



PTSD: Clinical Considerations and Unmet Needs

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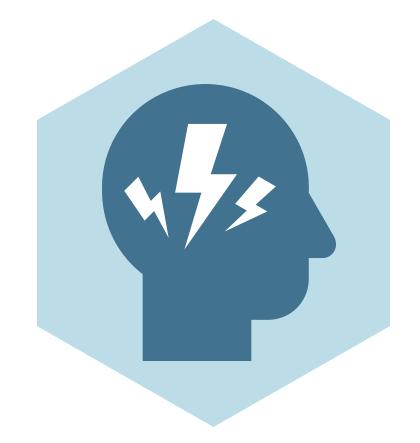


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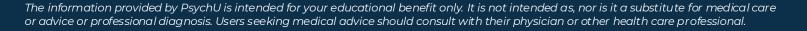
What is PTSD?

- Post-traumatic stress disorder (PTSD) is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event, series of events, or set of circumstances¹⁻³
 - An individual may experience PTSD as emotionally or physically harmful or lifethreatening, and their mental, physical, social, and/or spiritual well-being may be affected¹⁻³



PTSD, post-traumatic stress disorder.

- 1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. (2013) Fifth Edition. DSM-5TM. American Psychiatric Publishing.
- 2. Yehuda R et al.Nat Rev Dis Primers, 2015; 1, 15057.
- 3. Suomi Aet al. Cochrane Database of Systematic Reviews, 2019;12(12), CD011257.



Prevalence and incidence

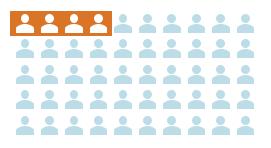
PTSD is a highly prevalent disorder worldwide and, in the US



- The global lifetime prevalence of PTSD is 4% to 10%¹⁻⁴
- 1-year prevalence rates range from 3% to 6%, depending on prior exposure to trauma¹⁻⁴



- PTSD is one of the most common mental health disorders in the US^{5,6}
- >80% patients are in the general population rather than the military population⁷⁻⁹



Among the general US population:

- ~13 million adults will experience PTSD during a given year (~4.9%)^{3,10-}
- 7 to 8 out of every 100 people will experience PTSD at some point in their lives^{1,3,10-13}

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

- 1. Koenen KC et al. Psychol Med. 2017; 47:2260-2274.
- 2. Yehuda R et al. Nat Rev Dis Primers. 2015; 1: 15057.
- 3. Kilpatrick DG et al. J Trauma Stress. 2013; 26: 537-547.
- 4. Kessler R et al. World Psychiatry. 2014; 13(3), 265-274
- 5. Lancaster CL. et al. J Clin Med. 2016; 5(11), 105.
- 6. Spottswood M et al. Harv Rev Psychiatry. 2017; 25(4), 159-169.
- 7. Davis LL et al. J Clin Psychiatry. 2022;83(3):21m14116.

- United Nations Department of Economic and Social Affairs. (1994). Retrieved from https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf.
- 9. Kessler RC et al. Arch Gen Psychiatry. 2005;62(6):617-627.
- 10. Lehavot K et al. Am J Pre Med. 2018;54(1), e1-e9.
- US Census Bureau. (2022). National Population by Characteristics: 2020-2022. Retrieved from https://www.census.gov/data/tables/time-series/demo/popest/2020s-national-detail.html. (Data on file).
- 12. RE_ Prevalence Estimate Follow-up email.pdf. (Data on file).
- 13. U.S. Department of Veterans Affairs. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 4.0. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.

