

Treating comorbid posttraumatic stress disorder and cardiovascular disease

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Mr. S, 64, has a history of post-traumatic stress disorder (PTSD), which has been well controlled for the past 15 years with cognitive-processing therapy and fluoxetine, 40 mg/d. However, over the past 6 weeks, Mr. S has experienced increased hypervigilance, nightmares, and flashbacks. He states that his primary care provider recommended an adjustment in pharmacotherapy to address this exacerbation of symptoms. Previous medication trials include sertraline, 200 mg/d, discontinued due to lack of perceived efficacy, and venlafaxine, 150 mg/d, discontinued due to increased blood pressure.

Mr. S's medical history includes hypertension, dyslipidemia, and myocardial infarction (MI) 5 years ago. His family history includes sudden cardiac death (mother and father) and major depressive disorder (sister). His blood pressure is currently uncontrolled on lisinopril, 5 mg/d, and metoprolol succinate, 50 mg/d. Today, serial blood pressure readings measured approximately 180/90 mm Hg, with a pulse 50-60 beats per minute.

What is the next step in treating Mr. S's hypertension and PTSD symptoms? Is

there any evidence to support concomitant therapy?

PTSD is characterized by emotional and behavioral symptoms following exposure to a traumatic event. Its 12-month prevalence in the United States is estimated at 3.5%. Diagnostic criteria necessitate the presence of intrusive symptoms, persistent effortful avoidance of distressing trauma-related stimuli, negative cognitions or mood, and alterations in arousal and reactivity. PTSD negatively impacts social and occupational functioning.¹

Cardiovascular disease (CVD) comprises a number of conditions, including coronary artery disease, cerebrovascular disease, congestive heart failure, and venous thromboembolism. CVD accounted for more than 17 million deaths worldwide in 2012, which is more than any other cause.²

Studies have revealed a correlation between the presence of psychosocial factors, such as depression and anxiety, and the occurrence of cardiovascular events.

Practice Points

- Posttraumatic stress disorder and cardiovascular disease often are comorbid, especially in geriatric patients.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may provide benefit in attenuation of hyperarousal symptoms and intrusive thoughts.
- Alpha-1 antagonists, particularly prazosin, may be useful in treating sleep disturbances and nightmares.

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Table 1

Increased CVD risk factors among veterans with PTSD

Risk factor	Odds ratio, male ^a	Odds ratio, female ^a
Hypertension	2.88	2.99
Dyslipidemia	2.70	2.68
Type 2 diabetes mellitus	2.57	2.86
Obesity	2.35	3.01
Tobacco use	3.63	3.58

CVD: cardiovascular disease; PTSD: posttraumatic stress disorder
^aCompared with veterans with no mental health diagnosis or with a mental health diagnosis other than PTSD
Source: Reference 3

The mechanism appears to consist of a behavioral component (eg, poor diet, tobacco use) and a direct pathophysiologic component (eg, excessive sympathetic nervous system activation) (Table 1).⁴ Management of concomitant PTSD and CVD presents a challenge to clinicians.

This article summarizes the evidence for the use of CVD medications in treating PTSD (Table 2, page 40) and how to apply these principles in patient care (Table 3,⁵⁻¹⁴ page 41).

ACEIs, ARBs, beta blockers, and calcium channel blockers

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin system: ACEIs prevent formation of angiotensin II, a potent vasoconstrictor, and ARBs prevent interaction between angiotensin II and its receptor. In one study, patients were recruited from a large public hospital serving primarily a highly traumatized, low-income population. Patients taking an ACEI or ARB who had experienced at least 1 traumatic event exhibited significantly decreased hyperarousal symptoms and decreased intrusive thoughts on the PTSD Symptom Scale and Clinician Administered PTSD Scale.⁵ Other studies have reported that blockade of angiotensin II AT1 receptors may result in decreased stress, anxiety, and inflammation.¹⁵

Evidence supports the use of the centrally acting, beta-adrenergic antagonist propranolol for decreasing the physiologic reactivity to acute trauma. Emotional arousal enhances the consolidation of emotional experiences into long-term memories via the adrenal stress hormones epinephrine and corticosterone. The amygdala mediates these stress hormones and releases norepinephrine, which subsequently activates noradrenergic receptors essential for memory enhancement. Several studies have reported that patients who received propranolol within several hours of a traumatic event experienced fewer physiologic signs of PTSD at follow-up 1 month later.¹⁶ Moreover, researchers have hypothesized that chronic treatment with propranolol may be effective in decreasing hyperarousal symptoms in patients with chronic PTSD by reducing tonically elevated norepinephrine signaling.⁶

