Women's Health 2024 | Beyond the Annual Visit

New Hope Emerging in the Treatment of PTSD in Women: Overcoming Suboptimal Outcomes

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Learning Objectives

- Utilize validated guideline-recommended screening tools to diagnose post-traumatic stress disorder (PTSD) in women
- Incorporate PTSD treatment guidelines into clinical practice to ensure evidence-based management
- Evaluate the inadequacies and risks associated with off-label treatments for PTSD
- Explain the link between the pathophysiology of PTSD and the pharmacological rationale for treatment
- Discuss new and emerging therapies and how they fit into the clinical management of PTSD

Faculty Disclosures

Dr. Goldberg has reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months:

- Receives Royalties: American Psychiatric Publishing, Cambridge University Press
- Consulting Fees: Genomind, Intracellular Therapies, Luye Pharmaceuticals, Neurelis, Neumora, Otsuka, Sage Pharmaceuticals Sunovion, Supernus
- Speakers Bureau: AbbVie, Alkermes, Axsome, Bristol Myers Squibb

Dr. McIntyre has reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months:

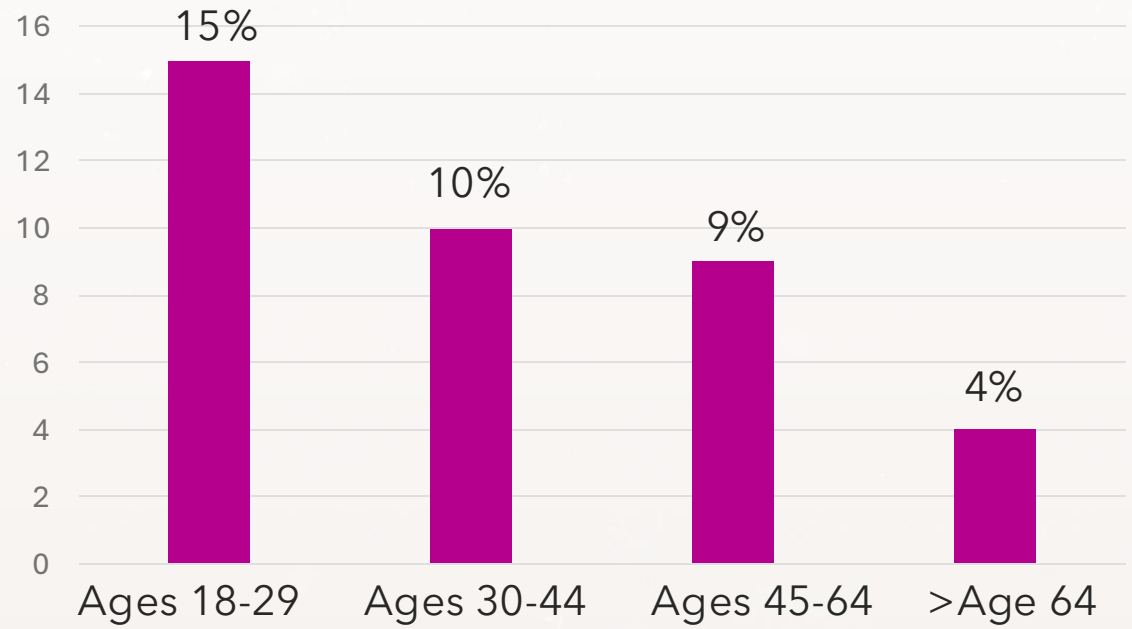
- Research: CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute
- Consulting Fees: Abbvie, Alkermes, Atai Life Sciences, Axsome, Bausch Health, Biogen, Boehringer Ingelheim, Eisai, Intra-Cellular, Janssen, Kris, Lundbeck, Mitsubishi Tanabe, Neumora Therapeutics, Neurocrine, NewBridge Pharmaceuticals, Novo Nordisk, Otsuka, Pfizer, Purdue, Sage, Sanofi, Sunovion, Takeda, Viatris
- CEO of Braxia Scientific Corp.

Post-Traumatic Stress Disorder

PTSD (DSM-5TR)	PTSD (ICD-11)
A. Exposure to actual or threatened death, serious injury, or sexual violence	• Exposure to an extremely threatening or horrific event or series of events
B. Intrusions C. Avoidance D. Changes in cognitions and mood E. Arousal and reactivity	• Re-experiencing • Avoidance • Persistent perceptions of heightened current threat
F. Duration more than 1 month	• Must last for at least several weeks • Significant impairment in personal, family, social, educational, occupational, or other important areas of functioning
G. Clinically significant distress or impairment of function	
H. Due to event, not due to physiological effects of a substance or medical condition	

PTSD: Epidemiology

- Lifetime prevalence[1-3]:
- General population: 6% (women: 8% vs men: 4%)
- Military veterans: 7% (women: 13% vs men: 6%)
- Age (veterans):



# of trauma types accounts for military vs civilian differences in women[2]

Within veterans, higher rates in women associated with childhood abuse, interpersonal violence, stressful life events

1. Goldstein RB, et al. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(8):1137-1148.
2. Lehavot K, et al. *Soc Psychiatry Psychiatr Epidemiol*. 2018;53(9):943-953.
3. Goldberg SB, et al. *Psychiatr Serv*. 2019;70(5):358-366.

