to
placebo. The first trial evaluated 187 outpatients
with sertraline doses ranging from 50 to 200 mg/
day. Compared to placebo, sertraline signifi-
cantly decreased the Clinician-Administered
PTSD Scale (CAPS) total score [-33.0 vs -23.2
(p=0.02)] and was well tolerated. Response rate
was defined as a greater than 30 percent reduc-
tion in CAPS total score and a Clinical Global
Impression - Improvement (CGI-I) score of 1 or
2. Overall, patients receiving sertraline had a
53 percent response rate versus 32 percent for
placebo. The second trial investigated 208 out-
patients with sertraline doses ranging from 50 to
200 mg/day. Once again, sertraline signifi-
cantly improved efficacy measures versus placebo,
notably the CAPS total score [-33.0 vs -26.2
(p=0.04)]. Criteria for response were defined
similarly to the previous trial. Overall, patients
receiving sertraline had a 60 percent response rate
versus 38 percent for placebo. In contrast
to the previous studies, a more recent 12-week
trial evaluated 169 outpatients with predomi-
nantly combat-related PTSD. Sertraline failed to
separate from placebo in primary or secondary
endpoints. Finally, sertraline was evaluated in
a 28-week trial examining its effects on relapse prevention. Patients completed both an initial 12-week and subsequent 24-week treatment phase and were considered sertraline treatment responders. A total of 96 patients then entered a 28-week, double-blind study and were randomized to continue sertraline therapy or initiate placebo. Continued treatment with sertraline resulted in significantly fewer patients relapsing, with 5.3 percent versus 26.1 percent for placebo.

Paroxetine is also FDA-approved for the treatment of PTSD. Paroxetine was shown to be effective in two placebo-controlled, 12-week trials. The first trial evaluated 307 patients with paroxetine doses ranging from 20 to 50 mg/day. The primary outcome was change in CAPS total score as well as the proportion of responders on the CGI-I. The average dose of paroxetine was 27.6 ± 6.72 mg/day. Compared to placebo, paroxetine significantly decreased the CAPS total score [-35.5 vs -24.7 (p = <0.001)]. The response rate was significantly greater for paroxetine than placebo at approximately 60 percent versus 40 percent, respectively. The second trial evaluated 551 patients randomized to receive either paroxetine 20 mg/day, 40 mg/day, or placebo. Paroxetine 20 mg/day, 40 mg/day, and placebo decreased the CAPS total score by -39.6, -37.9, and -25.3, respectively. Improvement was significantly greater for both active treatments versus placebo. The percentage of patients achieving response was 62 percent with paroxetine 20 mg/day, 54 percent with paroxetine 40 mg/day, and 37 percent with placebo.

While fluoxetine is not FDA-approved for the treatment of PTSD, literature exists supporting its use. An early trial of 64 patients evaluated fluoxetine versus placebo. Despite its short five-week duration, fluoxetine significantly decreased the CAPS total score. A randomized, placebo-controlled, 12-week trial of civilians examined fluoxetine in doses up to 60 mg/day. Of the 53 patients, 91 percent were women. The Duke Global Rating for PTSD was the primary outcome measure. When a Duke cut-off score of 1 was utilized, the response rate differed significantly, with 59 percent for fluoxetine and 19 percent for placebo. An internationally conducted randomized, placebo-controlled, 12-week trial consisted of 301 combat and civilian-related PTSD patients. Fluoxetine was dosed 20 to 80 mg/day. The primary efficacy measure was the change in Treatment Outcome PTSD rating scale (TOP-8) total score. Fluoxetine significantly improved the TOP-8 total score versus placebo as well as significantly improving the CAPS total score [-34.6 vs -26.8 (p = 0.021)]. Response rates were 59.9 percent for fluoxetine and 43.8 percent for placebo. Fluoxetine has also been studied for relapse prevention. A placebo-controlled discontinuation study evaluated 57 patients. Patients enrolled in the study received open-label fluoxetine treatment for six months. The patients were then randomized to receive fluoxetine 10 to 60 mg/day or placebo for an additional six months in a double-blinded fashion. Utilizing CGI-I scores, placebo had a significantly higher relapse rate of 50 percent versus fluoxetine at 22.2 percent. Furthermore, the time to relapse was significantly longer with fluoxetine than placebo.

