VA
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Service

A QUICK REFERENCE GUIDE (2019)

Posttraumatic Stress Disorder

A VA Clinician's Guide to Optimal Treatment of Posttraumatic Stress Disorder (PTSD)

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http://www.pbm.va.gov/PBM/academicdetailingservicehome.asp

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Abbreviations

Anti-Ach = anticholinergic

BEP = brief eclectic psychotherapy

BPH = benign prostatic hyperplasia

C = constipation

CAPS = clinician administered ptsd scale

COPD = chronic obstructive pulmonary disorder

CPT = cognitive processing therapy

CrCl = creatinine clearance

CVA = cerebrovascular accident disease

D = diarrhea

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, fifth edition

EMDR = eye movement desensitization and reprocessing

IPT = interpersonal psychotherapy

LUTS = lower urinary tract symptoms

MAOI = monoamine oxidase inhibitor

N = nausea/vomiting

NET = narrative exposure therapy

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PCT = present-centered therapy

PE = prolonged exposure

SARI = serotonin-2 antagonists/reuptake inhibitor

SIT = stress inoculation training

SNRI = selective norepinephrine reuptake Inhibitor

SSRI = selective serotonin reuptake inhibitor

TCA = tricyclic antidepressant

VA/DoD CPG = department of veterans affairs and department of defense clinical practice guideline

Disclaimer: This is a quick reference guide. For complete prescribing information, please see package insert.

PTSD Treatment Decision Aid

A tool that can be used in the shared-decision making process when working with the Veteran to decide on treatment. **https://www.ptsd.va.gov/apps/Decisionaid/**.

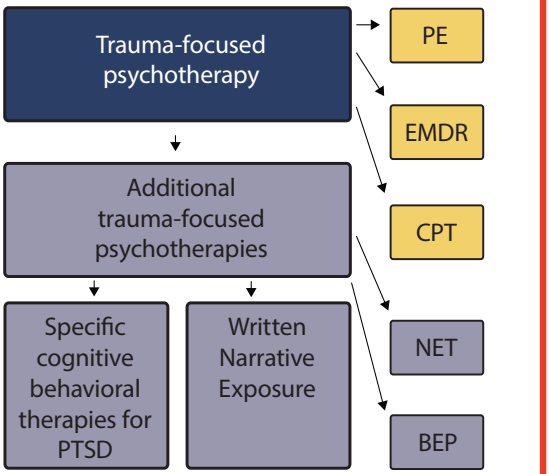
PTSD Checklist (PCL-5) 20-item, self-reported measure of the 20 DSM-5 symptoms of PTSD

PTSD Checklist[1]	
Purpose	**Score Correlation**
Screening and aiding in a diagnostic assessment of individuals for PTSD	• Initial score of 33 or higher may signal a need for additional evaluation
Monitoring symptom change during and after treatment	• Positive Response to Treatment: Reduction of five points from baseline • Clinically Significant Change: A 10-point change from baseline

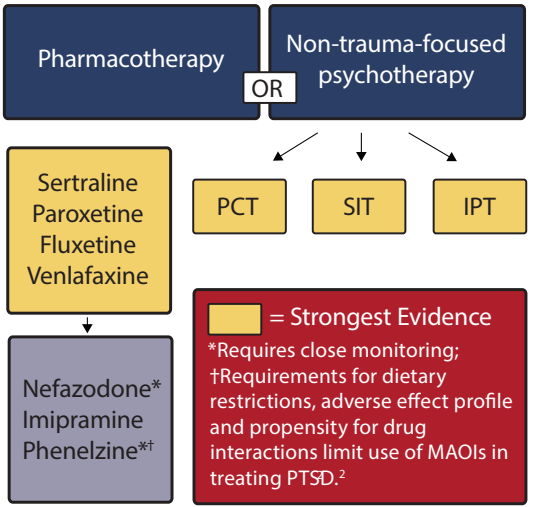
VA/DoD 2017 Clinical Practice Guideline: Treatment of PTSD[1]

Individual, manualized, trauma-focused psychotherapy is recommended above any other pharmacologic and non-pharmacologic treatments.