Defining PTSD: Trauma

TRAUMA

INTRUSION

AVOIDANCE

COGNITION/ MOOD

HYPER-AROUSAL

Exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:

1. Directly experiencing the traumatic event
2. Witnessing the event as it occurred to others
3. Learning the traumatic event occurred to a close family member or friend
4. Experiencing repeated or extreme exposure to aversive details of the event

Defining PTSD (cont'd): Intrusive Thoughts

TRAUMA

INTRUSION

AVOIDANCE

COGNITION/ MOOD

HYPER-AROUSAL

Presence of 1 (or more) of the following:

1. Recurrent and intrusive distressing memories of event
2. Recurrent distressing dreams of event
3. Dissociative reactions (eg, flashbacks) in which individual feels or acts as if event were recurring
4. Intense psychological distress at exposure to cues that symbolize/resemble aspect of event
5. Physiological reactivity on exposure to cues

Defining PTSD (cont'd): Avoidance

- TRAUMA
- INTRUSION
- AVOIDANCE
- COGNITION/ MOOD
- HYPER-AROUSAL

Persistent **avoidance** of stimuli associated with the trauma and numbing responsiveness, as indicated by 1 or both of the following:

1. Avoid distressing memories, thoughts, or feelings associated with trauma
2. Avoid external reminders (activities, places, people, conversations) that arouse distressing memories, thoughts, or feelings about the trauma

Defining PTSD (cont'd): Cognition/Mood

TRAUMA

INTRUSION

AVOIDANCE

COGNITION/ MOOD

HYPER-AROUSAL

As evidenced by 2 (or more of the following):

1. Can't recall important aspect of trauma
2. Negative beliefs or expectations about oneself, others, or the world
3. Distorted cognitions about the cause or consequences of the trauma that lead individual to blame self or others
4. Persistent negative emotional state (fear, horror, anger, guilt, shame)
5. Decreased interest/participation in activities
6. Feel detached or estranged from others
7. Inability to experience positive emotions

Defining PTSD (cont'd): Hyperarousal

TRAUMA

INTRUSION

AVOIDANCE

COGNITION/ MOOD

HYPER-AROUSAL

As evidenced by ≥ 2 of the following:

1. Irritability or outbursts of anger
2. Reckless or self-destructive behavior
3. Hypervigilance
4. Exaggerated startle response
5. Problems with concentration
6. Sleep disturbance

PTSD: Symptom Duration

- 80%: longer than 3 months
- 75%: longer than 6 months
- 50%: duration of at least 2 years
- Minority can remain symptomatic for years or decades
- Predictors of worse outcomes:
  - More PTSD symptoms
  - Comorbid medical illnesses
  - Childhood trauma
  - Additional traumas
  - Psychiatric history (mood, anxiety)
  - **Female**
  - Alcohol abuse

PTSD vs Acute Stress Disorder

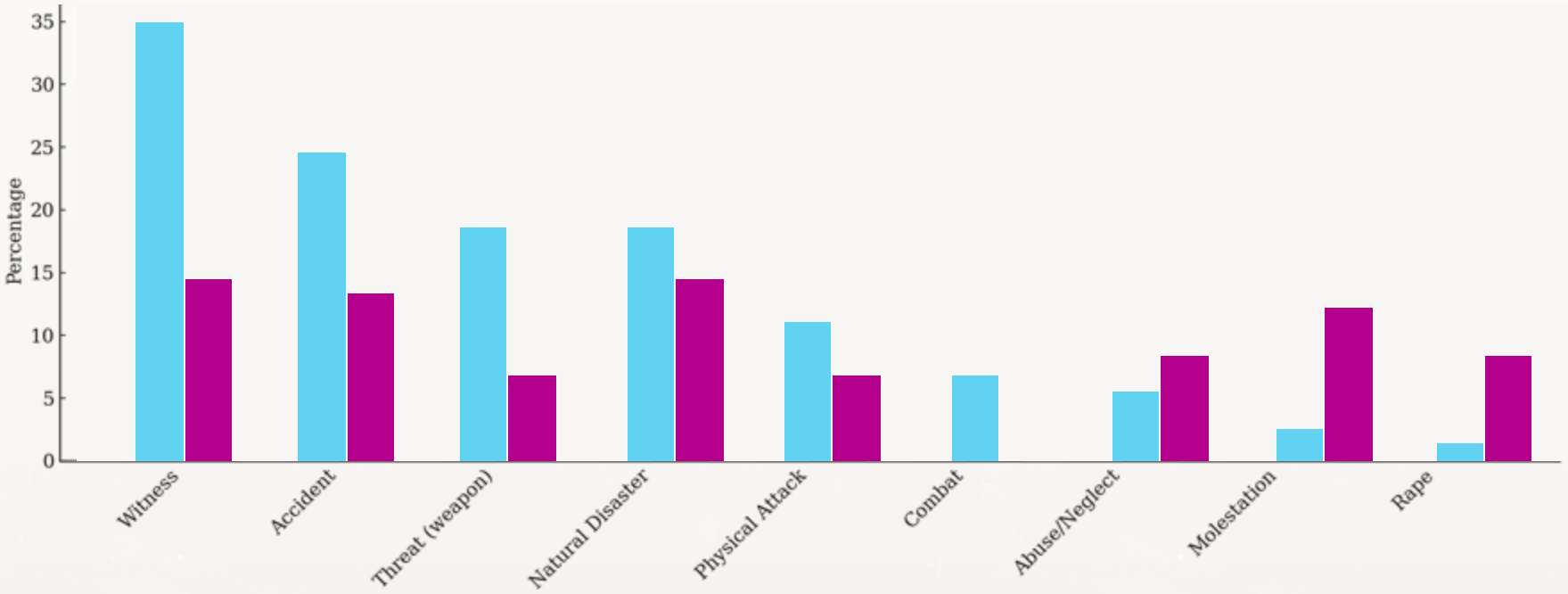
- Exposure to traumatic event
- 9 or more symptoms from any of the following categories:
  - Intrusion (memories, dreams, flashbacks)
  - Negative mood (can't experience positive emotions)
  - Dissociation (altered sense of reality, can't recall important aspect of trauma)
  - Avoidance (of memories, thoughts, feelings, external reminders)
  - Arousal (insomnia, irritability/anger, hypervigilance, poor concentration, exaggerated startle)
- Impaired function, significant distress
- Duration of symptoms: 3 days to 1 month after trauma