A second study examining relapse prevention selected patients responding to 12 weeks of acute treatment. Following acute treatment, a total of 131 patient responders were randomized in a double-blind fashion to receive either fluoxetine or placebo for an additional 24 weeks. The average dose by study endpoint was 53 mg/day. While fluoxetine failed to separate from placebo with regard to the CAPS total score, fluoxetine was able to significantly prevent relapse versus placebo. Other trials have failed to show any benefit with fluoxetine therapy. A placebo-controlled, 12-week trial evaluated fixed doses of fluoxetine 20 and 40 mg/day. The trial included predominately women and utilized the TOP-8 as the primary outcome measure. Fluoxetine failed to produce significant changes in the TOP-8 total score or in response rates. Similarly, fluoxetine 20 mg/day and 40 mg/day failed to separate from placebo with regard to the CAPS total score with changes of -42.9, -42.8, and -36.6, respectively. A possible explanation for the lack of benefit may involve the dosing of fluoxetine with higher overall doses potentially needed to produce the desired effects in PTSD.

The remaining SSRIs have also been investigated for the treatment of PTSD to varying degrees. Citalopram, recently scrutinized by the FDA for dose-dependent QT prolongation concerns, has favorable data from open-label trials. A double-blind comparison of citalopram, sertraline,
and placebo supported a beneficial class effect of SSRIs on PTSD. Escitalopram, the active S-enantiomer of racemic citalopram, has only preliminary open-label trial data suggesting efficacy. Fluvoxamine, predominantly utilized in obsessive-compulsive disorder, has demonstrated beneficial effects in PTSD, as well. Nevertheless, paroxetine, sertraline, and fluoxetine continue to be the most rigorously evaluated SSRIs for the treatment of PTSD.

**SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS**

There are currently four FDA-approved SNRIs available: venlafaxine (Effexor), desvenlafaxine (Pristiq), duloxetine (Cymbalta), and milnacipran (Savella). SNRIs inhibit the presynaptic reuptake of serotonin and norepinephrine to varying degrees. Venlafaxine, for example, inhibits the reuptake of serotonin at low doses, whereas higher doses are needed to additionally inhibit the reuptake of norepinephrine. Desvenlafaxine is the primary active metabolite of venlafaxine. Duloxetine is unique in that it is FDA-approved for a number of pain indications, including diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain. Milnacipran, the newest SNRI available, is currently only FDA-approved for the management of fibromyalgia. Side effects vary slightly among the SNRIs; however, a notable difference from SSRIs includes dose-dependent increases in blood pressure. Blood pressure should be monitored regularly throughout therapy. Similar to paroxetine, venlafaxine is prone to causing a discontinuation syndrome. A gradual taper is necessary when discontinuing, and patients should be counseled on the symptoms of the discontinuation syndrome.

Currently, venlafaxine is the only SNRI with published controlled trials in PTSD. A randomized, placebo-controlled, six-month trial investigated venlafaxine extended-release. A total of 329 patients with both civilian and combat-related PTSD were randomized to either venlafaxine extended-release ranging from 37.5 to 300 mg/day, sertraline 25 to 200 mg/day, or placebo. The primary outcome measure was change in CAPS score. Average doses were 225 mg and 151 mg for venlafaxine extended-release and sertraline, respectively. Changes in CAPS scores were -41.5, -39.4, and -34.2 for venlafaxine extended-release, sertraline, and placebo, respectively. Differences between venlafaxine extended-release and sertraline were not statistically significant.

**MISCELLANEOUS ANTIDEPRESSANTS**

A number of other antidepressants have been evaluated for the treatment of PTSD. Bupropion (Wellbutrin) inhibits the presynaptic reuptake of dopamine and norepinephrine. Common side effects include insomnia, dry mouth, nausea, and weight loss. Contraindications include patients with seizure disorders, a history of anorexia or bulimia nervosa, and the abrupt discontinuation of alcohol or sedatives. Ask patients or caregivers about seizure history if the patient is known to have suffered a head trauma. Overall, bupropion was found to be ineffective for PTSD in two controlled trials. Mirtazapine (Remeron) has multiple receptor effects, including 5-HT₂ receptor antagonism, 5-hydroxytryptamine (5-HT) receptor antagonism, specifically at 5-HT₂ and 5-HT₃ receptors, and histamine receptor antagonism. Common side effects include sedation and weight gain. Interestingly, the dose of mirtazapine and associated sedation are inversely proportional. In a small trial of 29 patients, mirtazapine was associated with a significantly greater rate of global response than placebo. Vilazodone (Viibryd), the newest available antidepressant, has not been studied in the treatment of PTSD.