1st



If individual trauma-focused psychotherapy is not readily available or not preferred, then consider:



First-Line Treatment: Trauma-focused Psychotherapies with the Strongest Evidence[1]

Treatment	Process	How it Works
Prolonged Exposure	Imaginal and in vivo exposure to safe situations that have been avoided because they elicit traumatic reminders	Teaches how to gain control by facing fears
Cognitive Processing Therapy	Focuses on maladaptive beliefs related to the trauma; may have a written component	Helps reframe negative thoughts about the trauma
Eye Movement Desensitization and Reprocessing	Attends to traumatic material in brief sequential doses while simultaneously focusing on an external stimulus	Facilitates accessing the traumatic memory network

First-Line Treatment: Trauma-Focused Psychotherapies with Sufficient Evidence[1]

Treatment	Process
Specific Cognitive Behavioral Therapies for PTSD	Consist of three goals: modifying excessively negative appraisals; correcting autobiographical memory disturbances; and removing problematic behavioral and cognitive strategies
Brief Elective Psychotherapy	Psychodynamic perspective with imaginal and written exposure, cognitive restructuring, relaxation techniques, and a metaphorical ritual closing to leave trauma behind
Narrative Exposure Therapy	Imaginal exposure through a structured oral life-narrative process; helps patient integrate and find meaning of multiple traumatic experiences during lifetime
Written Narrative Exposure	Focus on writing about the trauma memory

Comparison of Antidepressants Studied in PTSD[1–5]

Class	Drug	Safety					Notes
		Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	
SSRI	Sertraline			N,D			May cause diarrhea if dose increased quickly
	Paroxetine			N			Dosed at bedtime; avoid abrupt discontinuation
	Fluoxetine			N			No need to taper off with discontinuation
	Escitalopram*			N			Not a potent inhibitor of most cytochrome enzymes
SNRI	Venlafaxine			N			May increase blood pressure at high doses; avoid abrupt discontinuation
	Duloxetine*			N			Monitor liver function

*The 2017 VA/DoD Clinical Practice Guidelines do not recommend for or against monotherapy or augmentation with these agents.

Less Common Intermediate More Common

continued from page 7 (Comparison of Antidepressants Studied in PTSD[1–5])

Class	Drug	Safety					Notes
		Anti-Ach	Sedation	GI	Withdrawal	Drug Interactions	
TCA	Imipramine			C			Dosed at bedtime; postural hypotension; weight gain; overdose can cause seizures and cardiac arrhythmia; avoid TCAs within three months of an acute myocardial infarction
Other	Nefazodone			C,N			Hepatotoxicity; low incidence of sexual dysfunction
	Phenelzine			C			Low tyramine diet required; dose related orthostasis
	Mirtazapine*						Can increase appetite and cause weight gain

*The 2017 VA/DoD Clinical Practice Guidelines do not recommend for or against monotherapy or augmentation with these agents.

Less Common Intermediate More Common

Recommended Antidepressant For PTSD: Dosing[1–5]

Class	Agent	Initial Daily Dose (mg)	Titration Schedule	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (mg dosage range)	Renal	Hepatic
SSRI	Fluoxetine*	10–20	2 weeks	80	5–40 daily	No change	⬇ Dose 50%
	Paroxetine*	10–20	Weekly	50	10–40 daily	Max 40 mg CrCl <30 ml/min	Max 40 mg/day
	Sertraline*	25–50	Weekly	200	25–150 daily	No change	⬇ Dose 50%
SNRI	Venlafaxine ER*	37.5	Weekly	225	37.5–225 daily	CrCl = 10–70 ml/min, ⬇ dose 50%	⬇ Dose 50%
TCA	Imipramine	25–75		100–300	Avoid	Use with caution	Use with caution
SARI	Nefazodone†	25–100 divided doses	Weekly	150–600	50–600 in two divided doses	No change	Do not use

*Recommended first-line pharmacotherapy for PTSD; †Requires close monitoring.

continued from page 9 (Recommended Antidepressant For PTSD: Dosing[1–5])

Class	Agent	Initial Daily Dose (mg)	Titration Schedule	Maximum Dose/Day (mg)	Guidance in Special Populations		
					Geriatric (mg dosage range)	Renal	Hepatic
MAOI	Phenelzine†	15 three times	Weekly	60–90 given in divided doses (15 mg/day may be effective)	15–60 daily	Use with caution	Use with caution

*Recommended first-line pharmacotherapy for PTSD; †Requires close monitoring.