Demographics

PTSD can develop at any age and across genders and identities

 $QQ: \mathcal{O}$

- Gender: Incidence of PTSD is 2x higher in women than men^{1,2}
 - Women account for 66.4% of the overall PTSD population in the US^{1,2}
 - Lifetime prevalence of PTSD is 13% in women and 6% in men^{1,2}
 - Females in the general population experience PTSD for a longer duration than do males³



- Age: Typical onset age for PTSD is in young and middle adulthood⁴
 - The median age of onset among US adults is 23 years⁴



- Ethnicity: In the US, PTSD prevalence varies by group5
 - Black: 8.7%
 - White: 7.4%
 - Hispanic: 7.0%
 - Asian: 4.0%

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

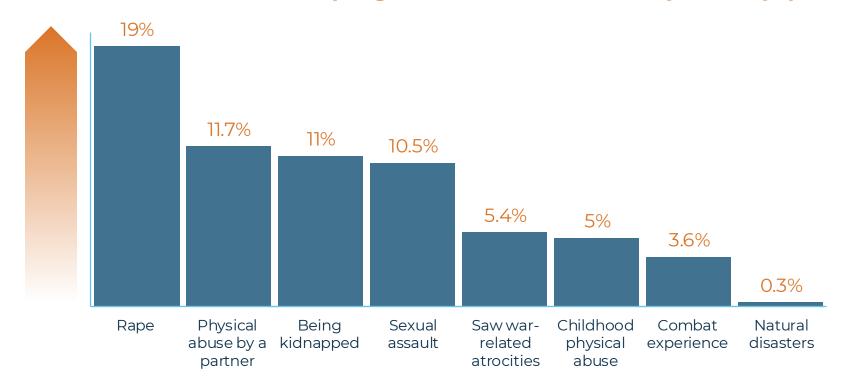
- 1. Davis LL et al. J Clin Psychiatry. 2022;83 (3):21m14116.
- 2. Kilpatrick DG et al. J Trauma Stress. 2013; 26: 537-547.
- 3. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5TM. American Psychiatric Publishing.
- 4. Kessler RC. Arch Gen Psychiatry. 2005;62(6), 617-627.
- 5. Alegría M et al. Medical Care. 2013;51(12):1114-1123.



Most common trauma types in PTSD

PTSD can develop after experiencing or witnessing a range of traumatic events

 The average risk of developing PTSD after a traumatic exposure is 4%, and up to 30%, varying by trauma type¹⁻⁴



Risk of developing PTSD after trauma exposure (%)¹

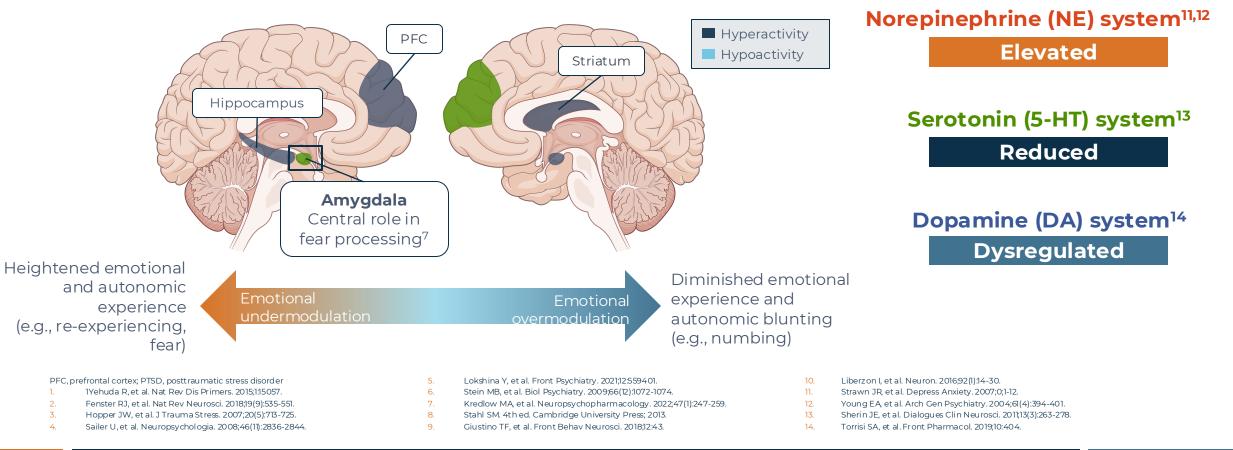
PTSD, post-traumatic stress disorder.

- 1. Kessler RC et al. Eur J Psychotraumatology. 2017;8(suppl 5), 1353383.
- 2. Liu H et al. JAMA Psychiatry. 2017;74(3):270-281.
- 3. Luz MP et al. J Psychiatr Res. 2016;72, 51-57.
- 4. Tortella-Feliu M et al. Neurosci Biobehav Rev. 2019;10:154-165.