Nefazodone (Serzone) is not widely prescribed; however, an evidence base supports its use for the treatment of PTSD. Nefazodone inhibits the reuptake of serotonin and norepinephrine and antagonizes the 5-HT₂A receptor.
Sedation, orthostatic hypotension, and blurred vision are common side effects. The widespread use of nefazodone has been limited by warnings of hepatotoxicity. The estimated rate of nefazodone-induced liver failure in the United States is 1 per 250,000 to 300,000 patient-years of nefazodone treatment. The majority of cases occurred after at least four weeks of treatment, with only a few occurring beyond six months. Nevertheless, routine liver function testing is advised throughout therapy. Drug interactions are also concerning as nefazodone strongly inhibits cytochrome P450 (CYP) 3A4. Interactions with several common medications such as dronedarone, simvastatin, and tamsulosin often require the prompt intervention of the pharmacist.

Data accumulated from open-label trials suggest nefazodone is an efficacious treatment for PTSD. A randomized, placebo-controlled, 12-week trial in a mixed civilian and veteran population of 41 patients also demonstrated its effectiveness. Nefazodone was dosed up to 600 mg/day with an average dose of 435 mg/day. Compared to placebo, nefazodone significantly decreased the CAPS total score [-19.1 vs -13.5 (p=0.04)]. Response rate was defined as ≥ 30 percent improvement in the CAPS total score. While there was a significant difference in responders at week four, by week 12 the difference in responders was not significant with 47 percent in the nefazodone group, and 42 percent in the placebo group. A head-to-head, 12-week trial of 37 patients compared nefazodone and sertraline therapy. While both treatments produced significant changes on each outcome measure, no significant difference was found between agents. Despite the small sample size, nefazodone was deemed as effective as sertraline for the treatment of PTSD.

Benzodiazepines enhance the activity of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the CNS, and possess anxiolytic, sedative, anticonvulsant, and myorelaxant properties. While benzodiazepines are frequently utilized in other anxiety disorders, their benefits in PTSD appear limited. Benzodiazepines may alleviate symptoms of anxiety or insomnia; however, they have not been shown to improve the core symptoms of PTSD or prevent its occurrence. Another disadvantage includes the potential for abuse, particularly in a population where substance abuse may be common. Overall, benzodiazepines should be avoided or minimized as they are ineffective for the treatment or secondary prevention of PTSD, harbor concerns of tolerance and dependence, and potentially worsen symptoms upon their discontinuation.

A crossover trial of 16 patients examined the effects of up to 6 mg/day of alprazolam (Xanax) versus placebo for five weeks. Three patients in each group left the study citing treatment as ineffective; therefore, 10 patients completed the study. After the initial five weeks in either treatment arm, patients were switched during a two-week interim phase and treated with the opposite treatment for an additional five weeks. Among the various rating scales utilized, alprazolam only demonstrated statistically significant improvement on the Hamilton Rating Scale for Anxiety (HAM-A) while failing to separate from placebo on any other measures. A small, randomized, single-blind, crossover trial of six patients investigated the effects of clonazepam (Klonopin) on sleep in combat-related PTSD. Patients were given clonazepam 1 mg at bedtime for one week, followed by 2 mg at bedtime for one-week. After the initial two weeks, patients underwent a one week washout period before switching to the alternate treatment for two weeks. Overall, clonazepam failed to separate from placebo and was mostly ineffective at improving sleep or nightmares.