Additional Medications Studied in PTSD: Dosing[1–5*]

Agent	Initial Dose (mg)	Titration Schedule	Maximum Dose/Day (mg)	Guidance in Special Populations		
				Geriatric (mg dosage range)	Renal	Hepatic
Duloxetine	60 daily or divided	n/a	60	20–40 daily	Avoid: CrCl <30	Avoid
Escitalopram	10 daily	Weekly	40	5–20 daily	Avoid: CrCl <20	Max 10 daily
Mirtazapine	15 at bedtime	Weekly	45	⬇ dose may be required 7.5–45	CrCl <40 Use caution	Titrate slowly

*The 2017 VA/DoD Clinical Practice Guidelines do not recommend for or against monotherapy or augmentation with these agents.

Switching Antidepressants[3]

Initial Medication	Medication Class Switching To:						Equivalent Doses (mg)
	SSRIs	SNRIs	Mirtazapine	Bupropion	TCAs	MAOIs‡	
Citalopram							20
Escitalopram							10
Fluoxetine*†							20
Fluvoxamine*							100
Paroxetine*							20
Sertraline							50–75
Duloxetine*							30

Direct switch probably safe

Cross-taper recommended

Washout period advisable

Cross-taper generally takes one to two weeks; *May increase serum concentration of TCAs, SNRIs, and bupropion; therefore, start at low dose to avoid toxicity; †When starting TCA and stopping fluoxetine, wait four to seven days then start TCA; ‡MAOIs – Wait two weeks after discontinuation of an MAOI before starting another antidepressant; wait two weeks after discontinuing an antidepressant before starting an MAOI, except fluoxetine which needs a washout period of at least five weeks.

continued from page 12 (Switching Antidepressants[3])

Initial Medication	Medication Class Switching To:						Equivalent Doses (mg)
	SSRIs	SNRIs	Mirtazapine	Bupropion	TCAs	MAOIs‡	
Venlafaxine ↓							75
Mirtazapine							15
Bupropion SA*							150
TCAs							
MAOIs‡							

Direct switch probably safe

Cross-taper recommended

Washout period advisable

Cross-taper generally takes one to two weeks; *May increase serum concentration of TCAs, SNRIs, and bupropion; therefore, start at low dose to avoid toxicity; †When starting TCA and stopping fluoxetine, wait four to seven days then start TCA; ‡MAOIs – Wait two weeks after discontinuation of an MAOI before starting another antidepressant; wait two weeks after discontinuing an antidepressant before starting an MAOI, except fluoxetine which needs a washout period of at least five weeks.

Antidepressants and Sexual Dysfunction

- PTSD increases the risk of sexual dysfunction by three-fold.[6]
- Medication-induced sexual dysfunction can lead to decreased medication adherence.

Risk Factors for Sexual Dysfunction:[7–12]	
Health-related	**Medication-related**
• Age (old for men, young for women) • Cardiovascular disease • Chronic pain • Depression and other psychiatric diagnoses • Diabetes • Hormone disorders • Substance use disorders (e.g., tobacco, marijuana, alcohol)	• Alpha blockers • Antidepressants • Antiepileptics • Antihypertensive • Antipsychotics • Mood stabilizers • Opioids • 5-alpha reductase inhibitors

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Percentage Incidence of Sexual Dysfunction*				
	Decreased Libido	**Impotence**	**Abnormal Ejaculation**	**Anorgasmia**
Citalopram	4	3	6	—
Fluoxetine	1–11	1–7	2–7	—
Fluvoxamine	2	2	8	2
Paroxetine	3–12	2–8	2–28	10
Sertraline	1–11	>1	7–19	—
Venlafaxine	1–6	2–6	2–13	2–3
Duloxetine	3	4–5	2–3	2
Bupropion	3	3	<1	—
Nefazodone	1	1	<1	<1
Mirtazapine	1	<1	<1	—

*Data from manufacturer prescribing information.

Sexual Dysfunction Treatment Strategies[3,13]

- Wait — Within six months, ~10% of patients report remission of sexual dysfunction and up to 15–20% report symptom improvement.
- Decrease dose — Higher doses have been associated with higher rates of dysfunction; however, decreasing the dose may lead to reduced antidepressant effect.
- Switch antidepressants — Bupropion, mirtazapine and nefazodone are associated with a lower incidence of sexual dysfunction.
- Adjunctive medications:
  - Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil) used to treat the physiologic aspects of sexual function; will have no effect in the absence of sexual stimulation; improve antidepressant-induced erectile dysfunction.
  - Bupropion may be effective as adjunctive therapy, especially in women at higher doses.