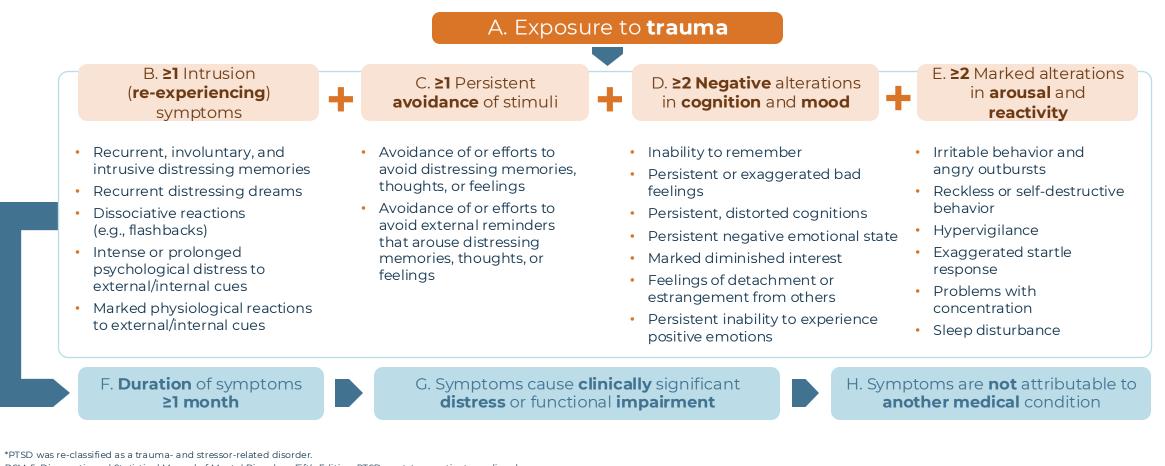


PTSD Pathophysiology Summary

PTSD is characterized by emotional dysregulation that may involve dysfunction of key brain regions important to fear conditioning and extinction¹⁻¹⁰



DSM-5 diagnosis of PTSD^{1,2,*}

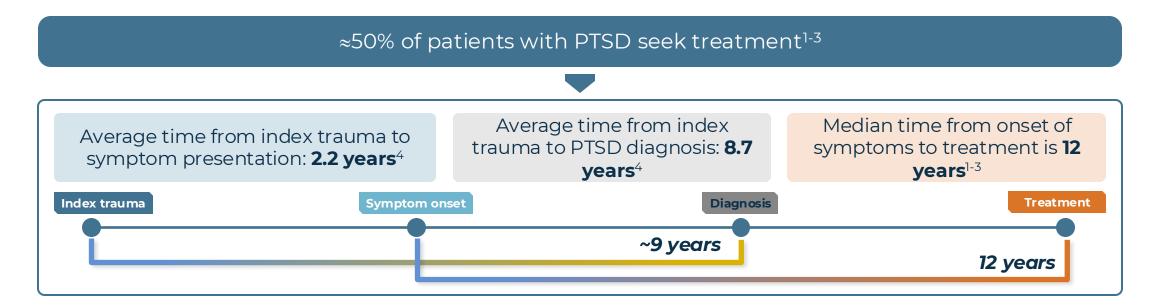


DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder.

- 1. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5TM. American Psychiatric Publishing.
- 2. Mann SK et al. (2023). Posttraumatic stress disorder. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK559129/.



Underdiagnosis of PTSD Individuals with PTSD may experience significant delays in diagnosis



Many patients and individuals with PTSD seek care for physical symptoms without mentioning psychiatric symptoms or trauma histories due to a lack of understanding regarding the relationship between trauma exposure and their own symptoms5

- 1. PTSD, post-traumatic stress disorder.
- 2. Nobles CJ et al. Gen Hosp Psychiatry. 2016;43:38-45.
- 3. Koenen KC et al. Psychol Med. 2017;47:2260-2274.
- 4. Wang PS et al. Arch Gen Psychiatry. 2005;62(6): 603-613.
- 5. Davis, LL et al.Patient journey of civilian adults diagnosed with posttraumatic stress disorder—A chart review study, Current Medical Research and Opinion, 2024;40:3,505-516,
- Greene T et al. J Clin Psychol Med Settings. 2016;23(2): 160-180.



