

Finding a Foothold in PTSD: Recent Advances for Trauma-Informed Clinicians

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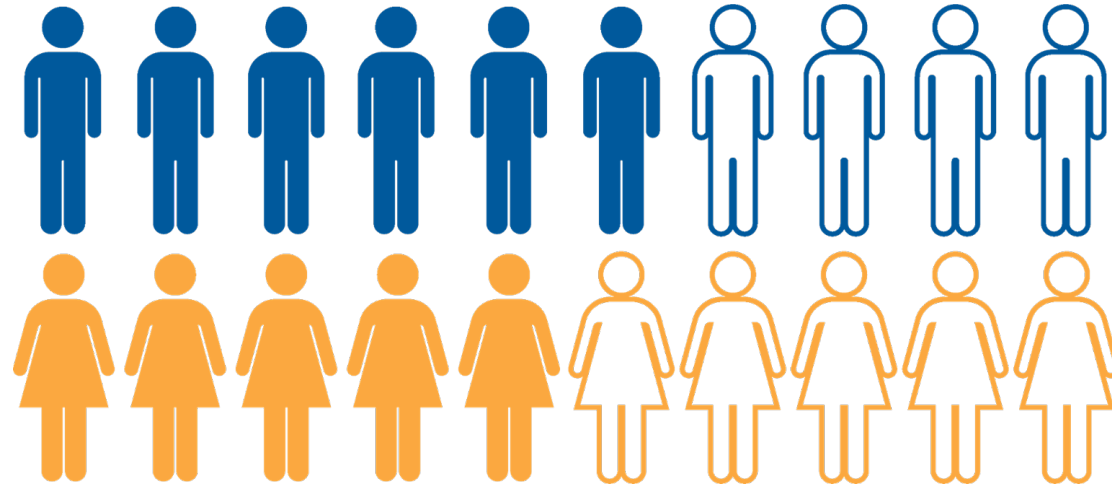
Learning Objectives

1. Describe the symptoms, prevalence, and impacts of post-traumatic stress disorder (PTSD)
2. Assess patients for PTSD using validated tools and according to current diagnostic criteria
3. Evaluate the latest clinical evidence and recommendations regarding available and emerging treatments for PTSD
4. Implement patient-centered and team-based strategies in the treatment of PTSD

Burden of PTSD



Incidence, Prevalence and Burden of PTSD



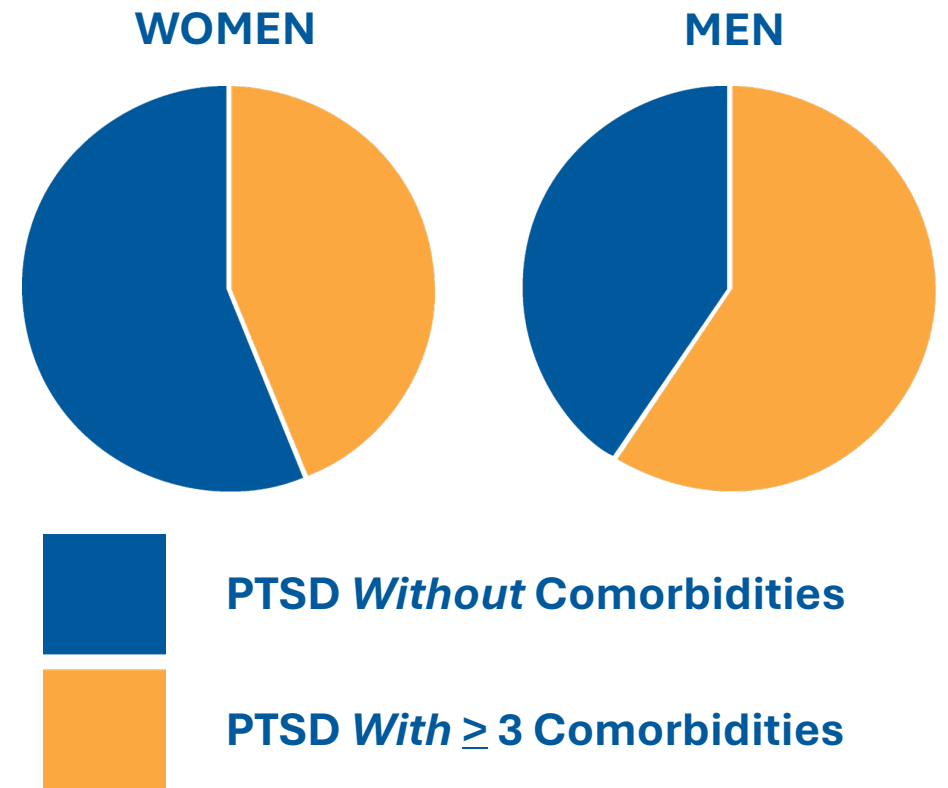
Prevalence of Trauma Exposure in Men and Women

- 6/10 men exposed to at least 1 traumatic event in lifetime
- 5/10 women exposed to at least 1 traumatic event in lifetime
- 6% of US adults will have PTSD at some point in their lifetime
- ~5% of US adults have PTSD in any given year (~13 million people in 2020)

Associated Comorbidities



- 90% have ≥ 1 comorbid psychiatric condition
- 59% of men and 44% of women have ≥ 3 comorbid psychiatric conditions
- Most common – MDD, SUD (predominantly ETOH), other anxiety disorders
- Link between PTSD and poor physical health
 - Cardiovascular illness
 - Pulmonary illness
 - Cancer



Risk Factors

- Trauma exposure with/without injury
- Female gender
- LGBTQIA+
- Lower-level socioeconomic status
- Younger age
- Lower levels of education
- Family hx mental illness
- Substance Use
- Occupational exposure
- Natural disaster



World health Organization. Post-traumatic stress disorder. Accessed October 17, 2024.

<https://www.who.int/news-room/fact-sheets/detail/post-traumatic-stress-disorder#:~:text=Women%20are%20more%20likely%20to,after%20a%20potentially%20traumatic%20experience>.