Complex PTSD (c-PTSD)

- Prolonged or repeated exposure to interpersonal trauma
- May include impulsivity, aggression, mood dysregulation or affective lability, dissociation, somatic complaints, and chaotic interpersonal relationships
- Not acknowledged in DSM-5 or ICD-10

PTSD: Key Concepts

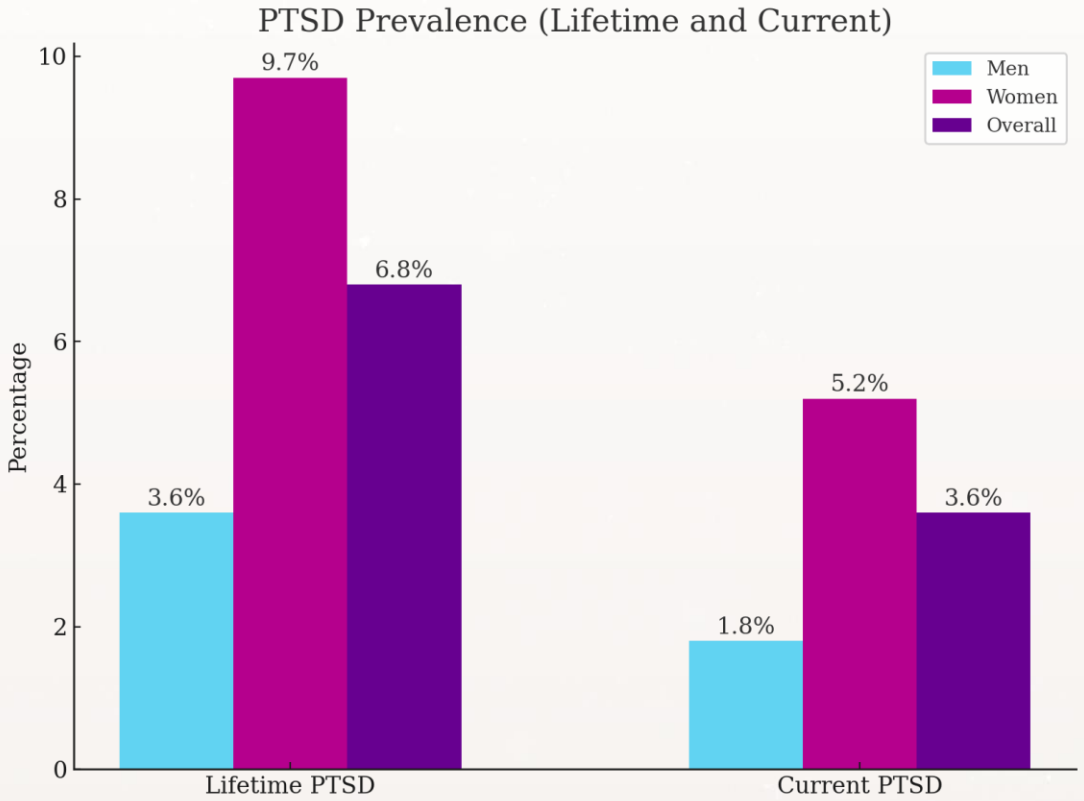
- 61% of men and 51% of women in the US experience at least 1 traumatic event in their lifetime
  - 34% of men and 25% of women experience >1 traumatic event



https://www.ptsd.va.gov

...But Most Trauma Survivors Do Not Develop PTSD

Trauma is not automatically synonymous with PTSD.



Kessler RC, et al. *Arch Gen Psychiatry*. 2005;62(6):593-602.

Sex Differences: PTSD Prevalence Rates Based on Type of Trauma

Traumatic Event	Prevalence of Event		Rate of PTSD in Response to Event	
	Men	Women	Men	Women
	percent			
Rape*	0.7	9.2	65.0	45.9
Molestation*	2.8	12.3	12.2	26.5
Physical assault*	11.1	6.9	1.8	21.3
Accident*	25.0	13.8	6.3	8.8
Natural disaster*	18.9	15.2	3.7	5.4
Combat*	6.4	0.0	38.8	—
Witnessed death or injury†	40.1	18.6	9.1	2.8
Learned about a traumatic event†	63.1	61.8	1.4	3.2
Sudden death of loved one†	61.1	59.0	12.6	16.2
Any traumatic event*	60.7	51.2	8.1	20.4
Any traumatic event†	92.2	87.1	6.2	13.0

* Data are from: Kessler RC, et al. *Arch Gen Psychiatry*. 1995;52(12):1048-1060.
† Data are from: Breslau N, et al. *Psychol Med*. 1999;29(4):813-821. Breslau N, et al. *Arch Gen Psychiatry*. 1998;55(7):626-632.

Yehuda R. *N Engl J Med*. 2002;346(2):108-114.

Risk Factors for PTSD in Aftermath of Trauma

Historical:

- Prior trauma
- Parental PTSD
- Psychiatric hx
- Family hx anxiety disorders
- Neurological compromise
- Lower educational level

Psychological:

- Disrupted parental attachments
- Personality disorder
- Self-criticism
- Cognitive appraisal of trauma
- Controllability
- Predictability
- Perceived threat
- Preparedness

Pathophysiology of PTSD

System	Pathology
Noradrenergic dysfunction[1]	Increased central and peripheral NE activity/reactivity
Dysregulated immune response[1]	↑'d IL-6, IL-17, ↓'d IL-4; Proinflammatory cytokines can ↓ neurogenesis
Mitochondrial dysfunction[1]	Dysregulated energy metabolism, pro-inflammatory state
Suppressed HPA activity[1]	↑'d catecholamines, ↑'d CRF, ↓'d cortisol, ↑'d glucocorticoid sensitivity