Underdiagnosis of PTSD

PTSD is often underdiagnosed or misdiagnosed as other mental health conditions

Most prominent barriers to care¹

- Concerns related to stigma, shame/rejection
- Low mental health literacy
- Lack of knowledge and treatment-related doubts
- Fear of negative social consequences
- Limited resources

• Individuals with PTSD are 80% more likely than those without PTSD to have symptoms that meet diagnostic criteria for at least one other mental health disorder (e.g., depressive, bipolar, anxiety, or substance use disorders)²



Misdiagnosis

In the primary care setting, of individuals meeting diagnostic criteria for PTSD³:

- 50% were diagnosed with depression
- 23% were diagnosed with anxiety or panic attacks
- 11% received a diagnosis of PTSD

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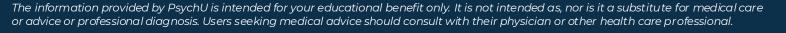


Under-diagnosis

 <50% of individuals who meet criteria for PTSD are correctly diagnosed in primary and secondary care settings⁴⁻⁶

PTSD, post-traumatic stress disorder.

- 1. Kantor V et al. Clin Psychol Rev . 2017;52: 52-68.
- 2. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5™. American Psychiatric Publishing.
- Meltzer EC et al. The Journal of Behavioral Health Services & Research, 2012;39(2): 190-201.
- Greene T et al. J Clin Psychol Med Settings. 2016;23(2):160-180.
- Liebschutz J et al. J Gen Intern Med. 2017;22(6):719-726.
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Underdiagnosis of PTSD

Decreased awareness in the general population and underuse of existing diagnostic tools

- Timely and appropriate diagnosis can be challenging due to¹⁻³: •
 - Variable onset of symptoms Inherent heterogeneity in presentation
 - Comorbidities Stigma

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PCL-5, PTSD Checklist for DSM-5; PC-PTSD-5, Primary Care PTSD 4.

Institute of Medicine, 2014. Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment.

- Misdiagnosis is associated with ineffective management, leading • to negative impact on⁴:
 - Treatment compliance
 - Treatment response
 - Patient satisfaction
- Screening tools: Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) • and PTSD Checklist for DSM-5 (PCL-5)⁵⁻⁷
 - Guideline recommended Underutilized in practice
 - Can aid with diagnosis

Kessler RC et al. Eur J Psychotraumatology, 2017;8(suppl 5):1353383

screen for DSM-5 PTSD, post-traumatic stress disorder

Washington, DC: The National Academies Press

Parrott S. Electronic News. 2022;17(3): 181-197.

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- U.S. Department of Veterans Affairs. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version4.0. 2023. www.healthguality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf (Accessed July 2023).
- Williamson MLC et al. J Clin Psychol. 2022;78(11): 2299-2308
- Geier TJ et al. Depress Anxiety. 2019;36(2): 170-178





Underdiagnosis and undertreatment prolong suffering and add to overall burden

• PTSD is underdiagnosed in both the US civilian and military populations¹⁻⁴

		Suciae attempts
		Overall poor quality of life ¹⁻⁴
Underdiagnosis Undertreatment Potential adverse	Higher risk of sustained, long-term PTSD ¹⁻⁴	
	adverse	Disruptions to daily life ⁵
	outcomes	Risk of isolation and distress ⁵
		Deterioration of family and social
		relationships ⁶
		Increased risk of mortality ⁷

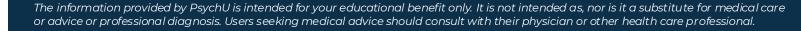
Early diagnosis and intervention are necessary for effective treatment and to minimize the longterm outcomes associated with PTSD⁸

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

- 1. Gagnon-Sanschagrin P et al. BMC Psychiatry. 2022;22(1):630.
- 2. Wimalawansa S. Res J Med. 2013;1:1-12
- Goenjian AK et al. Am. J. Psychiatry. 2005;162(12):2302-2308.
- 4. Priebe S et al. Croat. Med. J. 2009;50(5):465-475.