Antidepressants and Hyponatremia

- All antidepressants have been associated with cases of hyponatremia.[3,14,15]
- Onset can occur from three days to the first few weeks after starting medication.[3,16]
- Not thought to be dose related[3]
- Monitor for hyponatremia especially in higher risk patients:[3]
  - Serum electrolyte panel and symptoms (dizziness, nausea, lethargy, confusion, cramps, seizures)

Risk Factors for Hyponatremia[3,15,17]			
Demographic	**Medical Comorbidities**		**Comedications**
Old age*	Glomerular filtration rate <50 mL/min	Low body weight	Trimethoprim
Female	History of hyponatremia	Diabetes	Carbamazepine
Living in warm weather climate	Low baseline sodium	COPD	Antipsychotics
	Hypothyroidism	Head injury or CVA	Thiazide diuretics

*Hyponatremia is common in elderly patients, making monitoring essential.

continued from page 17 (Antidepressants and Hyponatremia)

Risk Factors for Hyponatremia[3,15,17]			
Demographic	**Medical Comorbidities**		**Comedications**
	Hypertension and/or heart failure	Recent history of pneumonia	NSAIDs and Tramadol
	Various cancers		Chemotherapy
			Omeprazole

Restarting an Antidepressant after Hyponatremia has Resolved

- Select an agent from a different class – There have been fewer case reports of recurrence of hyponatremia when an agent with a different MOA is selected (e.g., mirtazapine, bupropion, nortriptyline).[3,15,19]
- Consider withdrawing other medications associated with hyponatremia (e.g., thiazide diuretics, carbamazepine, NSAIDs, tramadol, proton pump inhibitors).[3,17]
- Start low, go slow, and monitor serum sodium closely.[3]
- Consider long-term maintenance strategies if drug therapy with offending agent is necessary (e.g., fluid restriction, careful use of oral demeclocycline).[3,17]

*Hyponatremia is common in elderly patients, making monitoring essential.

After discontinuation of the offending antidepressant, hyponatremia typically resolves within two weeks.[18]

Additional Pharmacotherapy Options for Veterans Refractory to Standard Treatments

If recommended treatments for PTSD have not been beneficial, consider the utilization of the following alternative or adjunct options for patients with PTSD refractory to standard treatments.

continued from page 19 (Additional Pharmacotherapy Options for Veterans Refractory to Standard Treatments)

Additional Antidepressants that have Demonstrated Results as Monotherapy or Adjunctive Therapy in Small Studies*

Duloxetine

A small, observational study in Veterans with treatment-refractory, combat-related PTSD suggests treatment with monotherapy duloxetine 30–120 mg daily improves PTSD symptoms compared to baseline (PCL-C score: 64.1 vs. 48.1, $p<0.001$).[20]

Mirtazapine

- A small randomized, controlled trial of mirtazapine as adjunctive therapy to sertraline demonstrated significant improvement in depressive symptoms but no difference in PTSD severity.[23]
- However, a randomized, open-label trial of 100 Veterans comparing sertraline and mirtazapine showed a significantly greater response rate measured by CAP-2 in the mirtazapine group compared to sertraline at six weeks (88% vs. 69%, $p=0.039$).[24]

Escitalopram

Open label, non-combat-related PTSD trial suggests treatment with monotheapy escitalopram (studied up to 40 mg) may be effective.[21]

Fluvoxamine

Open-label, combat-related PTSD trial found fluvoxamine monotherapy effective for the CAPS intrusion and avoidance/numbing subscales. However, high attrition rates limit conclusions.[22]

Topiramate for PTSD[25–27]