Consequences of **low cortisol** in the aftermath of acute trauma:

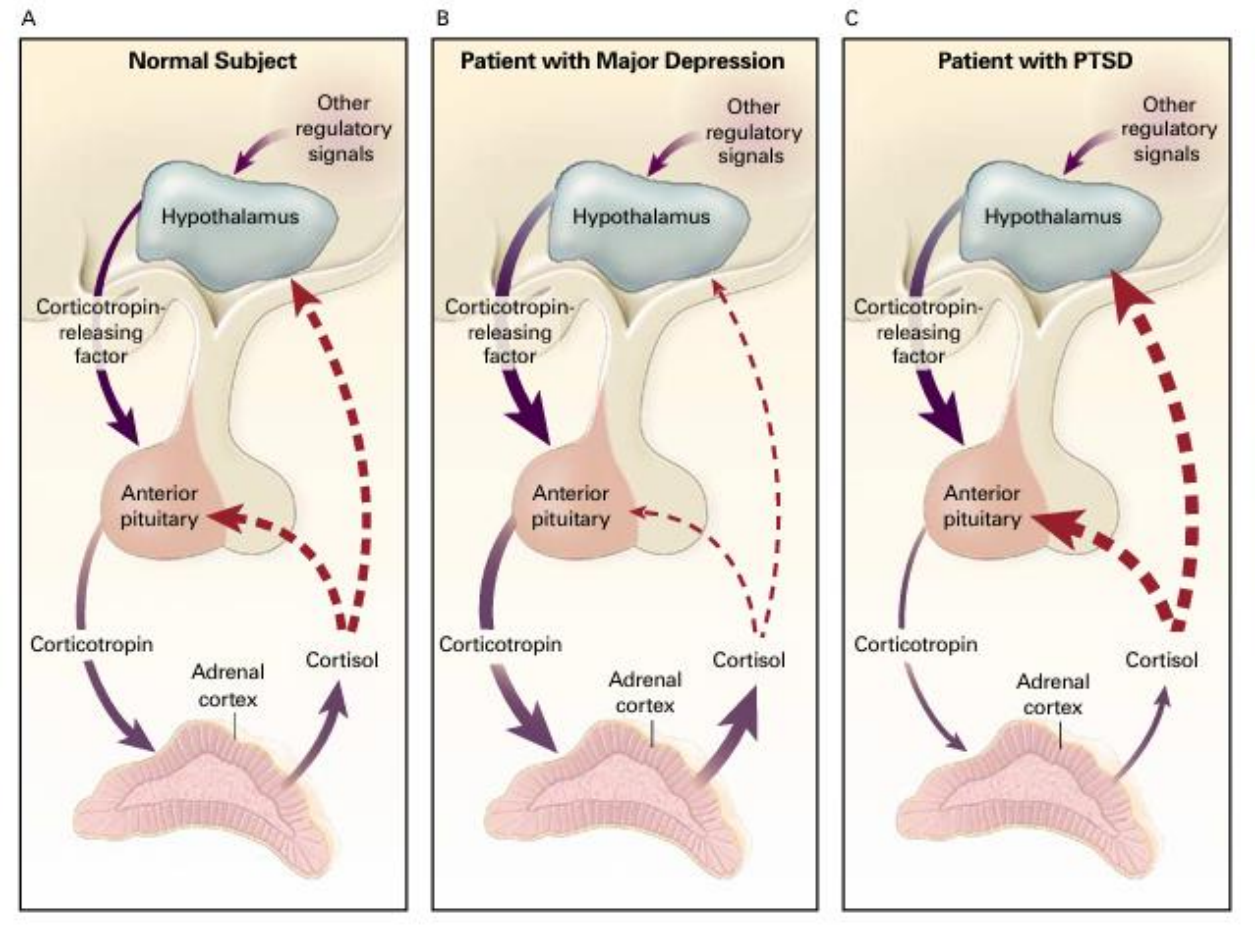
↑'d catecholamines → "overconsolidation" or pairing of memories and distress →

associative cues lead to increased fear and maladaptive cognitive responses →

failure of habituation and extinction → state of perpetual fear

1. Aliev G, et al. *J Clin Med.* 2020;9(9):2951.

Decreased HPA-Axis Negative Feedback Sensitivity in PTSD



Low cortisol in response to stress means failure to inhibit the release of corticotropin from the anterior pituitary and release of CRF from hypothalamus (therefore **CRF increases**)

Yehuda R. *N Engl J Med.* 2002;346(2):108-114.

Neuropeptides and Neurotransmitter Systems Implicated in PTSD

- Norepinephrine
- Serotonin
- Dopamine
- GABA
- Neuropeptide Y
- Endocannabinoid
- Oxytocin
- BDNF

Screening Tools to Diagnose PTSD

- PTSD Checklist for DSM-5 (**PCL-5**)
  - 20-item self-report measure, has military, civilian, and specific versions
- The Primary Care PTSD Screen for DSM-5 (**PC-PTSD-5**)
  - 5-item self-report screen for lifetime trauma; affirmative responses require further evaluation
- Other self-report scales:
  - The Davidson Trauma Scale (DTS), Dissociative Subtype of PTSD Scale (DSPS), Impact of Event Scale-Revised (IES-R), International Trauma Questionnaire (ITQ), Modified PTSD Symptom Scale (MPSS-SR), Posttraumatic Diagnostic Scale for DSM-5 (PDS-5), Trauma Symptom Checklist-40 (TSC-40)

Caveat: screens are screens, not proxies for diagnoses, and the presence of trauma is not synonymous with PTSD
Screening scales do not differ for women vs men

Sample Questions From PCL-5

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Keeping your worst event in mind, please read each problem carefully and then select one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