Benzodiazepine therapy has also been evaluated immediately following trauma for the prevention of PTSD. Patients were evaluated within two days of trauma and, following initial assessments, were screened by a research psychiatrist for appropriateness of benzodiazepine therapy. Of 162 patients evaluated, 13 were initiated on benzodiazepine therapy with either alprazolam or clonazepam. The 13 patients were then matched based on gender and symptom severity in the first week with an untreated control group. At both the one and six month follow-ups,
the benzodiazepine group failed to show a difference from the control group in mitigating the development of PTSD. In fact, nine patients (69 percent) in the benzodiazepine group and only two (15 percent) in the control group met the diagnostic criteria for PTSD.

**SYMPATHOLYTICS**

Excessive norepinephrine activity in the CNS has been implicated in the underlying pathophysiology of PTSD. Medications that blunt noradrenergic activity have been investigated in its treatment. Prazosin (Minipress), an α₁ adrenergic receptor antagonist, is utilized as an adjunct to antidepressant therapy. Prazosin, administered at bedtime, alleviates symptoms of hyperarousal such as sleep disturbances and nightmares. Dosages are initiated low and increased gradually to minimize orthostatic hypotension. Several retrospective chart reviews and open-label trials of civilian and combat-related PTSD have shown benefit with prazosin therapy.

Two placebo-controlled trials in combat-related PTSD and one in civilian-related PTSD support the use of prazosin as adjunctive therapy. The first combat-related PTSD trial evaluated 10 patients with trauma-related nightmares. Five patients received either prazosin or placebo for an initial nine weeks. After a two-week washout period, the patients were switched to the opposite treatment for an additional nine weeks. The dose of prazosin was gradually titrated to minimize orthostatic hypotension, and the average dose was 9.5 mg at bedtime. Prazosin was superior to placebo on all three primary outcome measures and was well tolerated. A second combat-related PTSD trial investigated 34 patients randomized to receive prazosin or placebo for eight weeks. Prazosin was initiated at 1 mg to minimize orthostatic hypotension and titrated to a maximum of 15 mg at bedtime. The average dose was approximately 13 mg. By week eight, prazosin significantly differed from placebo on all three primary outcome measures assessing nightmares. Recurrent distressing dreams decreased more than 50 percent, versus 15 percent for prazosin and placebo, respectively. Side effects were more common with prazosin therapy, with transient orthostatic hypotension, nasal or sinus congestion, and headache being the most common. Differences in blood pressure changes did not differ significantly between groups. Finally, a randomized, placebo-controlled, crossover trial examined 13 patients with civilian-related PTSD. Patients received either prazosin or placebo for three weeks, followed by a one-week washout period before switching to the opposite treatment. Prazosin was initiated at 1 mg at bedtime with an average dose of approximately 3.1 mg. Prazosin increased total sleep time [374 ± 86 minutes versus 280 ± 105 minutes (p<0.01)] and significantly decreased trauma-related nightmares.

A retrospective chart review compared prazosin and quetiapine (Seroquel) therapy over a six-month period. A total of 237 patients were included with 62 receiving prazosin and 175 receiving quetiapine. Authors relied on chart documentation of symptom improvement. Short-term effectiveness was similar between groups with symptom improvement noted in 61.3 percent of prazosin patients and 61.7 percent of quetiapine patients. Conversely, significantly more patients continued prazosin versus quetiapine to study end date, with 48.4 percent and 24 percent, respectively. In addition, significantly more patients discontinued quetiapine secondary to the side effects, including sedation and cardiometabolic disturbances.

**SECOND GENERATION ANTIPSYCHOTICS**

Second generation antipsychotics, also known as atypical antipsychotics, are increasingly utilized as adjunctive medications for treatment-refractory PTSD. Unlike first generation antipsychotics, such as haloperidol, which predominately exert effects via dopamine antagonism at the D₂ receptor, second generation antipsychotics are both D₂ and 5-HT₂A receptor antagonists. While pharmacologic differences afford the second generation antipsychotics lower rates of extrapyramidal symptoms, clinicians must continue to monitor for tardive dyskinesia with these agents. FDA has issued a black box warning against using these medications in the elderly with dementia-related psychosis. Second generation antipsychotics also have a propensity for causing cardiometabolic disturbances, including weight gain, hyperlipidemia, and diabetes mellitus. Current guidelines for monitoring metabolic parameters recommend that weight, waist
circumference, blood pressure, fasting plasma lipids, and glucose are monitored throughout therapy. Risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine have accumulated the most data as adjunctive therapies for PTSD.