The Mayo Clinic. Post-traumatic stress disorder (PTSD). Accessed March 11, 2025. <https://www.mayoclinic.org/diseases-conditions/post-traumatic-stress-disorder/symptoms-causes/syc-20355967>

Assessment and Diagnosis of PTSD



Making/Confirming a Diagnosis of PTSD

DSM-5 Criteria

- **Criterion A (1 required):** The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):
 - Direct exposure
 - Witnessing the trauma
 - Learning that the trauma happened to a close relative or close friend
 - Indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)

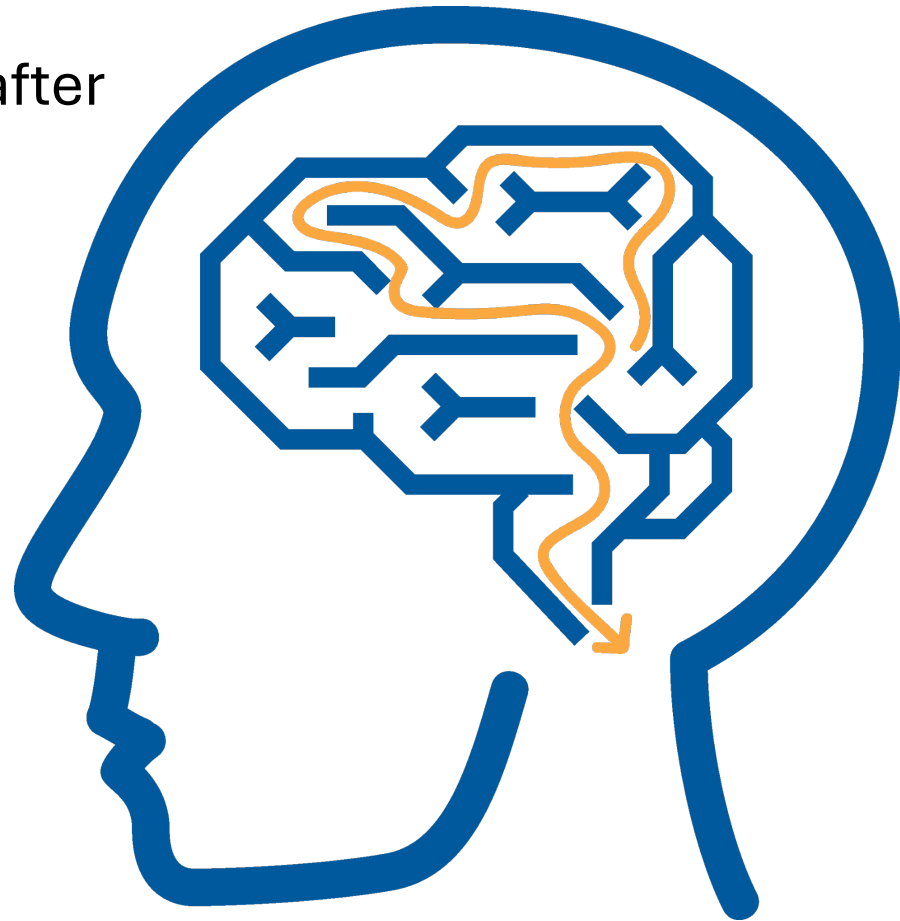
Making/Confirming a Diagnosis of PTSD (cont.)

- **Criterion B (1 required):** The traumatic event is persistently re-experienced, in the following way(s):
 - Unwanted upsetting memories
 - Nightmares
 - Flashbacks
 - Emotional distress after exposure to traumatic reminders
 - Physical reactivity after exposure to traumatic reminders



Making/Confirming a Diagnosis of PTSD (cont.)

- **Criterion C (1 required):**
Avoidance of trauma-related stimuli after the trauma, in the following way(s):
 - Trauma-related thoughts or feelings
 - Trauma-related reminders



Making/Confirming a Diagnosis of PTSD (cont.)



Criterion D (2 required): Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):

- Inability to recall key features of the trauma
- Overly negative thoughts and assumptions about oneself or the world
- Exaggerated blame of self or others for causing the trauma
- Negative affect
- Decreased interest in activities
- Feeling isolated
- Difficulty experiencing positive affect



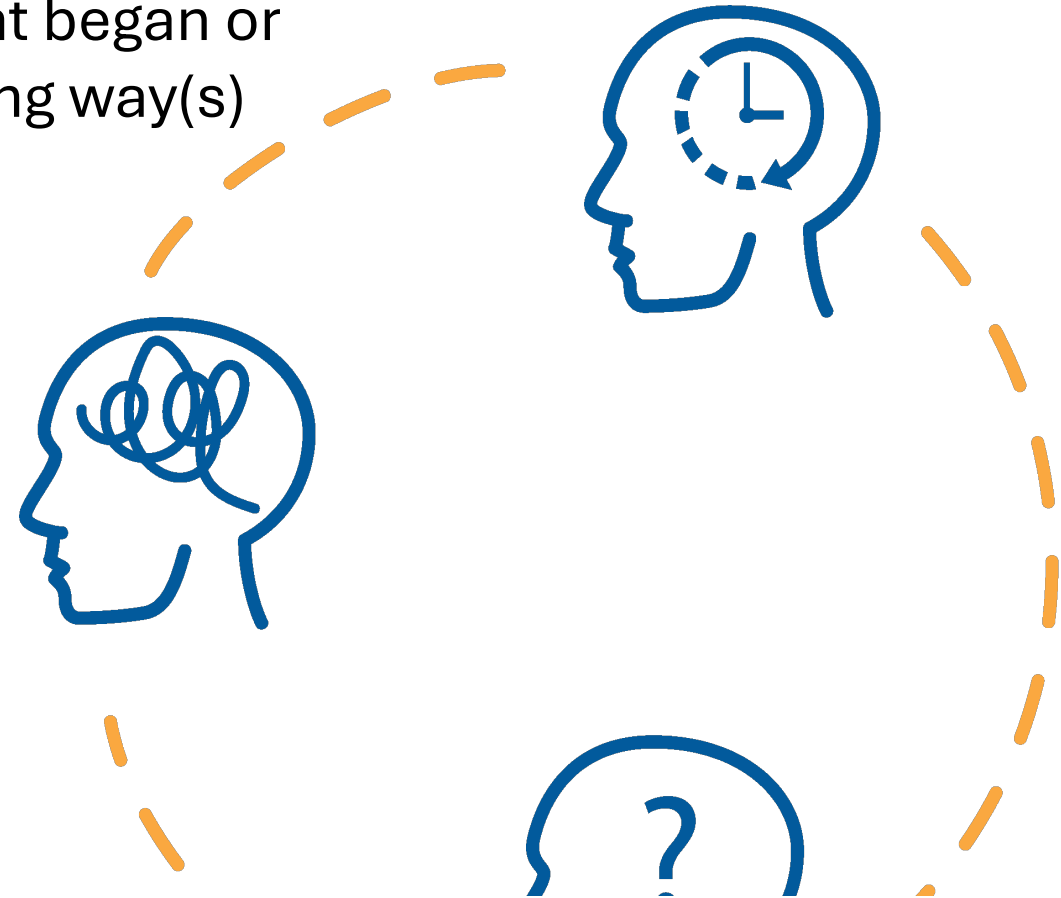
Making/Confirming a Diagnosis of PTSD (cont.)



Criterion E (2 required)

Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s)

- Irritability or aggression
- Risky or destructive behavior
- Hypervigilance
- Heightened startle reaction
- Difficulty concentrating
- Difficulty sleeping



Making/Confirming a Diagnosis of PTSD (cont.)