Your worst event: _____

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
2. Repeated, disturbing dreams of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
4. Feeling very upset when something reminded you of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
8. Trouble remembering important parts of the stressful experience?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0 ◯	1 ◯	2 ◯	3 ◯	4 ◯

Scoring:

20 items, each rated 0-4 (range 0-80)

A cutoff of **31-33** is considered "probable" PTSD

A 5- to 10-point change over time is considered "reliable change"; a 10- to 20-point change is considered "clinically meaningful"

Weathers FW, et al. The PTSD Checklist for DSM-5 (PCL-5). https://www.ptsd.va.gov

PTSD Treatment Considerations

- Threshold for "response" is customarily only 20%-30% improvement from baseline
- An adequate trial to judge response may take up to 12 weeks
- Very few FDA-approved treatments:
  - Paroxetine
  - Sertraline
  - Repetitive transcranial magnetic stimulation (rTMS)
- Behavioral interventions (eg, prolonged exposure therapy; EMDR) are often core components of treatment; CBT is a first-line intervention in nearly all practice guidelines[1]

1. Martin A, et al. *J Clin Med*. 2021;10(18):4175.

VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF POSTTRAUMATIC STRESS DISORDER AND ACUTE STRESS DISORDER

Department of Veterans Affairs
Department of Defense

Prepared by

Management of Posttraumatic Stress Disorder and
Acute Stress Disorder Work Group

With support from

Office of Quality and Patient Safety, Veterans Health Administration

and

Clinical Quality Improvement Program, Defense Health Agency

Key Recommendations From 2023 DoD Practice Guideline for PTSD

Recommendation
• Recommend **paroxetine, sertraline, or venlafaxine** as first-line pharmacotherapy
• There is insufficient evidence to recommend for or against amitriptyline, bupropion, buspirone, citalopram, desvenlafaxine, duloxetine, escitalopram, eszopiclone, fluoxetine, imipramine, mirtazapine, lamotrigine, nefazodone, olanzapine, phenelzine, pregabalin, rivastigmine, topiramate, or quetiapine for the treatment of PTSD.
• There is insufficient evidence to recommend for or against psilocybin, ayahuasca, dimethyltryptamine, ibogaine, or lysergic acid diethylamide for the treatment of PTSD.
• We suggest against divalproex, guanfacine, ketamine, prazosin, risperidone, tiagabine, or vortioxetine for the treatment of PTSD.
• We recommend against benzodiazepines for the treatment of PTSD.
• We recommend against cannabis or cannabis derivatives for the treatment of PTSD.
• We suggest against aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone for augmentation of medications for the treatment of PTSD.

Pharmacological Strategies in PTSD

- Antidepressants
  - SSRIs, SNRIs best studied
- Adrenergic agents (propranolol, clonidine, prazosin)
- Anticonvulsants/mood stabilizers (mostly negative findings; some preliminary favorable randomized data with topiramate[1])
- Atypical antipsychotics
- Psychedelics
  - MDMA-assisted psychotherapy

1. Yeh MSL, et al. *CNS Neurosci Ther.* 2011;17(5):305-310.

Meta-Analysis of Antidepressants for PTSD

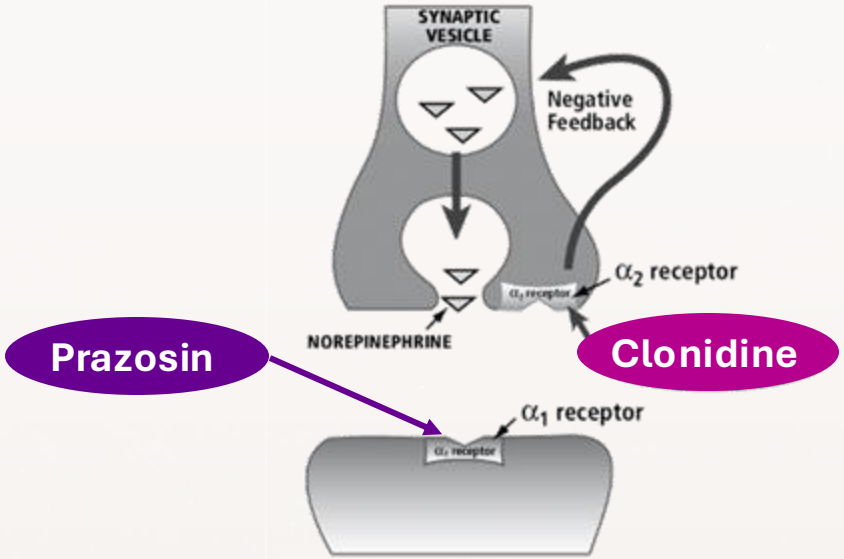
- 29 randomized trials, N = 4,575
- Small overall SMD (0.25; 95% CI = 0.17 to 0.32)
  - Paroxetine: SMD = 0.43
  - Sertraline: SMD = 0.12
- No significant impact for sex, age, or baseline severity

Guidetti C, et al. *Int Clin Psychopharmacol*. Published online June 14, 2024.
doi:10.1097/YIC.0000000000000554

Adrenergic System

- Alpha 2 receptors are both pre- and postsynaptic
- Presynaptic is an autoreceptor
- 2a = *pre*synaptic agonism ↓'s NE tone in PFC (reducing agitation, fight or flight response) *post*synaptic agonism ↑'s NE in PFC, enhancing attention

