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Treatment in PTSD:

Guidelines, Current Treatment Landscape, and Unmet Needs

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Module Overview:

Section 1:
Treatment guidelines

- US treatment guidelines

Section 2:
Current treatment landscape

- Trauma-focused psychotherapy
- FDA-approved pharmacotherapy
- Off-label medications and polypharmacy

Section 3:
Unmet needs in PTSD: Limitations and key considerations

- Psychotherapy
- Approved pharmacotherapy
- Combined treatment approach
- Other existing treatments
- Clinical barriers

Section 4:
Summary

PTSD treatment guidelines in the US

- American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder[1]

- US Department of Veterans Affairs and Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder[2]

- American Psychological Association (APoA) Clinical Practice Guidelines for the Treatment of PTSD[3]

Current evidence-based guidelines for the diagnosis and treatment of PTSD are valuable resources and can be used to help develop appropriate individual treatment plans for patients[1-4]

APA, American Psychiatric Association; APoA, American Psychological Association; PTSD, post-traumatic stress disorder; VA/DOD, Department of Veterans Affairs and Department of Defense; US, United States.

1. American Psychiatric Association. 2004. psychiatryonline.org/pb/assets/raw/sitewide/practiceguidelines/guidelines/acutestressdisorderptsd.pdf.
2. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf
3. American Psychological Association. Am Psychol. 2019;74(5):596-607.
4. Martin A et al 2021. J Clin Med.10(18):4175.

Guideline recommendations and implementation in clinical practice

- One systematic review of 14 international treatment guidelines for PTSD reported that both psychological and pharmacologic therapies are recommended as first-line interventions[1-3]
  - CBT as first-line psychological treatment
  - SSRIs as first-line pharmacologic treatment

- In practice, most patients with PTSD are treated with a combination of both psychotherapy and pharmacotherapy[1]
- ~**60%** of civilians and **58%** veterans received pharmacological treatment in their respective healthcare settings[4,5]
- In a meta-analysis of PTSD treatment in veterans by therapy type[6,*]:
  - **44%** received combination therapy
  - **32%** received pharmacotherapy alone
  - **24%** received psychotherapy alone

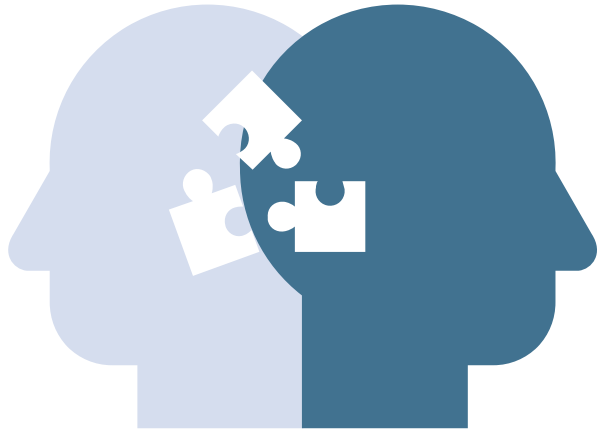
*n = 6313; 55 studies.

CBT, cognitive behavioral therapy; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

1. Martin A et al. J Clin Med.2021; 10(18):4175.
2. World Health Organisation. 2013. https://apps.who.int/iris/bitstream/handle/10665/85119/9789241505406_eng.pdf.
3. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
4. Harpaz-Rotem I et al. Psychiatr Serv. 2018;59:1184-1190.
5. Holder N et al. J Clin Psychiatry. 2021;82(3):20m13522.
6. Lee DJ et al. Depress Anxiety. 2016;33(9):792-806.

Clinical benefits of psychotherapy as the initial treatment for PTSD

- International and US guidelines strongly recommend trauma-focused cognitive behavioral therapy (TF-CBT) for first-line treatment[1,2]
  - TF-CBT had the most significant effect in individuals with PTSD compared to other psychotherapies and pharmacotherapy[3,4]
- Psychotherapy has demonstrated clinical benefits for PTSD, including reduced symptom severity and improved remission rates[1,3,5]
- Several considerations must be made in order to utilize psychotherapy effectively, including[6]:
  - Treatment cost
  - Resource availability
  - Patient preference
  - Comorbidities

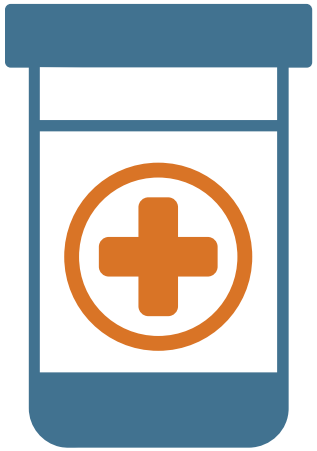


PTSD, post-traumatic stress disorder; TF-CBT, trauma-focused cognitive behavioral therapy.