- **Criterion F (required):** Symptoms last for more than 1 month.
- **Criterion G (required):** Symptoms create distress or functional impairment (eg, social, occupational).
- **Criterion H (required):** Symptoms are not due to medication, substance use or other illness.
- **Two specifications:**
 1. **Dissociative Specification**. In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:
 - *Depersonalization. Experience of being an outside observer of or detached from oneself (eg, feeling as if "this is not happening to me" or one were in a dream).*
 - *Derealization. Experience of unreality, distance, or distortion (eg, "things are not real").*
 2. **Delayed Specification.** Full diagnostic criteria are not met until at least 6 months after the trauma(s), although onset of symptoms may occur immediately.

Validated Screening Tools: Self-Report Instruments

- **PC-PTSD-5 (Primary Care PTSD Screen for DSM-5)**
5 items
- **Davidson Trauma Scale (DTS)**
17 items – DSM-IV
- **Modified PTSD Symptom Scale (MPSS-SR)**
17 items – DSM III-R
- **PTSD Symptom Scale Self-Report Version (PSS-SR)**
17 items – DSM-IV
- **PTSD Checklist for DSM-5 (PCL-5)**
20 items – provisional diagnostic/symptomatic monitoring after treatment
- **Impact of Event Scale – Revised (IES-R)**
22 items – DSM-IV
- **Mississippi Scale for Combat-related PTSD (MISS or M-PTSD)**
35 items – DSM-III; combat/civilian versions

PC-PTSD-5 Screening Tool

1

Sometimes things happen to people that are unusually or especially frightening, horrible, or traumatic. For example:

- A serious accident or fire
- A physical or sexual assault or abuse
- An earthquake or flood
- A war
- Seeing someone be killed or seriously injured
- Having a loved one die through homicide or suicide.

Have you ever experienced this kind of event?

YES NO

If no, screen total = 0. Please stop here.

If yes, please answer the questions below.

In the past month, have you ...

2

1. Had nightmares about the event(s) or thought about the event(s) when you did not want to?	YES	NO
2. Tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)?	YES	NO
3. Been constantly on guard, watchful, or easily startled?	YES	NO
4. Felt numb or detached from people, activities, or your surroundings?	YES	NO
5. Felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused?	YES	NO
Total score is sum of "YES" responses in items 1-5 A score of 3 indicates a positive PTSD screen	TOTAL SCORE	



Key Learning Points

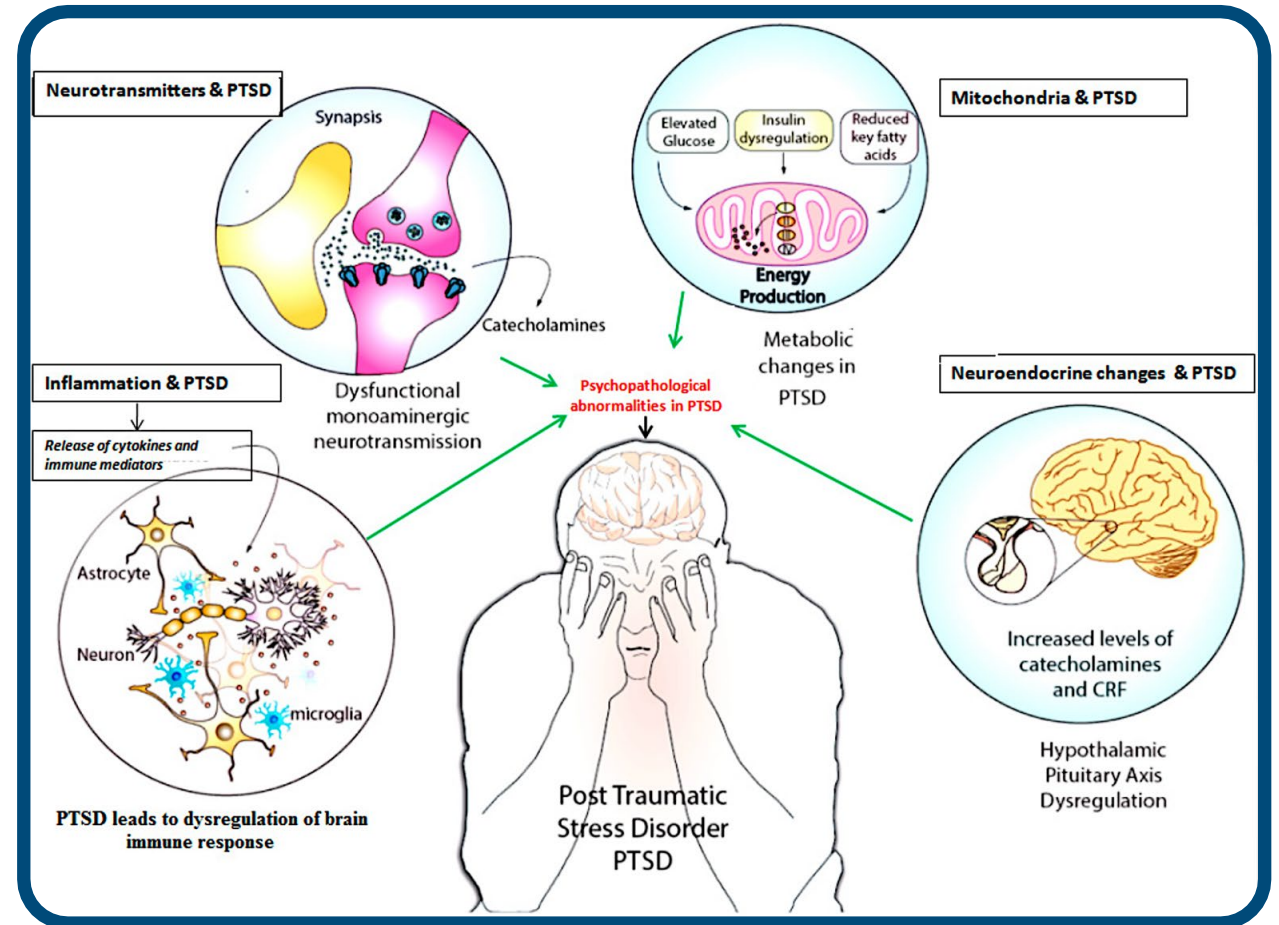
- ✓ Approximately 90% of individuals with PTSD have ≥ 1 psychiatric comorbidity
- ✓ The DSM-5-TR diagnostic criteria for PTSD require
 - ✓ Criterion A (exposure to traumatic event)
 - ✓ Criterion B (traumatic event persistently re-experienced)
 - ✓ Criterion C (avoidance of traumatic stimuli)
 - ✓ **Criterion D (2 or more symptoms** of negative thoughts that worsened after event)
 - ✓ **Criterion E (2 or more symptoms** of trauma-related arousal/reactivity that started or worsened after event)
- ✓ PTSD is more prevalent in women than men
- ✓ \$232.2 billion economic impact annually and can result in challenges in relationships, occupation and housing
- ✓ Many risk factors to consider in clinical practice

Neurobiology of PTSD



PTSD Is Associated with Multifactorial Disorders in the Human Body

- Dysregulation of the immune system fosters neurophysiological and psychopathological changes due to elevated pro-inflammatory mediators such as IL-6 and IL-17.
- Impaired balance in the catecholamine neurotransmitter levels (eg, monoaminergic neurotransmitters) across the synaptic neurotransmitter levels (eg, monoaminergic neurotransmitters) across the synaptic junction confers psychopathological changes in PTSD.
- Metabolic alterations and mitochondrial dysfunction in neurons foster the psychopathological and neurophysiological changes during PTSD.