- Ellis J et al. Continuum (Behavioral Neurology and Psychiatry). 2018;24(3):873-892.
- Smith BA. Healthcare (Basel). 2018;6(30):80.
- 7. Cooper J et al. Aust Fam Physician. 2014;43(11):754-757.
- 8. Mann SK et al. 2013. www.ncbi.nlm.nih.gov/books/NBK559129/.

Suicide attempts]-4





Psychiatric comorbidities in individuals with PTSD

• As demonstrated by National Surveys data¹⁻³:



Most common comorbidities:

Affective disorders (depression)⁴

- ~50% individuals with PTSD had comorbid major depressive disorder^{2,3,*}
 - Greater cognitive and functional impairment^{1,5,6}

Anxiety disorders⁴

 Individuals with PTSD have
2.4 -7.1 higher odds of having an anxiety disorder, with the majority comprising phobias (simple, social, agoraphobia) and generalized anxiety disorder⁴

Substance use disorder⁴

*Meta-analytic findings (57 studies); N = 6670 participants. PTSD, post-traumatic stress disorder.

- 1. Flory JD et al. Dialogues Clin Neurosci. 2015;17(2):141-150.
- 2. Rytwinski NK et al. J Trauma Stress. 2013;26(3):299-309.

- 3. Kessler RC et al. Arch Gen Psychiatry. 1995;52 (12):1048-1060.
- 4. Brady KT et al. J Clin Psychiatry. 2000;61(suppl 7):22-32.
- 5. Nijdam MJ et al. Eur. J. Psychotraumatol. 2013;4:19979.
- 6. Dutra SJ et al. Chronic Stress (Thousand Oaks). 2018;2:2470547018812400.



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 interventions¹⁻³
 - 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 pharmacotherapy¹
- ~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



CBT, cognitive behavioral therapy; PTSD, post-traumatic stress disorder; SSRI, selective seroton in 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

- U.S. Department of Veterans Affairs. 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
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Holder N et al. J Clin Psychiatry. 2021;82(3):20m13522.

Lee DJ et al. Depress Anxiety. 2016;33(9):792-806.





Summary of US guidelines for pharmacotherapy¹

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
Benzodiazepinesª	No		NA	-

+, recommendation for; -, recommendation against; - -, strong recommendation against; NA, not addressed.

^a Class of medications; ^b First-line treatment for night mares 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.

- 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 clusters¹⁻³
- Off-label treatments continue to be prescribed despite not being recommended by guidelines⁴
- A notable proportion of veterans are being treated with off-label medications²
 - ~20% receive FDA-approved SSRIs*
 - ~17% receive SSRIs that are not FDAapproved for PTSD[†]
 - ~14% receive SNRIs[‡]
 - ~6%-9% receive anxiolytics or sedativehypnotics,[§] atypical antipsychotics,[¶] or benzodiazepines¹

FDA, Food and Drug Administration; PTSD, post-traumatic stress disorder; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective 5. serotonin reuptake inhibitor; US, United States. 6.

- 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.

SNRIs

- Recommended by US guidelines⁵⁻⁸
- Variable efficacy^{1,9}
- May raise blood pressure^{1,9}

Atypical antipsychotics

- <16% used in patients as first-, second-, or third-line therapy⁴
- Recommended for augmentation in cases of incomplete response or residual symptoms¹²

Anxiolytics and benzodiazepines

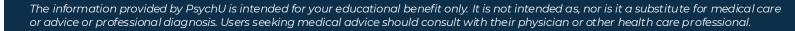
- Second highest use in newly diagnosed patients (up to 33%)⁴
- Prescribed to treat sleep disturbance and hyperarousal^{10,11}
- Strongly recommended by guidelines against use of benzodiazepines^{5,10,11}

Adrenergic antagonists

- Used for PTSD-related nightmares¹³
- Not efficacious in treating recurrent distressing dreams

or improving sleep quality¹³

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. Ravind ran 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.





Yehuda, R et al. Nat Rev Dis Primers. 2012;1:15057.