1. Yehuda R et al. Nat Rev Dis Primers. 2015;1:15057.
2. International Society for Traumatic Stress Studies. 2019. www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL-March-19-2019.pdf.aspx.
3. Lee DJ et al. Depress Anxiety. 2016; 33(9):792-806
4. American Psychological Association. Am Psychol. 2019;74(5):596-607.
5. Mavranezouli I et al. Psychol Med. 2020; 50(4):542-555.
6. Martin A et al. J Clin Med. 2021;10(18):4175.

Pharmacotherapy in PTSD

- Pharmacotherapy is a key component of PTSD management, and early and effective pharmacotherapy can improve[1-3]:
  - Core symptoms
  - Associated disability
  - Long-term outcomes
- Guidelines recommend SSRIs as first-line pharmacologic treatment when indicated[4-9]
  - Only SSRI 1 and SSRI 2 are FDA-approved[4,10-12]
  - SNRI is also recommended[4,11]
  - ~52% of patients treated with pharmacotherapy currently receive SSRIs or SNRIs[13]
- Long-term pharmacotherapy (>12 weeks) may be necessary to maintain functional improvements achieved during acute treatment period[3]



FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

1. Stein DJ et al. Cochrane Database Syst Rev. 2006;1:CD002795.
2. Williams T et al. Cochrane Database Syst Rev. 2022;3(3):CD002795.
3. Davis LL et al. CNS Drugs. 2006;20(6):465-476.
4. American Psychological Association. Am Psychol. 2019;74(5):596-607.
5. Martin A et al. J Clin Med. 2021;10(18):4175.
6. American Psychiatric Association. 2013. American Psychiatric Publishing.
7. Baldwin DS, Kosky N. Adv Psychiatr Treat. 2007;13:414-422.
8. Baldwin DS et al. J Psychopharmacol. 2014;28:403-439.
9. International Society for Traumatic Stress Studies. 2019. www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL-March-19-2019.pdf.aspx.
10. Yehuda R et al. Nat Rev Dis Primers. 2015;1:15057.
11. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
12. Brady KT et al. J Clin Psychiatry. 2000;61(suppl 7):22-32.
13. Cook, J. M et al. J Clin Psychol Med Settings. 2021;28(2):221–228.

Summary of US guidelines for pharmacotherapy[1]

Drug/class	FDA approved	VA/DoD Guidelines (2023)[2]	APoA Guidelines (2019)[4]	APA Guidelines (2004)[3]
SSRI 1	Yes	+	+	+
SSRI 2	Yes	+	+	+
SSRI 3	No	+	+	+
Other SSRIs[a]	No	Insufficient evidence	NA	NA
SNRI	No	+	+	Insufficient evidence
Atypical antipsychotic 1	No	-	NA	may be helpful[d]
Atypical antipsychotic 2	No	-	Insufficient evidence	may be helpful[d]
Tricyclic antidepressants[a]	No	Insufficient evidence + weak[c]	NA	may be beneficial
Adrenergic antagonist[b]	No	- weak	NA	NA
Benzodiazepines[a]	No	- -	NA	-

+, recommendation for; -, recommendation against; - -, strong recommendation against; NA, not addressed.
[a] Class of medications; [b] First-line treatment for nightmares in PTSD according to AASM and modified from Merians AN et al, 2023; [c] Weak recommendation for tricyclic antidepressants only (adapted from Merians AN et al, 2023); [d]Class III recommendation.

AASM, American Academy of Sleep Medicine; APA, American Psychiatrist Association; APoA, American Psychological Association; FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; US, United States; VA/DoD, US Department of Veterans Affairs and Department of Defense.

1. Merians AN et al. *Med Clin N Am*. 2023;107(1):85-99.
2. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
3. American Psychiatric Association. 2004. psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf.
4. American Psychological Association. *Am Psychol*. 2019;74(5):596-607.

