

Can medications prevent PTSD in trauma victims?

Extinguishing the process that trauma sets in motion may avoid chronic anxiety

Posttraumatic stress disorder (PTSD) is a preventable mental illness—without trauma, the illness does not occur. Primary prevention (such as eliminating war, rape, physical assaults, child abuse, or motor vehicle accidents) would be effective but is an unrealistic goal. Secondary prevention (such as preventing PTSD after individuals have been exposed to trauma) may be attainable.

No medication is FDA-approved to prevent PTSD, but patients recently exposed to trauma might benefit from drugs approved for other indications. Possibilities include noradrenergics such as propranolol, corticosteroids that affect the hypothalamic-pituitary-adrenal (HPA) axis, opioids, benzodiazepines, and antidepressants. Some investigational agents also might block the process that turns a traumatic experience into PTSD.

This article discusses these intriguing ideas and suggests which trauma victims might benefit now from acute pharmacologic PTSD prevention.

Who might be treated?

An estimated 8% to 10% of the U.S. population experiences PTSD at some point in life (*Box 1, page 48*).^{1,2} A person's risk of developing PTSD after a traumatic event depends on the type of trauma. For example, 10% of motor vehicle accident survivors develop PTSD, compared with 60% of rape survivors.¹

Targeting anyone who has experienced trauma for secondary PTSD prevention would expose large groups of people to medications they do not need.

continued



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Trauma-related predictors of PTSD appear to include acute excessive arousal and fear, dissociation, and depression

Box 1

PTSD: From short-term to chronic distress

More than half of all American adults have been exposed to at least one traumatic event at some point in their lives.¹ In most persons, the posttraumatic stress reaction causes short-term distress, with hyperarousal, agitation, intrusive memories, and exaggerated startle. Although these symptoms usually subside relatively quickly, they persist and evolve into posttraumatic stress disorder (PTSD) in a substantial number of trauma victims.

An estimated 8% to 10% of the U.S. population experiences PTSD at some point in life.² Emotional distress, social and occupational disability, and persistent decrements in quality of life make PTSD a major public health problem.

Table 1

Who develops PTSD? Risk and resiliency factors

Risk factors that may increase vulnerability for PTSD

- Diminished cognitive ability
- History of difficult childhood trauma, such as loss of a parent
- Genetic endowment
- History of abuse and neglect
- Trauma severity
- Limited social support
- Continued exposure to stress and trauma

Resiliency factors that may protect against PTSD

- Self-efficacy
- Cognitive ability and flexibility
- Optimism
- Moral compass or strong set of beliefs
- Faith and spirituality

Source: Reference 3

Targeting selected persons who are at the highest risk would be more efficient and cost-effective. In a group of acute trauma-exposed persons, 2 selection criteria could be considered simultaneously:

- Which patients may be most predisposed to PTSD?
- Which patients are showing early symptoms that may predict PTSD?

Risk factors and resiliency. Certain factors have been shown to increase a person's vulnerability for PTSD (*Table 1*).³ Other proposed risk factors include:

- personality types⁴
- psychophysiologic factors such as reactivity, conditionability, and resistance to extinction/habituation.⁵

Strong evidence also indicates that acute trauma-related symptoms—including excessive arousal and fear,⁶ peritraumatic dissociation, and depression—predict the later development of PTSD.

Once identified, individuals predisposed to developing PTSD could be given treatment to increase their resiliency after they have been exposed to trauma. Early evidence suggests that you also could consider giving these patients medications as secondary prevention (*Table 2*).

Targeting noradrenergic activity

Increased noradrenergic activity has been associated with persistent memories and PTSD. Therefore, medications that reduce noradrenergic tone by blocking receptors or reduce norepinephrine release are being explored for PTSD prevention.

Propranolol. Three small studies have examined whether the beta-noradrenergic receptor blocker propranolol can prevent PTSD.

In a randomized, double-blind, placebo-controlled trial,⁷ 41 emergency department patients who had a heart rate of ≥ 80 bpm within 6 hours of a traumatic accident received propranolol, 40 mg qid, or placebo for 10 days. After 1 month, the 11 patients who completed propranolol treatment showed a nonsignificant trend toward lower scores on the Clinician-Administered PTSD Scale (CAPS), compared with 20 patients taking placebo. At 3 months, the propranolol group had less physiologic reactivity (as measured by heart rate and skin conductance) to trauma-related cues than the placebo group.