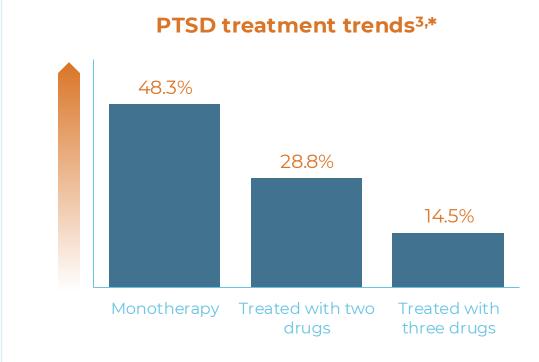
U.S. Department of Veterans Affairs. 2023. Accessed July 2023. <u>www.healthquality.va.gov/quidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf</u>.

Polypharmacy in PTSD

- The limited efficacy and available options of FDA-approved treatments for PTSD have necessitated polypharmacy for a vast majority of patients¹
- Following diagnosis, individuals are prescribed an average of 1.6 medications for PTSD alone²
- Common combinations include SSRIs, anxiolytics, and benzodiazepines to address depression and sleep disturbances
 - Treatment guidelines recommend against augmenting therapies with benzodiazepines³
 - Benzodiazepines may worsen patient outcomes, including overall severity and psychotherapy outcomes⁴

*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.

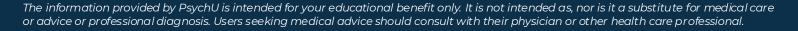


Decision Resources Group. 2018. Treatment Algorithms: Claims Data Analysis in Post-traumatic Stress Disorder. (Data on file).

Guina J et al. J Psychiatr Pract. 2015;21(4):281–303.

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Clinical barriers in PTSD management



- In a US-based survey, 41.8% of patients with PTSD reported an unmet need for treatment¹:
 - 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 traumarelated 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 care⁴
 - 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.
- Greene T et al. J Clin Psychol Med Settings. 2016;23(2):160-180.



Summary

PTSD is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event or series of traumatic events.¹⁻³

PTSD is a highly prevalent disorder worldwide and is one of the most common mental health disorders in the US.^{1,2,4} A majority of cases are predominantly in the general population and women.^{4,5}

Risk of developing PTSD after traumatic exposure varies by trauma type.⁶

Under- and mis-diagnosis are common in clinical practice.^{6,7}

Psychiatric comorbidities are common among individuals with PTSD and add to overall patient burden.⁸⁻¹⁰

Most guidelines recommend both psychological and pharmacologic therapies as first-line interventions in PTSD.¹¹⁻¹³ Though polypharmacy, off-label, and non-evidence-based treatments are often utilized in an attempt to address individual PTSD symptoms. ^{14,15}

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.^{16,17}

PTSD	, Post-traumatic stress disorder; US, United States
1.	Koenen KC et al. Psychol Med. 2017; 47: 2260-2274.
2.	Yehuda R et al. Nat Rev Dis Primers. 2015; 1: 15057.
3.	American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5™. American Psychiatric Publishing.
4.	Kilpatrick DG et al. J Trauma Stress. 2013; 26: 537-547.
5.	Kessler RC et al. Arch Gen Psychiatry. 2005;62(6):617-627.

Kessler RC et al. Eur J Psychotraumatology. 2017;8(suppl 5):1353383. Greene T et al. J Clin Psychol Med Settings. 2016;23(2):160-180.
Flory JD et al. Dialogues Clin Neurosci. 2015;17(2):141-150.
Rytwinski NK et al. J Trauma Stress. 2013;26(3):299-309.
Brady KT et al. J Clin Psychiatry. 2000;61(suppl 7):22-32.
Martin A et al. J Clin Med. 2021;10(18):4175.
World Health Organisation, 2013.

- apps.who.int/iris/bitstream/handle/10665/85119/9789241505406_eng.pdf. U.S. Department of Veterans Affairs. 2023.
- www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf.
- Krystal JH et al. Biol Psychiatry. 2017;82(7):e51-e59. 15. Reisman M. P&T. 2016;41(10), 623-634...
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