Chronic elevation of noradrenergic activity may induce lipoprotein lipase and suppress low-density lipoprotein (LDL) receptor activity, which in turn elevates serum cholesterol levels. The results of one study suggested that verapamil, a non-dihydropyridine calcium channel blocker, significantly improves serum cholesterol levels in patients with PTSD by increasing LDL receptor activity and decreasing norepinephrine release.⁷

Clinical Point

Patients who received propranolol within several hours of a traumatic event experienced fewer physiologic signs of PTSD at follow-up



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Table 2

Safety and efficacy of CVD medications in PTSD

Medication class	Safety	Efficacy
ACEIs/ARBs	Hyperkalemia, renal impairment, hypotension	ACEIs and ARBs may decrease hyperarousal symptoms
Beta-blockers	Sleep disturbances, bradycardia, hypotension	Propranolol may decrease signs and symptoms of PTSD, both acutely and chronically
Calcium-channel blockers	Constipation, hypotension	Verapamil may improve serum cholesterol in patients with PTSD
Alpha-1 antagonists	Dizziness, headache, orthostatic hypotension	Prazosin is well studied and shown to reduce frequency of PTSD nightmares. Doxazosin and terazosin may be considered second-line
Alpha-2 agonists	Dizziness, headache, orthostatic hypotension	Clonidine may reduce agitation. Guanfacine may reduce frequency of PTSD nightmares in children but not adults
Antihistamines	Drowsiness, confusion, increased appetite	Cyproheptadine and hydroxyzine may reduce the frequency of PTSD nightmares and improve sleep quality
Serotonin antagonists	Drowsiness, orthostatic hypotension. Priapism relatively rare	Trazodone and nefazodone may reduce the frequency of PTSD nightmares and improve sleep quality
TCAs	Conduction abnormalities. Not safe for use in patients with CVD	TCAs may be as effective as SSRIs in treating anxiety and depression associated with PTSD

ACEI: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CVD: cardiovascular disease; PTSD: posttraumatic stress disorder; TCA: tricyclic antidepressant

Clinical Point

Prazosin reduces the fight-or-flight and hyperarousal reactions related to nightmares caused by PTSD

Alpha-1 and alpha-2 antagonists

Alpha-1 antagonists relax vascular smooth muscle by blocking norepinephrine stimulation at postsynaptic α -1-adrenergic receptors. They frequently are prescribed for hypertension and benign prostatic hypertrophy. One α -1 antagonist in particular, prazosin, appears especially useful in treating sleep disturbances, which occur in up to 90% of patients with PTSD.¹⁷ Because of its relatively greater lipophilicity, prazosin crosses the blood-brain barrier and acts centrally to reduce the fight-or-flight and hyperarousal reactions related to nightmares caused by PTSD.¹⁸ Common adverse effects include dizziness and orthostatic hypotension. These usually can be mitigated with titration to effective dose. In a study of active-duty soldiers who returned from Iraq and Afghanistan, Raskind et al¹⁸ found that prazosin doses up to 25 mg/d in men and 12 mg/d in women were tolerated

with weekly adjustments and blood pressure monitoring.

Other α -1 antagonists have shown efficacy in a limited number of trials and may be considered second-line treatment of PTSD hyperarousal symptoms. Doxazosin has a longer half-life compared with prazosin (22 hours vs 3 hours) and may be useful in treating daytime hyperarousal with once-daily dosing. However, its hydrophilicity prevents it from crossing the blood-brain barrier to the same degree as prazosin.¹⁹ Terazosin also has a longer half-life (12 hours) and reaches peak plasma concentration in 1 hour. It undergoes minimal first-pass metabolism, leaving almost the entire circulating dose in the parent form, but clinical data are limited to only a small case report.¹⁰

Alpha-2 agonists inhibit sympathetic outflow in the CNS, which ultimately relaxes vascular smooth muscle like α -1 antago-