In a nonrandomized study,⁸ PTSD developed within 2 months in 1 of 11 trauma victims who agreed to take propranolol, 40 mg tid, immediately after the trauma,

Table 2

Medications being studied for PTSD prevention

Mechanism of action	Medication	FDA-approved indications		
		Psychiatric	Nonpsychiatric	
Noradrenergic	Clonidine	No	Yes	
	Guanfacine	No	Yes	
	Prazosin	No	Yes	
	Propranolol	No	Yes	
Hypothalamic-pituitary-adrenal axis	Hydrocortisone	No	Yes	
Opioid	Morphine	No	Yes	
Antidepressant	Dual action	Duloxetine	Yes	Yes
		Venlafaxine	Yes	No
	SSRIs	Citalopram	Yes	No
		Fluoxetine	Yes	No
		Paroxetine	Yes	No
		Sertraline	Yes	No
	TCAs	Amitriptyline	Yes	No
Imipramine		Yes	No	
GABA-benzodiazepine	Alprazolam	Yes	No	
	Temazepam	Yes	No	
Corticotropin-releasing hormone (CRH)	CRH antagonist	Investigational		
Substance P	Substance P antagonist	Investigational		
Neuropeptide Y	Neuropeptide Y agonist	Investigational		

SSRIs: selective serotonin reuptake inhibitors
TCAs: tricyclic antidepressants

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Agents such as propranolol and prazosin that target noradrenergic activity are being explored for possible PTSD prevention

compared with 3 of 8 victims who refused the medication.

In an unpublished randomized, double-blind trial,⁹ 48 patients admitted to a level I trauma center received propranolol, 40 mg tid; gabapentin, 400 mg tid; or placebo for PTSD prevention. Gabapentin was chosen because it has few side effects or metabolic interactions and preliminary evidence of anxiolytic efficacy.

Neither propranolol nor gabapentin showed statistically significant benefit in preventing PTSD compared with placebo. Effect sizes with the 2 treatments were too small to suggest that larger samples would produce a statistically significant result.

Prazosin—an alpha-1 adrenergic receptor antagonist—has been evaluated in 3 controlled studies and found to reduce intrusive nightmares typical of chronic PTSD.

Ten combat veterans with chronic PTSD

showed significantly improved sleep, fewer severe nightmares, and improved global clinical status after receiving prazosin (mean dose 9.5 mg at bedtime) in a 20-week, placebo-controlled, double-blind, crossover study.¹⁰

In a larger randomized, parallel group trial,¹¹ the same authors compared prazosin with placebo in 40 combat veterans (mean age 56) with chronic PTSD. After 8 weeks, veterans taking prazosin (mean 13.3 ± 3 mg) had significantly fewer trauma nightmares, improved sleep (including return of normal dreams), and improved global clinical status vs placebo. Overall CAP scores did not decline significantly, however.

In a third placebo-controlled study,¹² a midmorning dose of prazosin was added to the regimens of 11 civilian trauma patients already taking the drug at bedtime to suppress trauma-related nightmares. Their daytime PTSD symptoms improved,



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Benzodiazepine trials have found these drugs surprisingly unhelpful (and perhaps harmful) in patients with acute trauma

Table 3

4 considerations when choosing a drug for PTSD prevention

Potential benefits	Practicality, ease of use, and safety of the proposed medication
Potential drug-drug or drug-disease interactions	Asthma, diabetes, and trauma are relative contraindications to the use of antiadrenergics and corticosteroids
Psychiatric comorbidities	A patient's history of substance use disorder makes opioid analgesics a concern
Clinical experience	Agents already prescribed safely and broadly in clinical practice are easiest to test and to use

as shown by reduced psychological distress in response to verbal trauma cues.

Prazosin can reduce chronic PTSD manifestations of nightmares and disturbed sleep, but it has not been shown to ameliorate the full PTSD syndrome. Prazosin has not been studied as an early PTSD intervention.