Centrally induced sedation via locus coeruleus



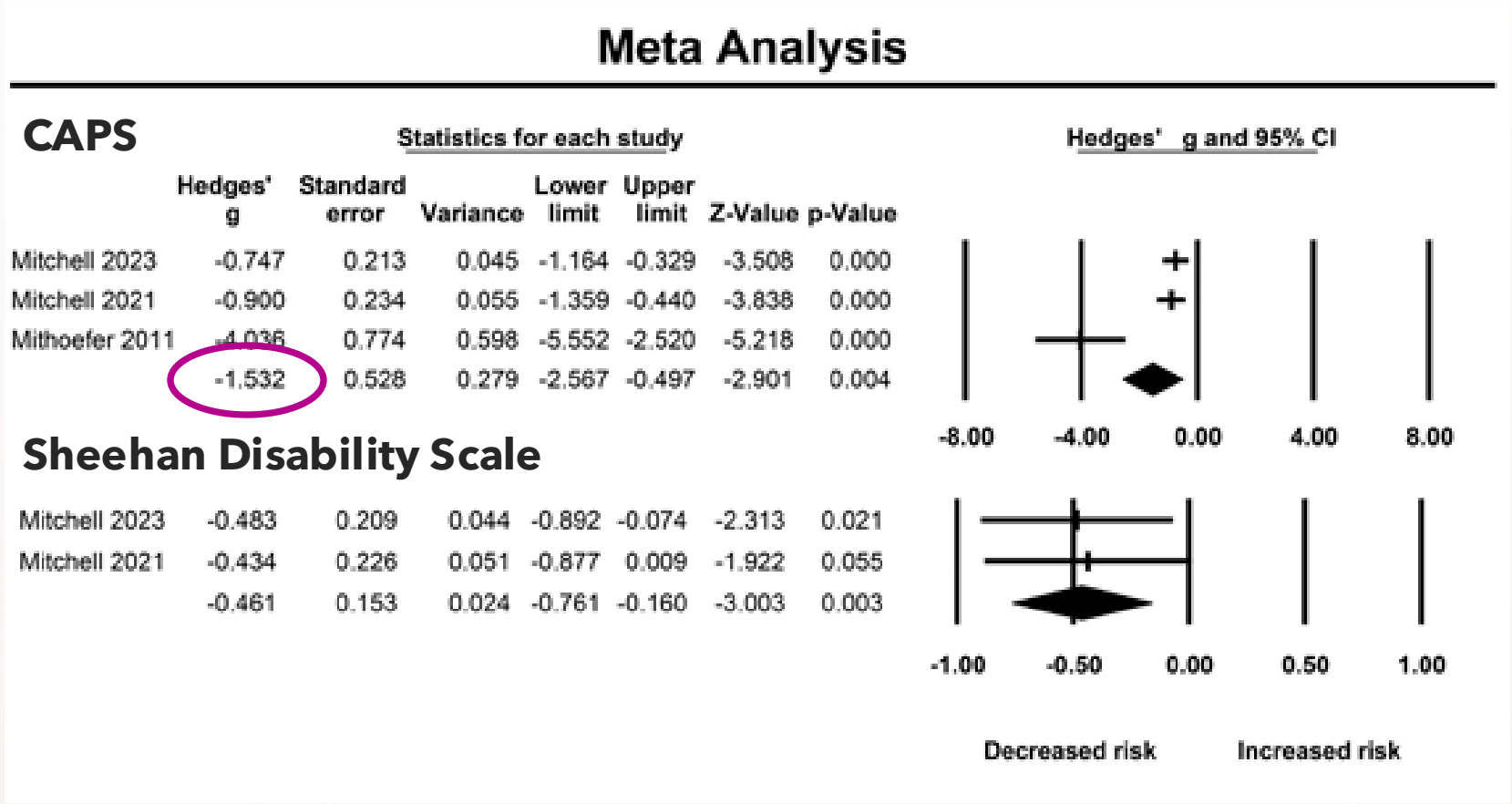
CLONIDINE, GUANFACINE (alpha-2 agonist):
Clonidine dosing 0.1-1 mg/day
Mainly case reports
Guanfacine: negative randomized trials[1]

PRAZOSIN, TRAZODONE (alpha-1 antagonists):
- May help sleep/nightmares
- May be less useful in chronic than acute PTSD[2]
- Prazosin dosing: 1 mg qHS x 3 nights then titrate to mean dose of 10 mg
- Trazodone dosing: 50-200 mg at night

BETA-BLOCKERS?
Initial reports suggested possible value to decouple emotion from memory consolidation immediately after trauma exposure but unconfirmed by meta-analyses[3]

1. Neylan TC, et al. *Am J Psychiatry*. 2006;163(12):2186-2188. 2. Raskind MA, et al. *N Engl J Med*. 2018;378(6):507-517. 3. Argolo FC, et al. *J Psychosom Res*. 2015;79(2):89-93.

3,4-Methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy



Why the FDA voted against approval:

- Blinding versus placebo wasn't really "blinding"
- Lack of subject diversity
- Overzealous suppression of adverse events (eg, some subjects were told to view worsening symptoms as "evidence of healing and spiritual awakening")
- Minimization of abuse potential
- FDA requested an additional phase 3 trial

Yang J, et al. *Psychiatr Res*. 2024;339:116043.

Meta-Analysis of Atypical Antipsychotics for PTSD

- 9 randomized trials (n = 497) involving olanzapine, risperidone, quetiapine, ziprasidone
- Significant but modest overall effect (SMD = -0.289, *P* = 0.002)
- Intrusion: SMD = -0.373, *P* < 0.001
- Avoidance: SMD = -0.166, *P* = NS
- Hyperarousal: SMD = -0.369, *P* = NS

Han C, et al. *J Psychiatr Res*. 2014;56:72-81.