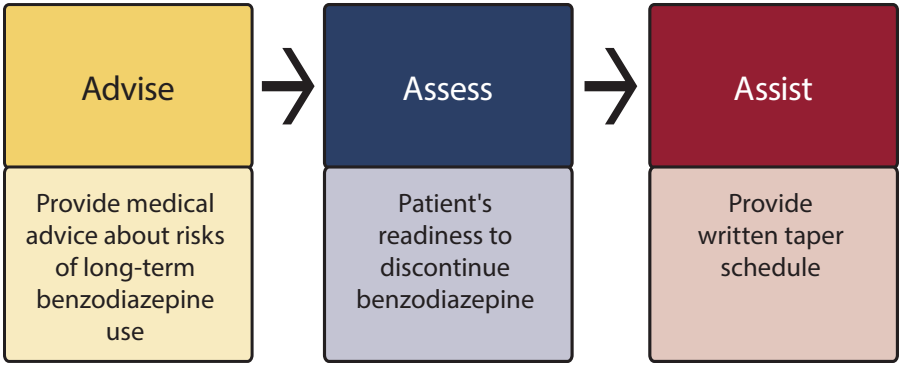
- Possible alternative or adjunct option for patients refractory to standard PTSD treatments
- May be beneficial for the treatment of PTSD and comorbid AUD.

*The 2017 VA/DoD CPG does not recommend for or against monotherapy or augmentation with these agents.

Discussing Benzodiazepine Withdrawal[3,18,28–31]

1. Assess patient's willingness to discontinue or reduce the dose of benzodiazepine.

- Explore and acknowledge perceived benefits and harms and allow Veteran to express his/her concerns.
- Explain the risks of continued use (disinhibition, ineffectiveness, loss of mental acuity) and the benefits of stopping.
- If previous attempts have been made without success, explain that it is worth trying again.



continued from page 21 (Discussing Benzodiazepine Withdrawal[3,18,28–31])

2. Agree on Timing and Discuss the Symptoms Likely to Occur with Withdrawal[3]

- Patients may experience withdrawal after more than four weeks of benzodiazepine use.
- Timeline of withdrawal: Occurs within one to seven days and can last four to 14 days (lasting longer usually with long half-life agents).

Benzodiazepine Withdrawal Symptoms[3]	
Psychological	**Physical**
• Anxiety/irritability • Insomnia/nightmares • Depersonalization • Decreased memory and concentration • Delusions and hallucinations • Depression	• Stiffness • Weakness • Gastrointestinal disturbance • Flu-like symptoms • Paresthesia • Visual disturbances • Seizures

3. Provide written instructions for a structured medication taper. Be prepared to slow the taper if the patient reports significant withdrawal symptoms.

continued from page 21 (Discussing Benzodiazepine Withdrawal[3,18,28–31])

Benzodiazepine Equivalent Doses[3,18,28,29]						
	Chlordiazepoxide	**Diazepam**	**Clonazepam**	**Lorazepam**	**Alprazolam**	**Temazepam**
Approximate Dosage Equivalents (mg)	25	10	1	2	1	15
Elimination Half-life* (hour)	>100	>100	20–50	10–20	12–15	10–20

Benzodiazepine example dosage reduction and/or discontinuation:†

- Switching to a longer acting benzodiazepine may be considered if clinically appropriate.**
- Reduce dose by 50% the first four weeks and maintain on that dose for one to two months, then reduce dose by 25% every two weeks.†

*Includes active metabolites. †These are suggestions only and a slower taper may be used (e.g. 10–25% every four weeks). **High dose alprazolam may not have complete cross tolerance; a gradual switch to clonazepam or diazepam before taper may be appropriate. In geriatric patients, consider tapering the short acting agent until withdrawal symptoms are seen, then switch to a longer acting agent. Other treatment modalities (e.g., antidepressants for anxiety) should be considered if clinically appropriate.

continued from page 21 (Discussing Benzodiazepine Withdrawal[3,18,28–31])

Example Taper: Lorazepam 4 mg twice daily		
Milestone Suggestions	**Month**	**Common Side Effects**
Week 2: Decrease dose by 25% Week 4: Decrease dose by 25%	1	Convert to 40 mg diazepam daily Week 1: 35 mg/day Week 2: 30 mg/day (25% of initial dose) Week 3: 25 mg/day Week 4: 20 mg/day (50% of initial dose)
Weeks 5–8: Hold dose one to two months	2	Weeks 5–8: Continue at 20 mg/day for one month
Week 9 – Discontinuation: Decrease dose by 25% every two weeks Additional information and taper calculator: **https://spsites.cdw.va.gov/sites/PBM_AD/_layouts/15/ReportServer/RSViewerPage.aspx?rv:RelativeReportUrl=/sites/PBM_AD/AnalyticsReports/Benzodiazepine/BZDTaperCalculator_Shellv2.rdl&rv:Toolbar=Navigation**	3	Weeks 9–10: 15 mg/day Weeks 11–12: 12.5 mg/day
	4	Weeks 13–14: 10 mg/day Weeks 15–16: 7.5 mg/day
	5	Weeks 17–18: 5 mg/day Weeks 19–20: 2.5 mg/day
	6	Weeks 21–22: 2 mg/day Weeks 23–24: 1 mg/day then discontinue