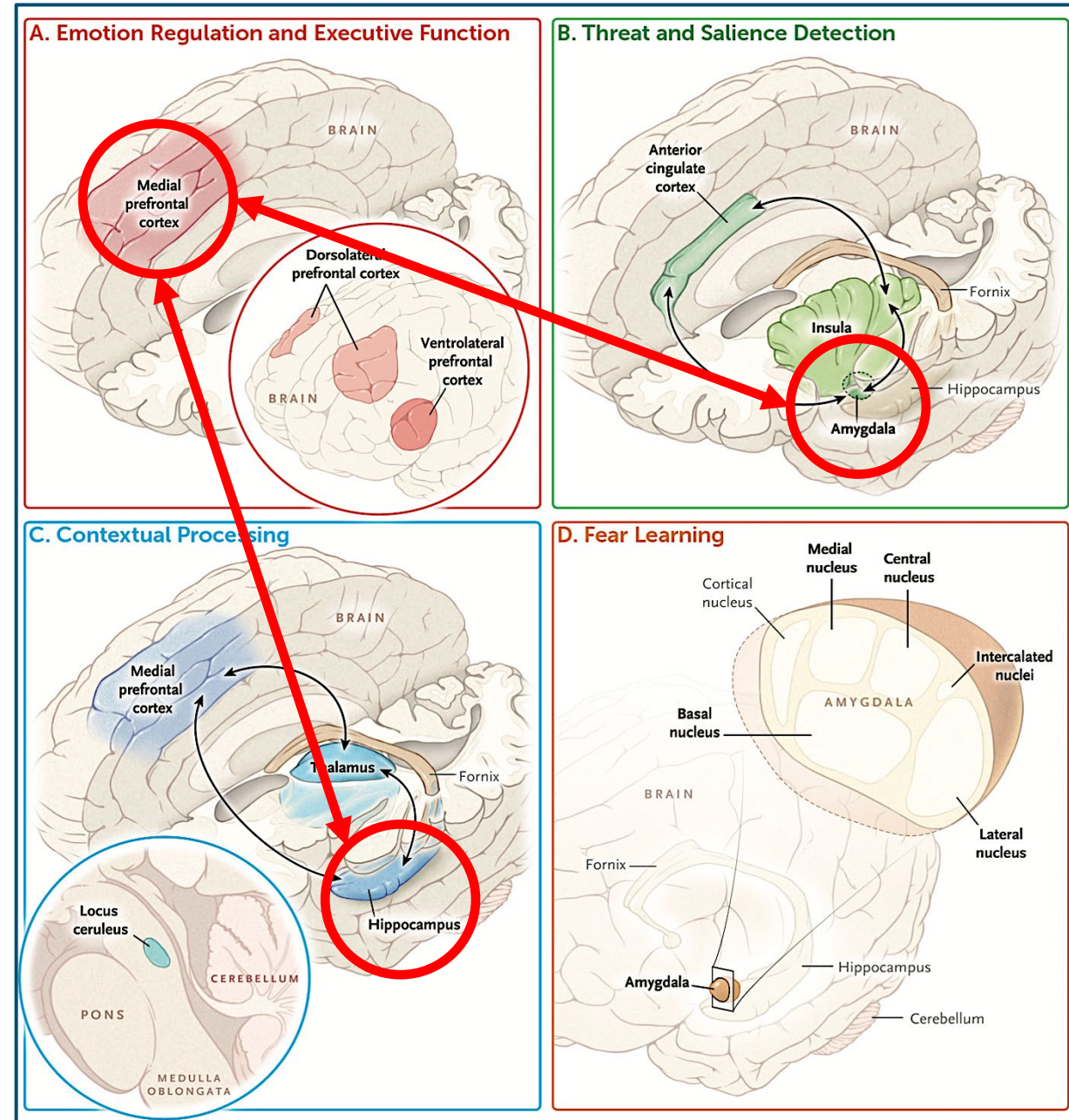


Brain Regions Involved in PTSD – PTSD Appears to ‘Burrow’ Deep into the Brain

PTSD is a multi-system disorder of:

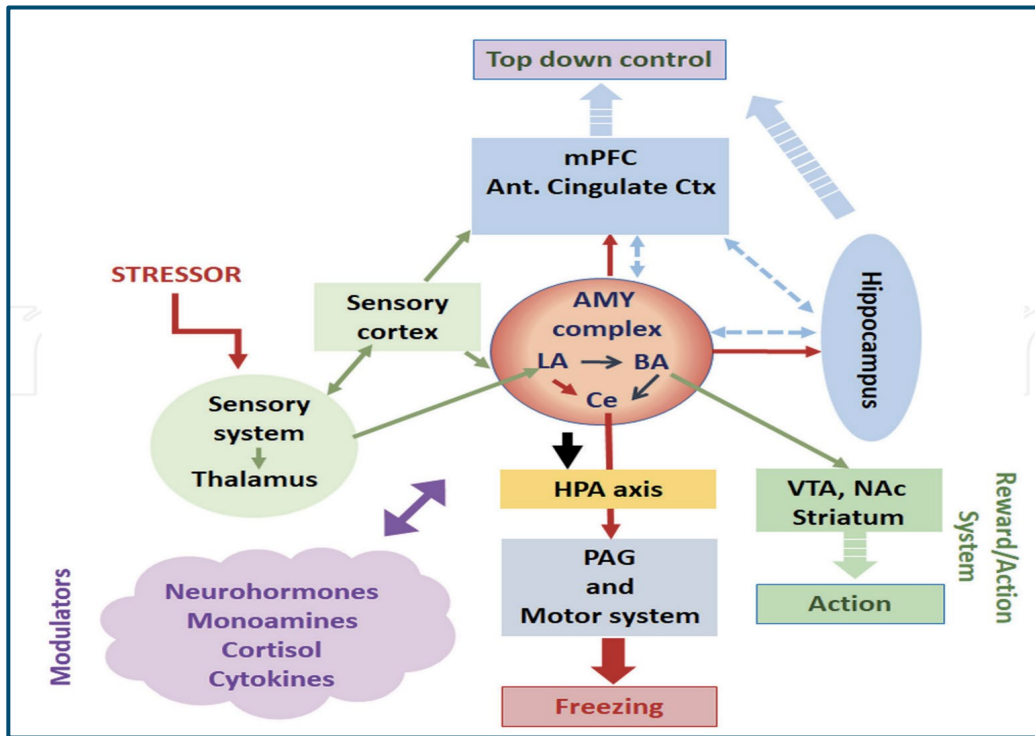
- Emotional regulation
- Threat detection
- Contextual processing
- Fear learning