Off-label pharmacologic treatments

- Off-label and potentially non-evidence–based treatments are utilized in attempts to address the four core PTSD symptom clusters[1-3]
- Off-label treatments continue to be prescribed despite not being recommended by guidelines[4]
- A notable proportion of veterans are being treated with off-label medications[2]
  - **~20%** receive FDA-approved SSRIs
  - **~17%** receive SSRIs that are not FDA-approved for PTSD
  - **~14%** receive SNRIs
  - **~6%-9%** receive anxiolytics or sedative-hypnotics, atypical antipsychotics, or benzodiazepines

SNRIs

- Recommended by US guidelines[6,7]
- Variable efficacy[1,9]

Atypical antipsychotics

- <16% used in patients as first-, second-, or third-line therapy[4]
- Recommended for augmentation in cases of incomplete response or residual symptoms[12]

Anxiolytics and benzodiazepines

- Second highest use in newly diagnosed patients (up to 33%)[4]
- Prescribed to treat sleep disturbance and hyperarousal[10,11]
- Strongly recommended by guidelines against use of benzodiazepines[5,10,11]

Adrenergic antagonists

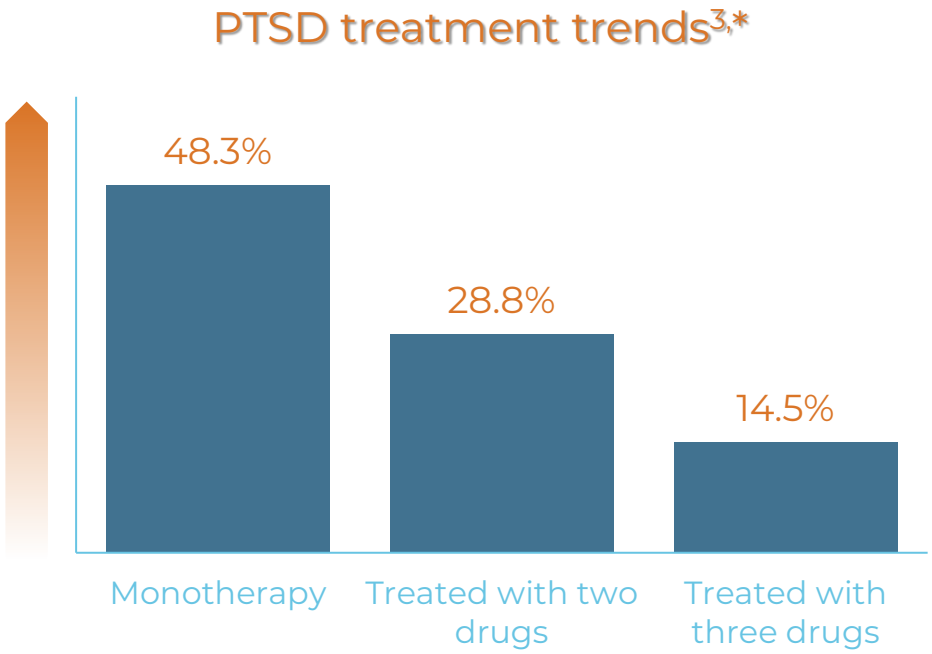
- Used for PTSD-related nightmares[13]
- Not efficacious in treating recurrent distressing dreams or improving sleep quality[13]

FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; US, United States.

1. Decision Resources Group. 2018. (Data on file)
2. Holder N et al. J Clin Psychiatry. 2021; 82(3):20m13522.
3. Schrader C et al. Mo Med. 2021;118(6):546–551.
4. Cook, J. M et al. J Clin Psychol Med Settings. 2021;28(2):221–228.
5. Yehuda, R et al. Nat Rev Dis Primers. 2012;1:15057.
6. U.S. Department of Veterans Affairs. 2023. Accessed July 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
7. American Psychological Association. www.apa.org/ptsd-guideline/ptsd.pdf.
8. Davidson JR et al. Psychiatr Ann. 2005; 35(11):887–900.
9. Alexander W. P&T. 2012;37(1):32–38.
10. Guina J et al. J Psychiatr Pract. 2015;21(4):281–303.
11. Ravindran LN et al. Brain Res. 2009; 1293:24–39.
12. Bajor LA et al. Psychiatry Res. 2022; 317:114840.
13. Raskind MA et al. N Engl J Med. 2018; 378(6):507–517.