Prazosin Tips

Prazosin Dosing and Common Side Effects[32–38]		
Suggested Prazosin Titration Schedule to Reduce Orthostatic Side Effects		Common Side Effects
Schedule	Dose (mg/day)	
Days 1–3	1	• First dose hypotension • Headache • Nasal congestion • Palpitations • Edema
Days 4–7*	2	
Week 2	4	
Week 3	6	
Week 4	10	

*Increase dose if nightmares are still present and adverse effects are absent or mild. Prazosin dosages studied range from 1–20 mg with an average effective dose of 9–13 mg nightly.

Monitor and document objective improvement in sleep with the PTSD check list or sleep quality assessment. If no improvement seen, discontinue prazosin.

Note: The 2017 VA DoD PTSD Clinical Practice Guidelines found insufficient evidence to recommend for or against prazosin for the treatment of PTSD associated nightmares.

Prazosin Precautions[32–38]

If prazosin therapy is interrupted for three or more days, then re-initiate prazosin at lowest dose and re-titrate according to schedule.

Increased risk of orthostatic hypotension:

- Younger women
- Elderly
- Beta-blockers
  - Increased risk or first dose hypotension
  - Doses may need to be lowered
- Phosphodiesterase inhibitors
- Concomitant antihypertensive
  - Doses may need to be lowered to increase tolerability of prazosin

Managing PTSD Nightmares in Veterans with LUTS Associated with BPH[39–43]

Patients with PTSD-related Nightmares and LUTS Managed with Alpha-1 Adrenergic Antagonist	Patients with PTSD-related Nightmares and LUTS Symptoms that are Not Managed with Prazosin Monotherapy
• Consider conversion to prazosin monotherapy. • Direct conversion should cover BPH symptoms. • Low daytime dose (1–2 mg) may be needed to treat residual daytime LUTS. • Higher doses may be needed for nightmare management.	• Continue dose of prazosin that manages PTSD-related nightmares. • Consider adding a uroselective alpha-1a adrenergic antagonist (e.g., tamsulosin). • Patients unable to tolerate the combination of prazosin and a uroselective alpha-1a adrenergic antagonist should be considered for alternative BPH treatment (e.g., finasteride) or referral to urology.

These recommendations were adapted from the VA Pharmacy Benefits Management Services recommendations developed based on medical evidence, clinician input, and expert opinion.[44]

continued from page 27 (Managing PTSD Nightmares in Veterans with LUTS Associated with BPH[39–43])

Estimated Alpha-1 Adrenergic Antagonist Equivalent Dosing (mg)		
Terazosin	**Doxazosin**	**Prazosin Equivalents**
1	1	1
2	2	2
5	4	5
>5	>4	5*

*Covert to 5 mg prazosin then titrate to an effective dose for PTSD-related nightmare control.

Other Medications Studied in PTSD-Related Nightmares

Treatment	Doxazosin[5,45–48]	Clonidine[49*]	Trazodone[5,50,51]	Topiramate[49†]
Studied Dosing Ranges	2–8 mg	0.2 mg (twice daily)	25–200 mg	25–400 mg (Average 100–150 mg)
Common Side Effects	Hypotension Dizziness Vertigo Headache Fatigue Somnolence Edema	Dry mouth Drowsiness Dizziness Constipation Sedation	Dizziness Somnolence/fatigue Headache Nausea/vomiting Xerostomia Constipation or Diarrhea Blurred vision Nervousness Dream disorder	Paresthesia Anorexia/weight loss Nausea/diarrhea Hypoesthesia Nervousness Speech disorders Memory difficulty Drowsiness/fatigue Dizziness

Note: The medications listed above have limited or mixed evidence to support their use for PTSD-related nightmares. If utilized, monitor and document objective improvement in sleep with the PTSD check list or sleep quality assessment; if no improvement, discontinue use.

*Should be reduced gradually over two to four days to avoid withdrawal symptomatology. †Medication utility limited by side effects.

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