It involves connections between both cortical (mPFC) and sub-cortical (Amygdala & Hippocampus)

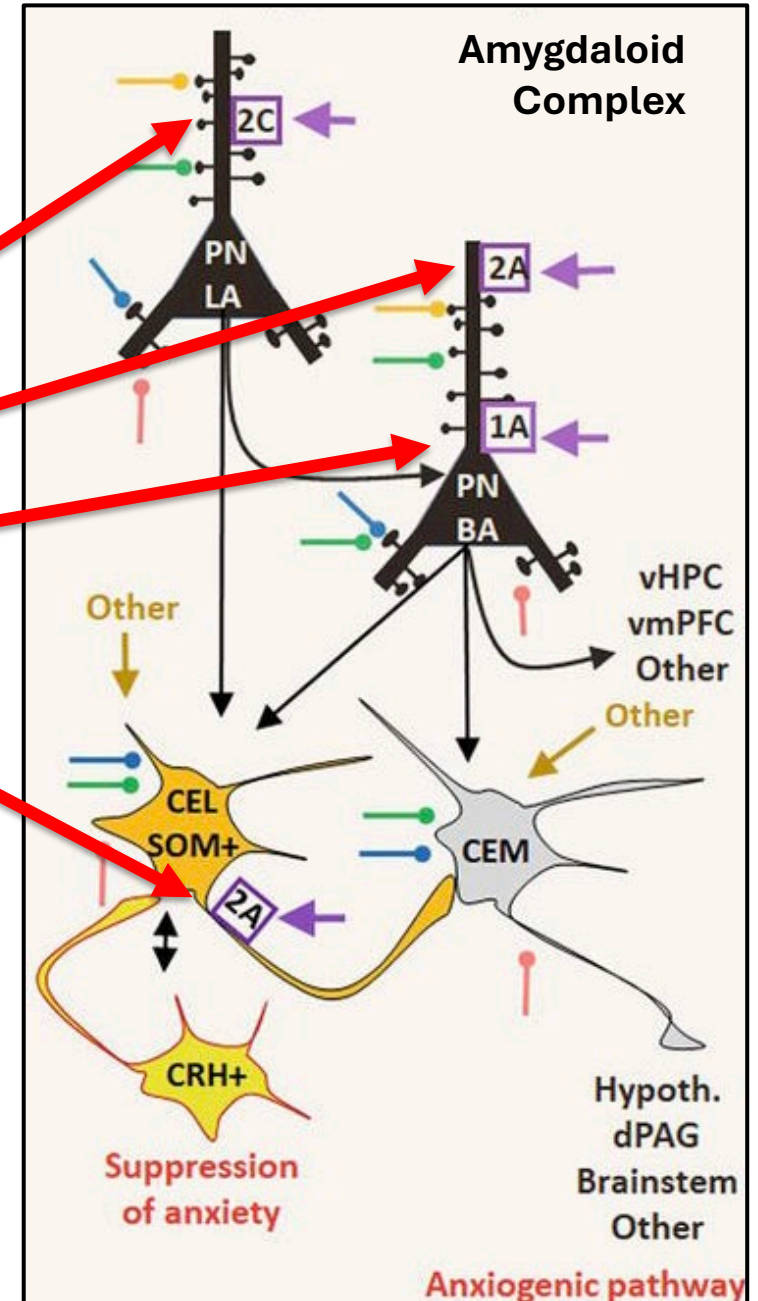


Critical Role of Serotonin in PTSD

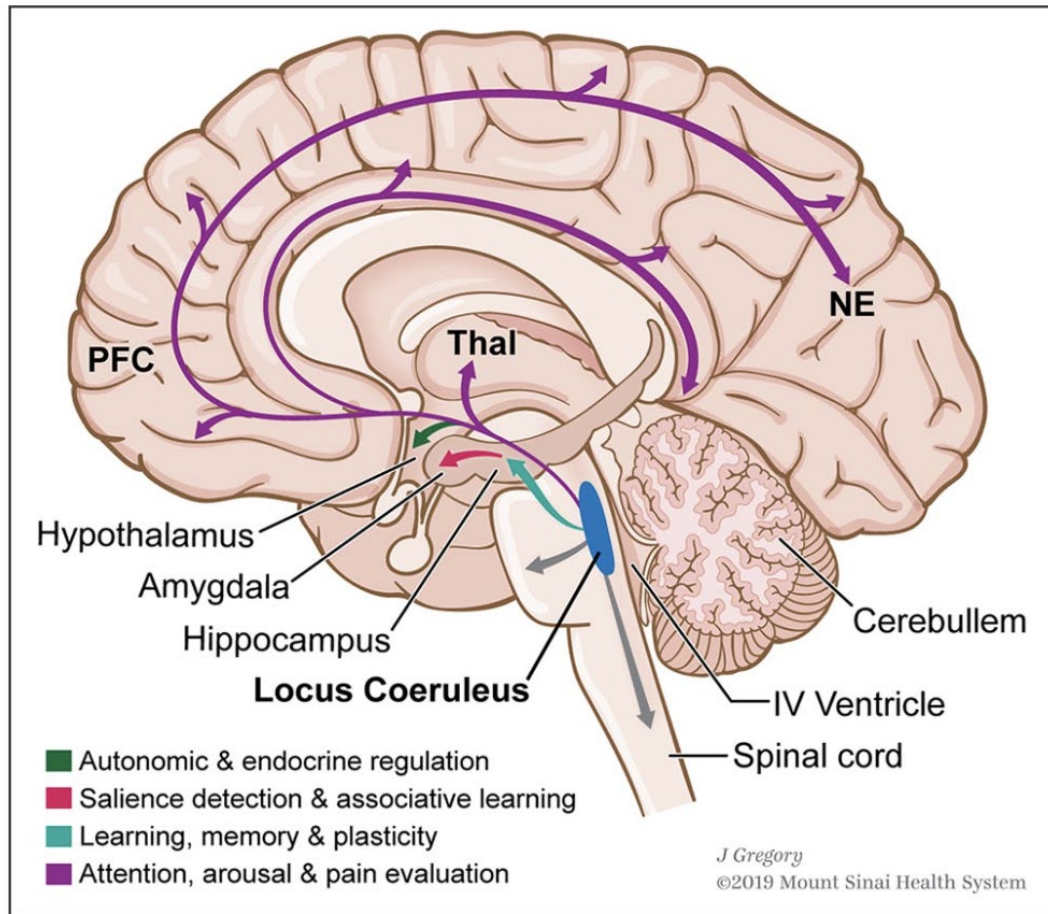
... And Why Both SSRIs and Atypicals Make Neurobiological Sense