Polypharmacy in PTSD

- The limited efficacy and available options of FDA-approved treatments for PTSD have necessitated polypharmacy for a vast majority of patients[1]
- Following diagnosis, individuals are prescribed an average of 1.6 medications for PTSD alone[2]
- Common combinations include SSRIs, anxiolytics, and benzodiazepines to address depression and sleep disturbances
  - Treatment guidelines recommend against augmenting therapies with benzodiazepines[3]
  - Benzodiazepines may worsen patient outcomes, including overall severity and psychotherapy outcomes[4]



*Data generated from analyses of prescribing trends in recently treated patients with PTSD.[3]

FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

1. Krystal JH. et al. Biol Psychiatry. 2017; 82(7), e51–e59.
2. Holder N et al. J Clin Psychiatry. 2021; 82(3):20m135223.
3. Decision Resources Group. 2018. (Data on file).
4. Guina J et al. J Psychiatr Pract. 2015;21(4):281–303.

Psychotherapy consideration in clinical practice

- There is a discrepancy between the efficacy of psychotherapy interventions in clinical trials versus clinical practice[1]
  - ~40% of patients with PTSD meet IAPT criteria for recovery following a course of psychotherapy, suggesting a large proportion of patients require further intervention[1,2]

- The efficacy may be limited in clinical practice due to a combination of[1]:
  - High demand
  - Limited resources
  - Visit frequency needs
  - HCP expertise
  - Access in rural areas[3]

- Patient barriers include [2,4]:
  - A perceived lack of usefulness
  - Significant comorbidities
  - Preference for drug treatment

Despite guideline consensus regarding psychotherapy as first-line treatment, identified patient and clinical factors should be considered[1-4]

HCP, healthcare provider; IAPT, Improving Access to Psychological Therapies.

1. Murray H et al. Cogn Behav Ther. 2022;15(e33):1-15.
2. National Institute for Health and Care Excellence (2018). Accessed July 2023. https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-report-on-the-use-of-iaptservices
3. Morland LA et al. Curr Treat Options Psychiatry. 2020; 7:221–241.
4. Martin A et al. J Clin Med. 2021; 10(18):4175.

Approved PTSD treatments: clinical considerations

- <40% likelihood of patients responding adequately to treatment with SSRI 1 or SSRI 2 compared to placebo[1]
- Monotherapy with SSRIs has demonstrated efficacy in short-term (10-12 weeks) randomized controlled trials; however, effect sizes were reported to be small[2]

SSRI 1[1,3]

- Demonstrates improvements in a subset of PTSD symptoms
  - Efficacy driven by improvements in negative mood and cognition[4]
- Improvements not observed on depressive or anxious symptoms

SSRI 2[5]

- Improves re-experiencing, avoidance, and hyperarousal symptoms
- Does not address all symptom clusters, such as depressive or anxious symptoms

No new drugs have received approval for PTSD treatment in over two decades[6,7]

FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder.

1. Williams T et al. Cochrane Database Syst Rev. 2022;3:CD002795.
2. Hoskins MD et al. Eur J Psychotraumatol. 2021;12(1):1802920.
3. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
4. U.S. Food and Drug Administration. 1998. www.accessdata.fda.gov/drugsatfda_docs/nda/99/19-839S026_Zoloft_Clinr_P1.pdf.
5. Popiel A et al. J Behav Ther Exp Psychiatry. 2015;48:17-26.
6. Pfizer. (sertraline hydrochloride). 2016. www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839S74S86S87_20990S35S44S45lbl.pdf.
7. GlaxoSmithKline. 2012. www.accessdata.fda.gov/drugsatfda_docs/label/2012/020031s067,020710s031.pdf.

Combined psychotherapy and pharmacotherapy data are limited

Combined treatment approaches are used in clinical practice for some patients with PTSD, but effectiveness data are limited[1]

- Greater improvements of PTSD symptoms and a significantly greater impact than pharmacotherapy alone at long-term follow-up, as reported in a network meta-analysis[1]

- However, in an earlier analysis, combined therapy did not demonstrate any significant superiority to either treatment alone[2]

PTSD, post-traumatic stress disorder.