Risperidone is the most extensively studied second generation antipsychotic with a total of seven placebo-controlled trials and several open-label trials. Overall, results appear to be mixed. Risperidone has significantly improved the CAPS total score versus placebo; however, small sample sizes and other limitations often affect the generalizability of these study results. The most recent risperidone trial evaluated its use as an adjunct to antidepressant therapy. This six-month, randomized, placebo-controlled trial consisted of 247 combat-related PTSD patients. Doses of risperidone up to 4 mg/day were utilized. At the end of 24 weeks, risperidone failed to separate from placebo on the primary outcome measure of CAPS total score [-16.3 versus -12.5 (p=0.11)]. Furthermore, the rate of patients achieving remission did not significantly differ between risperidone and placebo at 5 percent and 4 percent, respectively.

ANTICONVULSANTS
Anticonvulsants have also been evaluated as adjunctive treatment to first-line pharmacotherapy. Case reports and open-label trials have suggested benefit with divalproex (Depakote); however, two recent randomized, placebo-controlled trials demonstrated a lack of clear benefit. An eight-week trial consisting of 85 patients with combat-related PTSD examined change in the CAPS hyperarousal subscale. Doses of divalproex averaged 2,309 ± 507 mg/day and serum levels averaged 82 ± 30 mg/L. No significant differences were found between divalproex and placebo on the primary outcome measure. Another trial of divalproex evaluated 29 patients with predominantly combat-related PTSD. Divalproex was not superior to placebo, and the placebo group managed to significantly improve the CAPS avoiding/numbing subscale. Lamotrigine (Lamictal) was evaluated in a small randomized, placebo-controlled trial of 15 patients. A slow dose titration was required to minimize the risk of rash. Two patients in both the lamotrigine group (20 percent) and placebo group (50 percent) developed rashes and dropped out of the study. Overall, lamotrigine was more effective than placebo; however, the small sample size may limit the generalizability of the results. Topiramate (Topamax) has been studied in open-label trials as well as one placebo-controlled trial in civilian-related PTSD and two placebo-controlled trials in combat-related PTSD. Data with topiramate are limited at this time, and results have been mixed. Further study is needed for levetiracetam (Keppra) after a retrospective analysis of 23 partial or nonresponders to antidepressant therapy suggested benefit. Finally, tiagabine (Gabitril), a GABA reuptake inhibitor, failed to separate from placebo in a large randomized, controlled trial.

CONCLUSIONS
PTSD is an anxiety disorder resulting from direct exposure to or witnessing of a traumatic event. Core symptoms of PTSD are divided into three symptom clusters: re-experiencing, avoidance/numbing, and hyperarousal. Non-pharmacologic and pharmacologic treatment strategies have been investigated in the treatment of PTSD. With regard to pharmacologic treatment, the SSRIs and venlafaxine are first-line pharmacotherapeutic options secondary to their safety, efficacy, and tolerability. Prazosin appears to be an effective adjunct for sleep disturbances and nightmares. Anticonvulsants and second generation antipsychotics have mixed results as adjuncts to antidepressant therapy. Finally, benzodiazepines are not recommended secondary to lack to efficacy in treating core symptoms as well as potentially harmful effects. It is important to tailor treatment to the needs of each individual patient.

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CONTINUING EDUCATION QUIZ
Select the correct answer.

1. Which of the following non-pharmacologic treatment options is recommended in the two to three weeks following the trauma to minimize or possibly prevent the development of PTSD?
   a. Cognitive behavioral therapy
   b. Eye movement desensitization and reprocessing
   c. Group therapy
   d. Relaxation techniques

2. The use of non-pharmacologic therapy in the treatment of PTSD can best be described as:
   a. The mainstay, first-line treatment for all PTSD patients
   b. Essential methods of therapy that are primarily responsible for preventing relapses
   c. A collection of diverse treatments that are used in combination with medications
   d. A necessary tool that assists the patient until the medications start working

3. Which of the following would be a re-experiencing symptom in a rape victim with PTSD?
   a. Recurrent thoughts of gun battles making her vigilant for snipers in the windows
   b. Hallucinations of a plane crash where she can smell fuel and smoke
   c. Feelings of helplessness whenever she hears a tornado siren
   d. Vivid dreams of the attack that wake her up