Other antiadrenergics that reduce the release of norepinephrine—including clonidine and guanfacine—have been studied in open trials as treatment for PTSD. The only controlled study¹³ showed no benefit from guanfacine for PTSD prevention.

De-stressing the HPA axis

Hydrocortisone has been proposed to prevent PTSD by reducing HPA axis activation, acting as a countermeasure to elevated corticotropin-releasing factor found in patients with chronic PTSD.

IV hydrocortisone's effect on the development of PTSD was compared with placebo in 20 septic shock survivors after discharge from intensive care.¹⁴ One of 9 patients (11%) in the hydrocortisone group was diagnosed with PTSD at follow-up (mean 31 months), compared with 7 of 11 (64%) in the placebo group.

In a similar study, the same researchers gave patients hydrocortisone before, during, and after cardiac surgery. Follow-up interviews revealed significantly lower PTSD and chronic stress symptom scores in the treatment group vs the placebo group.¹⁵

These studies—although provocative—are limited by the narrow range of trauma related to severe medical illness or extensive medical procedures.

Norepinephrine-blocking opioids

When the noradrenergic system is activated, one physiologic response is the activation of endogenous opioid systems, which may promote recovery by inhibiting the HPA axis. Opioid systems might be involved in PTSD, as suggested by:

- preclinical evidence that opioids modulate memory¹⁶
- studies showing low pain thresholds¹⁷ and abnormal beta-endorphin (an opioid peptide neurotransmitter)¹⁸ and methionine enkephalin (an opioid peptide)¹⁹ levels in PTSD patients.

In theory, opioid administration immediately after trauma may attenuate norepinephrine release, thus thwarting arousal-charged memory consolidation, hyperarousal, and re-experiencing.

One uncontrolled report of pediatric burn victims found a significant association between the morphine dose given for pain during hospitalization and reduced PTSD symptoms 6 months later.²⁰ Decreased pain did not explain the reduction in PTSD, as no significant correlation was seen between pain symptoms and PTSD outcome measures. Similarly, a longitudinal study of substance use among Vietnam War veterans with PTSD found decreased hyperarousal symptoms in heroin users.²¹

Using opioids to prevent PTSD would be feasible and efficient in acute care settings because 80% to 90% of traumatically-injured patients are discharged on opioid analgesics (compared with <10% on beta blockers or corticosteroids).²² However, 20% to 40% of physically injured inpatients are diagnosed with a substance use disorder at some point in life, making the use of opioid analgesics a practical concern.²³

GABA-benzodiazepine paradox

The GABA-benzodiazepine system plays an important role in mediating anxiety, which is consistent with the potent anxiolytic effects of benzodiazepines. Even so, trials of benzodiazepines have found these drugs surprisingly unhelpful—and perhaps harmful—in patients with acute trauma.

Alprazolam did not reduce PTSD symptoms in a small randomized, double-blind study.²⁴ Another trial found that receiving benzodiazepines shortly after trauma exposure was associated with increased PTSD risk in trauma survivors. Nine of 13 patients (69%) who received alprazolam or clonazepam met PTSD diagnostic criteria 6 months after the trauma, compared with 3 of 13 controls (15%).²⁵

Similarly, in a randomized controlled trial, 22 patients were given temazepam for 7 nights, starting approximately 14 days after exposure to a traumatic event. Six weeks later, 55% of those receiving temazepam and 27% of those receiving placebo met criteria for PTSD.²⁶

In summary, benzodiazepines might be helpful when given for a few days after traumatization to control overwhelming anxiety but could be harmful over a longer term.

Other agents for PTSD

Antidepressants. Early trauma-related symptoms of depression predict later development of PTSD.²⁷ Thus, antidepressants have been proposed for early intervention in addition to their well-established role as first-line treatment of PTSD.²⁸

One study supports this idea: a 7-day randomized double-blind trial that compared the tricyclic antidepressant imipramine with chloral hydrate in pediatric burn patients with acute stress disorder (ASD). Imipramine was more effective (83% response) than chloral hydrate (38% response) in reducing ASD symptoms.²⁹

Drugs in development. Three new medications being explored for treating anxiety and depression also might be useful for PTSD prevention. Neuropeptide Y (NPY) agonists,³⁰ substance P antagonists,³¹ and CRH-antagonists³² are thought to hold

Box 2

3-step acute treatment of recently traumatized patients

Manage the post-trauma environment:

- Move the victim to safety.
- Treat pain effectively.
- Avoid stress from interrogations, separation from loved ones, or unstable housing.