1. Merz J et al. JAMA Psychiatry. 2019;76(9):904-913.
2. Hetrick SE et al. Cochrane Database Syst Rev. 2010;(7):CD007316.

Existing PTSD treatments: additional considerations

SSRIs and SNRIs

- Common side effects include nausea, headache, diarrhea, anxiety, and sexual dysfunction, which may negatively impact patients' daily functioning and health-related quality of life[1,2]
  - Reasons for SSRI discontinuation include AEs, relapse, and clinical deterioration[3]
  - Non-adherence to treatment is associated with a greater risk of relapse and exacerbation of symptoms[3,4]
  - Greater risk of treatment discontinuation with SSRI due to TEAEs[1]

Benzodiazepines[5,6]

- Ineffective for treatment and prevention of PTSD
- Risks outweigh potential short-term benefits:
  - Worsen overall severity
  - Increase risk of developing PTSD
  - Worsen aggression/depression/ substance use

AE, adverse event; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse event.

1. Williams T et al. Cochrane Database Syst Rev. 2022;3:CD002795.
2. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
3. Davis, LL et al. CNS Drugs. 2006;20(6):465-476.
4. Batelaan NM et al. BMJ. 2017;358:j3927.
5. Yehuda R et al. Nat Rev Dis Primers. 2015;1:15057
6. Guina J et al. J Psychiatr Pract. 2015;21(4):281-303.

Clinical barriers in PTSD management

In a US-based survey, 41.8% of patients with PTSD reported an unmet need for treatment[1]:

- 16.4% of these did not want to see a professional
  - 25% of those who did not want to see a professional, did not believe the treatment will help

Fear of re-experiencing traumatic events or certain trauma-related memories is a significant trauma-related barrier to mental health service use[2,3]

- Note, re-experiencing is one of the techniques used in psychotherapy

<50% of people with PTSD are correctly diagnosed in primary care[4]

- Patients continue to experience symptoms due to the delay in receiving appropriate treatment

Lack of belief in effective PTSD treatments and concerns about revisiting traumatic memories prevent patients from seeking treatment

PTSD, post-traumatic stress disorder; US, United States.

1. Nobles CJ et al. *Gen Hosp Psychiatry*. 2016;43:38-45.
2. Kantor V et al. *Clin Psychol Rev*. 2017;52:52-68.
3. Kazlauskas E. *Glob Health Action*. 2017;10(1):1322399.
4. Greene T et al. *J Clin Psychol Med Settings*. 2016;23(2):160-180.

Summary

Most guidelines recommend both psychological and pharmacologic therapies as first-line interventions in PTSD[1-3]

The efficacy of psychotherapy may be limited in clinical practice due to the high demand for services combined with limited resources; a large proportion of patients require further intervention after psychotherapy[1-3]

In practice, a combination of both psychotherapy and pharmacotherapy are used, but more data on effectiveness are needed[1,4,5]

No new drugs have been approved for PTSD treatment in over two decades; only SSRI 1 and SSRI 2 are currently approved, which target a subset of PTSD symptoms[3,6,7]

Polypharmacy, off-label and non–evidence-based treatments are often utilized in an attempt to address individual PTSD symptoms[8,9]

Lack of belief in effective treatment, fear of re-experiencing trauma, perceived lack of efficacy for approved medications, and inadequate treatments that may affect adherence and daily function represent significant unmet needs[10,11]

PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

1. Martin A et al. *J Clin Med*. 2021;10(18):4175.
2. World Health Organisation. 2013. apps.who.int/iris/bitstream/handle/10665/85119/9789241505406_eng.pdf.
3. U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
4. Murray H et al. *The Cognitive Behaviour Therapist*. 2021;15(e33):1-15.
5. National Institute for Health and Care Excellence (2018). https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-report-on-the-use-of-iaptservices (Accessed July 2023).
6. Yehuda R et al. *Nat Rev Dis Primers*. 2015;1:15057.
7. American Psychological Association. *Am Psychol*. 2019;74(5):596-607.
8. Krystal JH et al. *Biol Psychiatry*. 2017;82(7):e51-e59.
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10. Kantor V et al. Clin Psychol Rev. 2017; 52:52–68.
11. Davis, LL et al. CNS Drugs. 2006; 20(6): 465–476.

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