Serotonin

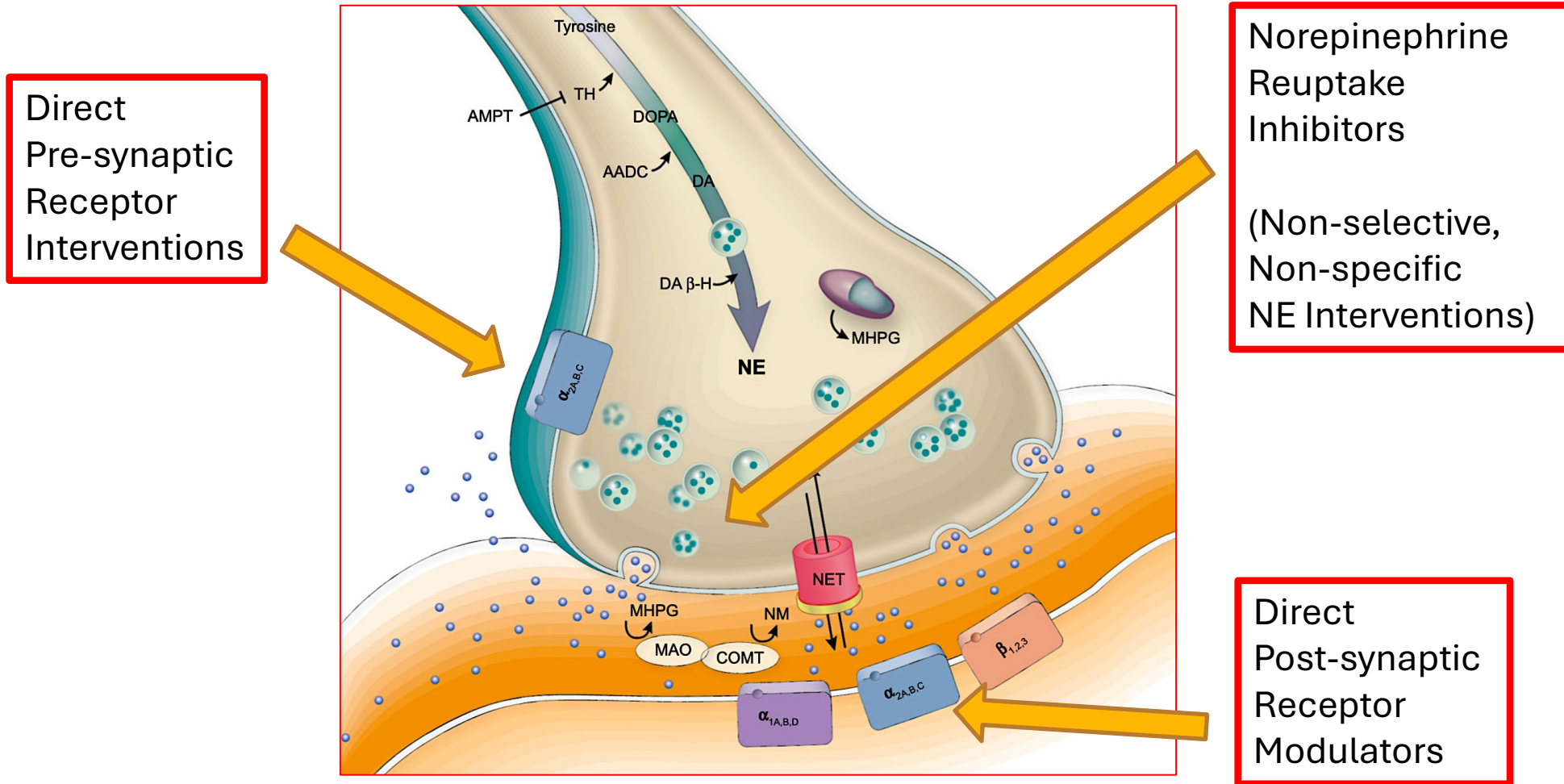


Norepinephrine (NE) and Locus Coeruleus (LC) Are Critical in PTSD



Major locus coeruleus (LC) projections throughout the central nervous system play distinct functional roles. Ascending LC projections innervate the **hypothalamus** for **autonomic** and **endocrine** regulation; the **amygdala** for salience detection and associative learning; the **hippocampus** to influence learning, memory and plasticity; and the **cortex**, for regulation of attention, arousal and the **cognitive** evaluation of **pain**. Descending LC projections (gray) reach the periaqueductal gray and other brainstem nuclei, as well as the **spinal cord**.

Moving Towards Norepinephrine Receptor Activity Modulators

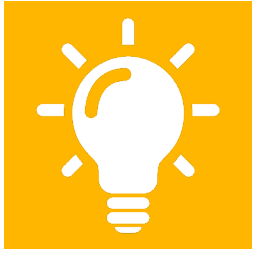


Direct
Pre-synaptic
Receptor
Interventions

Norepinephrine
Reuptake
Inhibitors

(Non-selective,
Non-specific
NE Interventions)

Direct
Post-synaptic
Receptor
Modulators



Key Learning Points

- ✓ PTSD is Mind-Body disorder with multiple implications for both other psychiatric disorders and for cardiovascular diseases
- ✓ PTSD is associated with structural and functional brain abnormalities, particularly in the amygdala, hippocampus, and medial prefrontal cortex
- ✓ Monoamines such as – 1. Serotonin, 2. Dopamine, and 3. Norepinephrine play a central role in its pathogenesis
- ✓ We need to remain mindful of this monoaminergic signaling abnormality as we employ both pharmacological and non-pharmacological interventions, with the goal of optimal patient outcomes.

Current Psychotherapies and Pharmacotherapies for PTSD



Clinical Benefits of Psychotherapy as the Initial Treatment for PTSD



International and US guidelines strongly recommend TF-CBT for first-line treatment

Several considerations must be made in order to utilize psychotherapy effectively, including

- Treatment cost
- Resource availability
- Patient preference
- Comorbidities



Treatment efficacy may be limited in clinical practice due to a combination of:

- High demand
- Limited resources
- Visit frequency needs
- HCP expertise
- Access in rural areas

Components of Trauma Focused - CBT

Therapy sessions follow a preset sequence (PRACTICE)

Psychoeducation and parenting skills

Relaxation skills

Affective regulation skills

Cognitive coping skills

Trauma narrative

In vivo mastery of trauma reminders

Cognitive processing of the traumatic events

Enhancing safety and future developmental trajectory

Treatment is broken down into 3 phases

- a) Stabilization
- b) integration, and
- c) consolidation

TF-CBT is traditionally completed within 12–15 sessions with approximately equal sessions for each of the 3 phases

For more complex trauma, treatment can be extended to up to 16 to 25 sessions

Top 10 Myths Regarding TF-CBT

1. Trauma-focused treatments are not suitable for complex/multiple trauma
2. Stabilization is always needed before memory work
3. Talking about trauma memories is 'retraumatizing'
4. Some traumas shouldn't be relived
5. CT-PTSD is a talking therapy
6. PTSD can't be treated remotely
7. Dissociation rules out work on trauma memories
8. PTSD is about fear
9. Exposure needs to be graded
10. CT-PTSD is protocolized and inflexible