Brexpiprazole in PTSD: Preclinical Studies

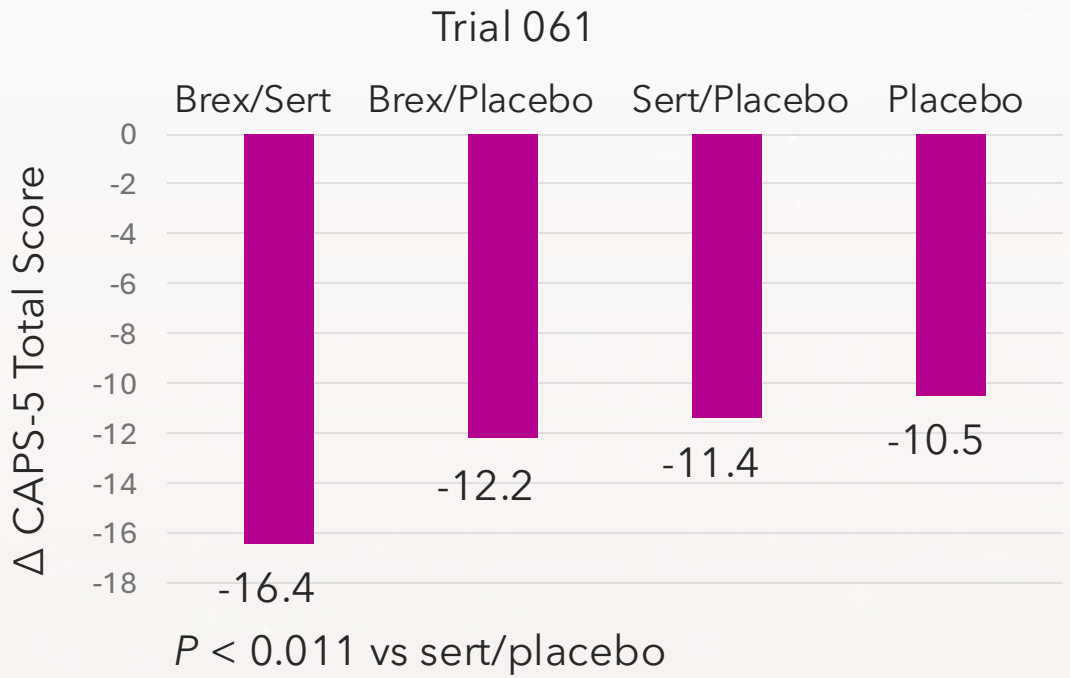
Rodent trials:

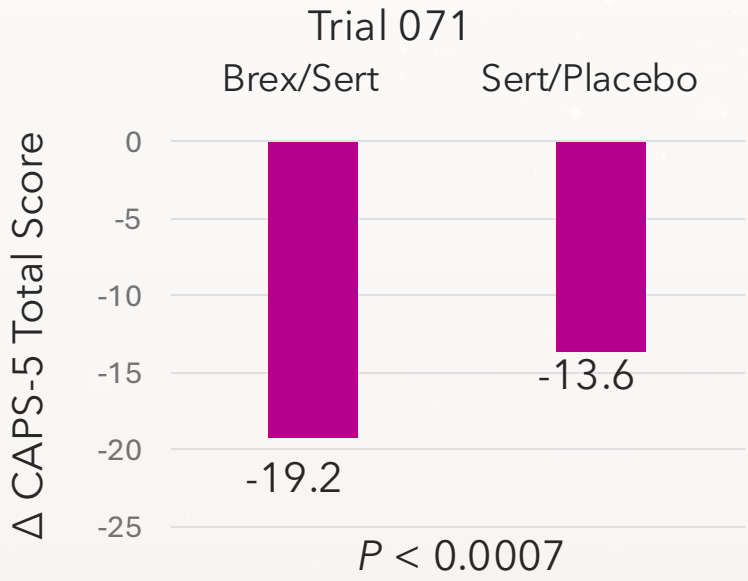
- Brexpiprazole 7 days post-trauma blocks expression of maladaptive fear memory for trauma-related cues
- Promotes the switch from PTSD-like to normal fear memory
- Normalizes alterations in the hippocampal–amygdalar network activation associated with PTSD-like memory

Ducourneau EG, et al. *Mol Psychiatry*. 2021;26(7):3018-3033.