Avoid crisis incident stress debriefing

(CISD), which could enhance physiologic hyperarousal and is not recommended as first-line treatment for most trauma victims. CISD was designed for and is best received by emergency personnel.

Consider prescribing antidepressants

for patients thought to be particularly vulnerable to develop posttraumatic stress disorder (PTSD). Risk factors include:

- history of PTSD, depression, or anxiety disorder
- severe trauma (such as from sexual assault or torture)
- physical injury, when antidepressants with analgesic properties might be useful.

promise because of their more proximate roles—compared with monoamine neurotransmitters such as dopamine, norepinephrine and serotonin—in mediating the stress response.

Analyzing the evidence

Insufficient evidence exists to determine which strategies might be most effective to prevent PTSD, what optimal dosing might be, and which traumatized individuals might be best targeted with these approaches.

- Beta-blockers and corticosteroids—the most theoretically compelling strategies—are the most difficult agents to use for PTSD prevention because they have the most medical contraindications. In addition, evidence supporting their ability to prevent PTSD is meager at best.

- Prazosin is intriguing but has contraindications similar to those of beta blockers, no studies of secondary prevention, and no

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Antidepressants may be useful for acute trauma intervention because early depression symptoms predict PTSD development



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Consider starting an antidepressant for victims with severe trauma, pain, past history of PTSD, depression, or anxiety disorder

clear indication that it works for the overall PTSD syndrome.

- Opioids are restricted agents with substantial contraindications.
- Evidence is limited but points most strongly toward earlier use of antidepressants. Early trauma-related symptoms of depression predict later development of PTSD,²⁷ and a number of selective serotonin reuptake inhibitors—such as citalopram, fluoxetine, paroxetine, and sertraline—are FDA-approved or used off-label for treating PTSD.³³

Prescribing recommendations. Consider practicality, ease of use, and safety of the proposed medication when choosing a drug for PTSD prevention (*Table 3, page 50*).²² Based on the evidence, the most reasonable posttrauma approach (*Box 2, page 51*) might be to consider starting an approved antidepressant for individuals thought to be particularly vulnerable to PTSD because of:

- past history of PTSD, depression, or anxiety disorder
- severity of the trauma (such as in cases of sexual assault or torture)
- pain (antidepressants with analgesic properties—such as venlafaxine or duloxetine—might be useful in patients whose trauma is associated with physical injury, although neither is FDA-approved for treating PTSD).

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Related Resources

- Mental health and mass violence: Evidence-based early psychological intervention for victims/survivors of mass violence. A workshop to reach consensus on best practices. Rockland, MD: National Institute of Mental Health; 2002. www.nimh.nih.org.
- Post-traumatic stress disorder: the management of PTSD in adults and children in primary and secondary care (clinical guideline 26). London, UK: National Institute for Clinical Excellence; 2005. www.nice.org.uk.
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Drug Brand Names

Alprazolam • Xanax	Imipramine • Tofranil
Amitriptyline • Elavil	Lamotrigine • Lamictal
Citalopram • Celexa	Paroxetine • Paxil
Clonazepam • Klonopin	Prazosin • Minipress
Clonidine • Catapres	Propranolol • Inderal
Duloxetine • Cymbalta	Sertraline • Zoloft
Fluoxetine • Prozac	Temazepam • Restoril
Gabapentin • Neurontin	Venlafaxine • Effexor
Guanfacine • Tenex	

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Bottom Line

Acute use of medications might help prevent posttraumatic stress disorder (PTSD) in vulnerable trauma patients. Antidepressants may be the best choice as early intervention because of their safety and efficacy in treating chronic PTSD. Avoid using benzodiazepines for more than a few days. Theoretically, other drugs might be useful for patients with nightmares or pain, but evidence is preliminary.

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Antidepressants with analgesic properties might be useful in patients whose trauma is associated with physical injury

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