EMDR in PTSD: A Broad-Spectrum Treatment

EMDR

Symptoms of PTSD ($g = 20.662$; 95% confidence interval (CI): 20.887 to 20.436),

Depression

($g = 20.643$; 95% CI: 20.864 to 20.422),

Anxiety

($g = 20.640$; 95% CI: 20.890 to 20.390)

Subjective Distress

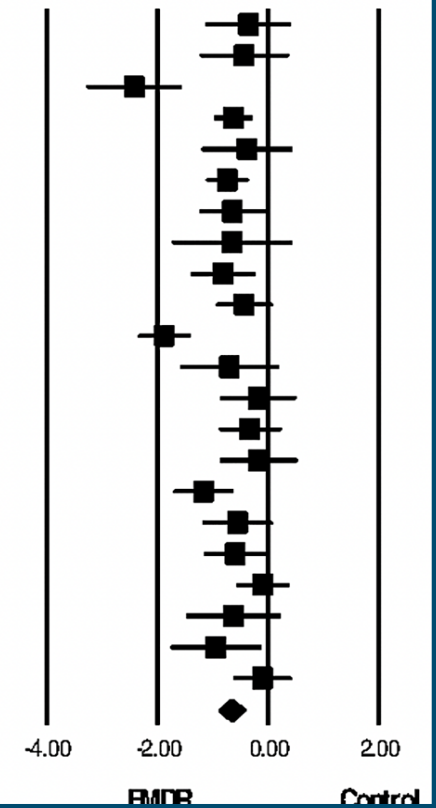
($g = 20.956$; 95% CI: 21.388 to 20.525)

Study name

Statistics for each study

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Jensen(1994)	-0.352	0.390	0.152	-1.117	0.413	-0.902	0.367
Vaughan et al.,(1994)	-0.426	0.407	0.166	-1.224	0.372	-1.047	0.295
Rothbaum et al.(1997)	-2.416	0.434	0.188	-3.267	-1.565	-5.567	0.000
Marcus et al.,(1997)	-0.627	0.175	0.031	-0.970	-0.284	-3.581	0.000
Devilley et al.,(1998)	-0.375	0.416	0.173	-1.190	0.440	-0.902	0.367
Scheck et al.,(1998)	-0.733	0.192	0.037	-1.109	-0.358	-3.826	0.000
Carlson et al.,(1998)	-0.637	0.304	0.093	-1.233	-0.041	-2.095	0.036
Rogers et al.,(1999)	-0.646	0.549	0.301	-1.723	0.430	-1.178	0.239
Devilley&Spence(1999)	-0.813	0.297	0.088	-1.395	-0.231	-2.739	0.006
Wilson et al.,(2001)	-0.425	0.254	0.065	-0.923	0.074	-1.670	0.095
Power et al.,(2002)	-1.874	0.235	0.055	-2.335	-1.413	-7.964	0.000
Ironson et al.,(2002)	-0.693	0.453	0.205	-1.581	0.195	-1.529	0.126
Chemtob et al.,(2002)	-0.179	0.346	0.120	-0.857	0.500	-0.516	0.606
Lee et al.,(2002)	-0.320	0.281	0.079	-0.870	0.230	-1.140	0.254
Lytte et al.,(2002)	-0.165	0.356	0.127	-0.862	0.533	-0.463	0.643
Jaberghaderi et al.,(2004)	-1.160	0.272	0.074	-1.692	-0.627	-4.270	0.000
Rothbaum et al.(2005)	-0.549	0.316	0.100	-1.168	0.070	-1.737	0.082
Van der Kolk et al.,(2007)	-0.587	0.285	0.081	-1.145	-0.029	-2.060	0.039
Ahmad et al.,(2007)	-0.096	0.240	0.058	-0.567	0.375	-0.400	0.689
Hogberg et al.,(2007)	-0.625	0.434	0.188	-1.476	0.226	-1.439	0.150
Kemp et al.,(2009)	-0.938	0.417	0.174	-1.755	-0.121	-2.251	0.024
Karatzias et al.,(2011)	-0.101	0.264	0.070	-0.619	0.417	-0.381	0.703
random-effect model	-0.662	0.115	0.013	-0.887	-0.436	-5.750	0.000

Hedges's g and 95% CI



Pharmacotherapy Considerations for PTSD



Summary of US Guidelines for Pharmacotherapy

Drug Class	VA/DoD Guidelines (2023)	APA Guidelines (2004)	APoA Guidelines (2019)
SSRIs	Strong For	For	For
SNRIs	Strong For	For	For
Atypical antipsychotics	Against	Insufficient Evidence	Insufficient Evidence
Tricyclic antidepressants	Insufficient Evidence + Weak	NA	NA
Alpha-1 antagonist	Weak	NA	NA
Benzodiazepines	Strong Against	NA	NA

AASM = American Academy of Sleep Medicine; APA = American Psychiatric Association; APoA = American Psychological Association; VA/DoD = US Department of Veterans Affairs and Department of Defense. Merians AN, et al. *Med Clin N Am*. 2023;107(1):85-99. U.S. Department of Veterans Affairs. 2023. Accessed October 9, 2024. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf. Ursano R, et al. Treatment of Patients With Acute Stress Disorder and Posttraumatic Stress Disorder. American Psychiatric Association. 2004. Accessed March 11, 2025. psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/acutestressdisorderptsd.pdf. American Psychological Association. *Am Psychol*. 2019;74(5):596-607.