Brexpiprazole + Sertraline for PTSD

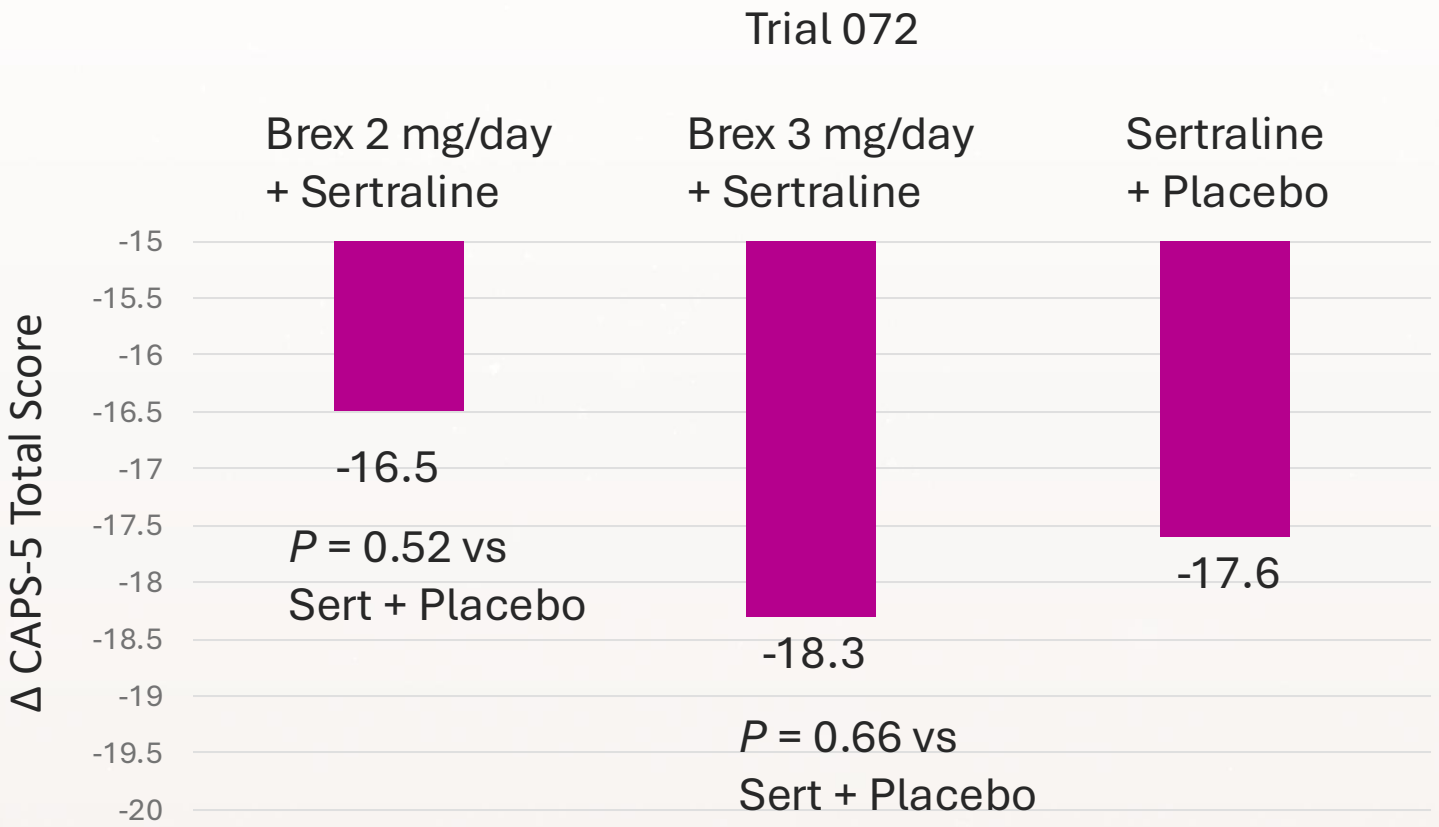
- Three 11-week randomized trials of brexpiprazole (1-3 mg/day) or placebo + sertraline (100-200 mg/day) in adults with PTSD symptoms for ≥6 months





Behl S, et al. ASCP 2024. Poster T7.

Brexpiprazole + Sertraline for PTSD



Behl S, et al. ASCP 2024. Poster T7.

Transcranial Magnetic Stimulation (TMS) for PTSD

- **Repetitive TMS (rTMS)**: **High frequency rTMS (HF rTMS)**, i.e., 5-20 Hz stimulation; **Low frequency rTMS (LF rTMS)**, i.e., ≤ 1 Hz stimulation.
- **Theta burst stimulation (TBS)**: **Intermittent TBS (iTBS)**, i.e., 2 seconds of three bursts of pulses at 50 Hz followed by 8s pause; **Continuous TBS (cTBS)**, i.e., 2 seconds of three bursts of pulses at 50 Hz without interruption.
- **Deep TMS (dTMS)**: Using a novel form of H-coil to stimulate the deeper cortex.
- **Synchronized TBS (sTMS)**: Synchronizing the magnetic pulses with the individual's natural brain rhythms.
- **Accelerated TMS (aTMS)**: Multiple sessions of TMS over a shorter period.
- **Priming TMS (pTMS)**: Brief pretreatment with low intensity and high frequency stimulation.

Meta-analysis of 21 trials, 981 participants[1]

PTSD symptom reductions (versus sham controls) seen with:

- HF-rTMS (SMD = 0.97, 95% CrI = 1.58 to 0.33)
- iTBS (SMD = 0.92, 95% CrI = 1.92 to 0.02)
- LF-rTMS (SMD = 0.76, 95% CrI = 1.44 to 0.05)

1. Liu H, et al. *J Anxiety Disord*. 2024;106:102912.

*Novel Pharmacotherapies for PTSD**

Agent	Rationale	Overall Findings
Oxytocin	Modulates glucocorticoids	40 IU IN BID x 7 days may reduce avoidance behavior in women
Hydrocortisone	Facilitates extinction learning	30 mg before prolonged exposure can reduce CAPS scores
N-acetylcysteine	Antioxidant, neurotrophic	2400 mg/day x 8 weeks can improve overall symptoms
D-serine	NMDA receptor co-agonist	30 mg/kg/day showed trend to reduce CAPS scores
Creatine	↑ brain energy metabolism?	3-4 mg/day shows modest improvement in CAPS scores
Cannabidiol	Mitigate fear memory by disrupting memory consolidation	300-600 mg/day in case series show improved PCL-5 scores

* Based on preliminary trials. As summarized from Goldberg JF, Stahl SM. Chapter 19: Trauma and post-traumatic stress disorder. In: *Practical Psychopharmacology*. Cambridge University Press; 2021.

Evidence-Based Psychotherapies for PTSD

- Trauma-focused psychotherapies
  - Exposure therapy
  - Cognitive behavioral therapy
  - Eye Movement Desensitization and Reprocessing (EMDR)
- Non-trauma-focused psychotherapies
  - Mindfulness-based therapies
  - Supportive therapies
- Group therapy

Summary

- PTSD is considered an abnormal response to severe trauma
- Higher rates in women than men may reflect increased vulnerabilities related to childhood trauma and interpersonal violence
- Complex pathophysiology involves dysregulation of adrenergic, glucocorticoid, and other neural circuitry
- Only modest data to support most existing evidence-based pharmacotherapies (notably SSRIs, SNRIs, and alpha-adrenergic agents)
- Cognitive-behavioral therapies are a cornerstone of treatment
- Emerging database with some atypical antipsychotics, TMS, possible role for some psychedelic agents that await further study