Table 3

Typical dosing discussed in studies

Medication	Typical dosing used
ACEIs/ARBs	Secondary analysis of data taken from a larger cross-sectional study. Medications presumably dosed to desired anti-hypertensive effect ⁵
Propranolol	Acute: 40 mg, 3 times daily, for the 7 days immediately following trauma, then a taper period of 8 to 12 days ⁶
Verapamil	120 mg/d in divided doses ⁷
Prazosin	1 mg at bedtime to 25 mg/d in divided doses (dosing may depend on the sex of the patient) ⁸
Doxazosin	4 to 8 mg in the evening ⁹
Terazosin	2 to 10 mg at bedtime ¹⁰
Clonidine	0.15 to 0.3 mg/d in divided doses ¹¹
Guanfacine	1 to 4 mg (extended-release) at bedtime, in pediatric patients ¹¹
Cyproheptadine	4 to 12 mg at bedtime ¹²
Hydroxyzine	100 mg at bedtime ¹³
Trazodone	50 to 200 mg at bedtime ¹⁴
Nefazodone	200 to 600 mg/d in divided doses ¹⁴

ACEI: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

nists. Clonidine exhibits sedative properties, which derive from its nonspecific binding to α -2a-, -2b-, and -2c-adrenergic receptors. Several case studies have described a reduction in agitation in PTSD patients with the use of clonidine, likely through the induction of sleep and relaxation. Guanfacine, on the other hand, selectively binds to the α -2a-adrenergic receptor and therefore lacks the sedative properties of clonidine. Several placebo-controlled trials showed no alleviation of PTSD symptoms in adults with the use of guanfacine.¹¹ However, case reports and open-label trials have suggested that guanfacine may reduce trauma-induced nightmares in pediatric patients. Further investigation is needed to clarify the potential use of guanfacine in pediatric PTSD.¹⁹

Antihistamines and antidepressants

Several second-line pharmacologic agents may be useful in patients with PTSD who are already taking cardiovascular medication. A limited number of studies have demonstrated reduced frequency of PTSD

nightmares with the histamine-1 antagonists cyproheptadine and hydroxyzine, both of which exhibit minor anti-serotonergic properties.^{12,13} Likewise, the serotonin antagonists nefazodone and trazodone have been shown to reduce the frequency of PTSD nightmares, as well as improve overall sleep quality.¹⁴ Nefazodone should be considered an option only after treatment failure of multiple other medications, because it is associated with a small, but significant, risk of life-threatening hepatotoxicity.²⁰

Tricyclic antidepressants (TCAs) may reduce anxiety and depression associated with PTSD to the same degree as SSRIs.²¹ However, their effect on PTSD-associated sleep disturbances is much less pronounced than other available medications.¹⁴ TCAs should be avoided in patients with CVD because they may exacerbate cardiac conduction abnormalities. This is especially true for those recovering from acute MI.²²

CASE CONTINUED

Mr. S is started on prazosin, 1 mg at bedtime, titrated weekly to 6 mg at bedtime with regu-

Clinical Point

Case reports and open-label trials have suggested that guanfacine may reduce trauma-induced nightmares in pediatric patients

Clinical Point

TCA's should be avoided in patients with CVD because they may exacerbate cardiac conduction abnormalities

lar blood pressure monitoring because of the risk of orthostatic hypotension. Although the frequency of his nightmares decreases to 1 or 2 per month, he still experiences flashbacks at the same frequency and intensity as before. Prazosin, 1 mg every morning, is added, titrated weekly to 4 mg every morning. This combination of morning and bedtime dosing leads to resolution of both nightmares and flashbacks along with a significant reduction in hyperarousal. Lisinopril is increased from 5 to 10 mg/d to address Mr. S's uncontrolled hypertension; this change also could have contributed to the reduction in hyperarousal. CPT and fluoxetine are continued.

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Related Resource

- U.S. Department of Veterans Affairs. National Center for PTSD. <http://www.ptsd.va.gov>.

Drug Brand Names

Clonidine • Catapres	Nefazodone • Serzone
Cyproheptadine • Periactin	Prazosin • Minipress
Doxazosin • Cardura	Propranolol • Inderal
Fluoxetine • Prozac	Sertraline • Zoloft
Guanfacine • Tenex	Terazosin • Hytrin
Hydroxyzine • Atarax	Trazodone • Oleptro
Lisinopril • Zestril	Venlafaxine • Effexor
Metoprolol succinate • Toprol XL	Verapamil • Calan

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