4. Imaging studies have shown that which of the following brain structures appear to be involved with the development of PTSD?
   a. Amygdala and hippocampus
   b. Amygdala and pituitary
   c. Prefrontal cortex and hippocampus
   d. Prefrontal cortex and hypothalamus

5. What neurotransmitter is clearly involved in the development of PTSD?
   a. Corticotropin releasing factor
   b. Dopamine
   c. Norepinephrine
   d. Serotonin

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6. The role of cortisol in PTSD is best described as being:
   a. Lower than expected at the time of the trauma
   b. Higher than expected at the time of the trauma
   c. Suppressed less than expected in the months following the trauma
   d. Not involved in the development of PTSD symptoms

7. Which of the following is true regarding the goals of therapy for PTSD patients?
   a. Complete control of re-experiencing symptoms is unlikely.
   b. Long-term medication use is often needed to prevent relapse.
   c. Psychotherapy is superior to medication in preventing relapses.
   d. Treatment is patient specific and no family involvement is needed.

8. R.S. is a scuba diver who was severely injured when a boater did not recognize his diver down flag and drove over him. Which of the following is true of acute PTSD:
   a. It occurs only at the time of the trauma.
   b. It lasts from one to three months.
   c. It lasts eight months.
   d. It is only diagnosed when the victim or witness required hospitalization.

9. M.H. is a domestic abuse survivor. Now in a healthy marriage with a 2-year-old child, she experiences panic and fear when the child hits her while throwing a tantrum. M. H. is subsequently diagnosed with:
   a. Acute PTSD
   b. Chronic PTSD
   c. Delayed-onset PTSD
   d. No diagnosis of PTSD can be made more than six months after the trauma

10. All of the following are symptom clusters of PTSD, EXCEPT:
    a. Avoidance/numbing
    b. Depression
    c. Hyperarousal
    d. Re-experiencing

11. Antidepressants are considered first-line pharmacologic treatment options because they alleviate the following symptoms associated with PTSD:
    a. Avoidance/numbing
    b. Hyperarousal
    c. Re-experiencing
    d. All of the above

12. Which of the following are the only FDA-approved medications for the treatment of PTSD?
    a. Alprazolam and clonazepam
    b. Fluoxetine and venlafaxine
    c. Paroxetine and sertraline
    d. Prazosin and risperidone

13. Which of the following SSRIs is most likely to cause discontinuation syndrome with missed doses?
    a. Escitalopram
    b. Fluoxetine
    c. Paroxetine
    d. Sertraline
14. Which of the following medications inhibits the reuptake of serotonin and norepinephrine into presynaptic neurons?
   a. Bupropion
   b. Duloxetine
   c. Mirtazapine
   d. Vilazodone

15. M. J. suffered a traumatic brain injury and now experiences seizures. Which of the following medications is contraindicated in patients with a seizure disorder?
   a. Bupropion
   b. Nefazodone
   c. Quetiapine
   d. Risperidone

16. Which of the following statements regarding benzodiazepine therapy in the treatment of PTSD is TRUE?
   a. Benzodiazepines are useful for treating co-morbid depression
   b. Benzodiazepines do not produce tolerance and dependence
   c. Benzodiazepines have not been shown to improve core symptom clusters
   d. Benzodiazepines prevent the occurrence of PTSD following a trauma.

17. Adjunctive prazosin therapy is most helpful for which of the following symptoms:
   a. Flashbacks
   b. Difficulty concentrating
   c. Impulsivity
   d. Nightmares

18. All of the following are required monitoring parameters for second generation antipsychotics, EXCEPT:
   a. Fasting plasma lipids
   b. Tardive dyskinesia
   c. Thyroid function
   d. Waist circumference

19. Risk factors for the development of SSRI-induced hyponatremia include all of the following, EXCEPT:
   a. Concurrent diuretic use
   b. Low serum sodium
   c. Male gender
   d. Older age

20. Which of the following antidepressants is a strong inhibitor of CYP3A4, thereby contraindicating its use with CYP3A4 substrates such as dronedarone, simvastatin, and tamsulosin.
   a. Desvenlafaxine
   b. Mirtazapine
   c. Nefazodone
   d. Paroxetine