Pharmacotherapy Is a Key Component of PTSD Management

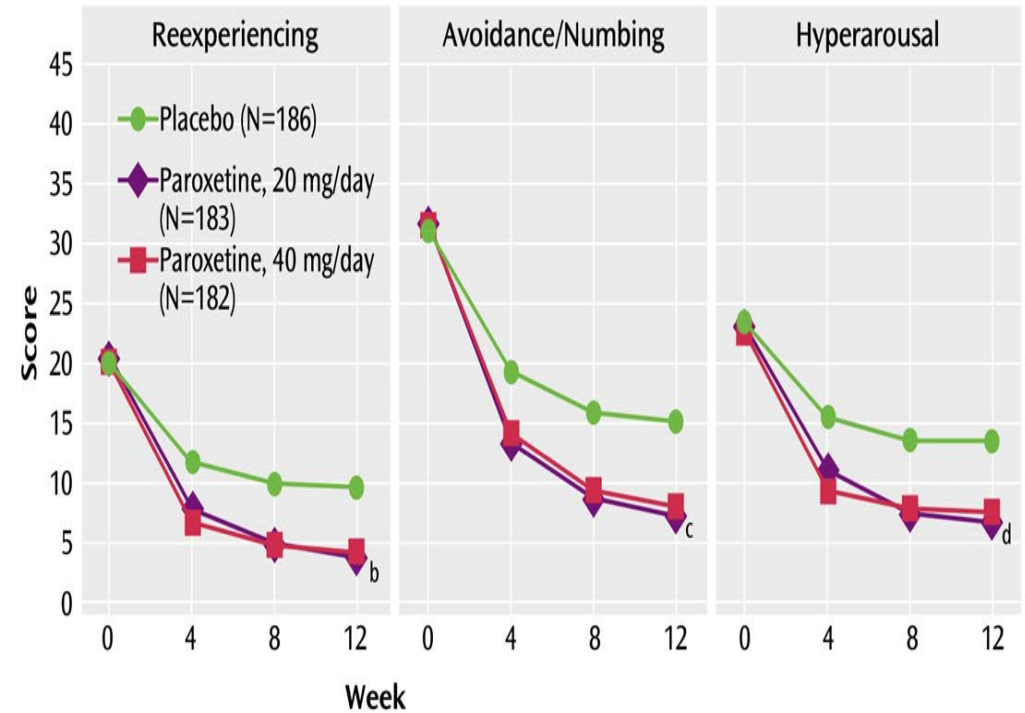
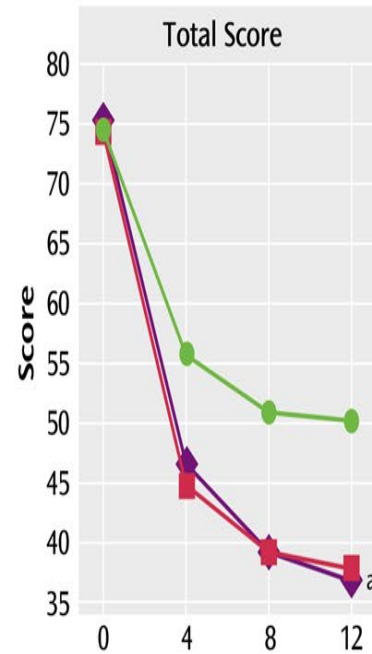
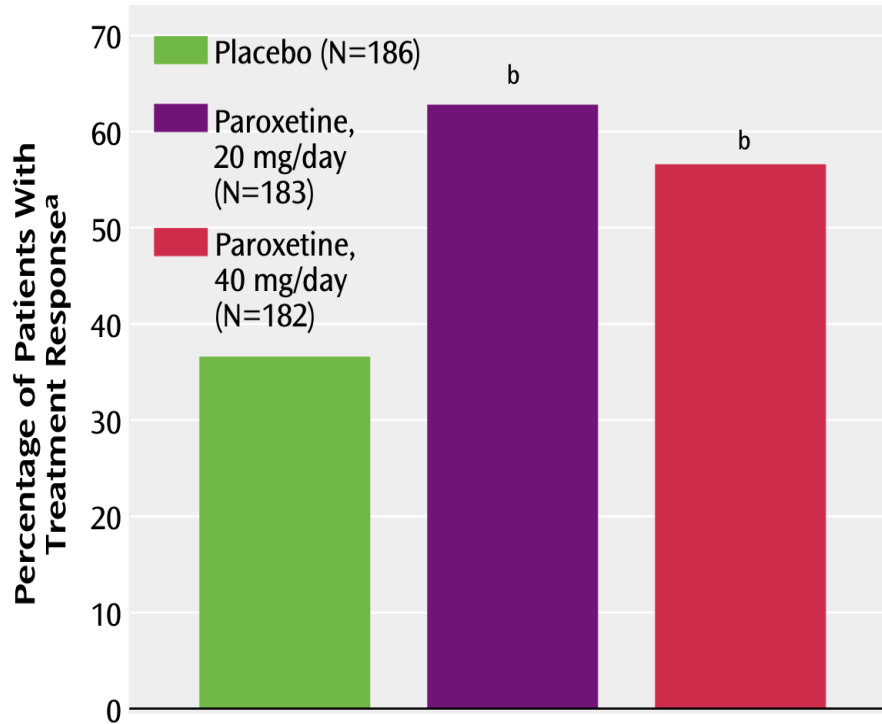
- Early and effective pharmacotherapy can improve
 - Core symptoms
 - Associated disability
 - Long-term outcomes
- Guidelines recommend SSRIs as first-line pharmacologic treatment when indicated
- ~52% of patients treated with pharmacotherapy receive SSRIs or SNRIs
- Long-term pharmacotherapy (>12 weeks) may be necessary to maintain functional improvements achieved during acute treatment period
- No new pharmacologic treatments approved for PTSD treatment in over two decades



Stein DJ, et al. *Cochrane Database Syst Rev.* 2006;1:CD002795. Williams T, et al. *Cochrane Database Syst Rev.* 2022;3(3):CD002795. Davis LL, et al. *CNS Drugs.* 2006;20(6):465-76. American Psychological Association. *Am Psychol.* 2019;74(5):596-607. Martin A, et al. *J Clin Med.* 2021;10(18):4175;. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* APA Publishing; 2013. Baldwin DS, et al. *Adv Psychiatr Treat.* 2007;13:414-22. Baldwin DS, et al. *J Psychopharmacol.* 2014;28:403-39. International Society for Traumatic Stress Studies. 2019. Accessed October 9, 2024. <https://istss.org/clinical-resources/trauma-treatment/new-istss-prevention-and-treatment-guidelines>. Cook JM, et al. *J Clin Psychol Med Settings.* 2021;28(2):221-28. U.S. Department of Veterans Affairs. 2023. Accessed July 7, 2024. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf. Yehuda R, et al. *Nat Rev Dis Primers.* 2015;1:15057.



Paroxetine in PTSD: An FDA Approved Treatment Option



The most commonly reported adverse events associated with paroxetine use (with an incidence of at least 10% and twice that of placebo) were asthenia, diarrhea, abnormal ejaculation, impotence, nausea, and somnolence. The majority of the treatment-emergent adverse events were rated as mild to moderate in severity and most occurred at the beginning of treatment.



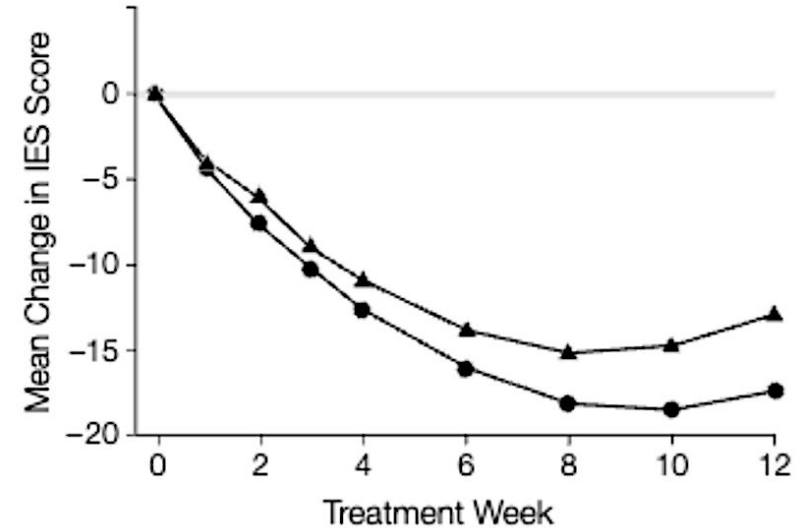
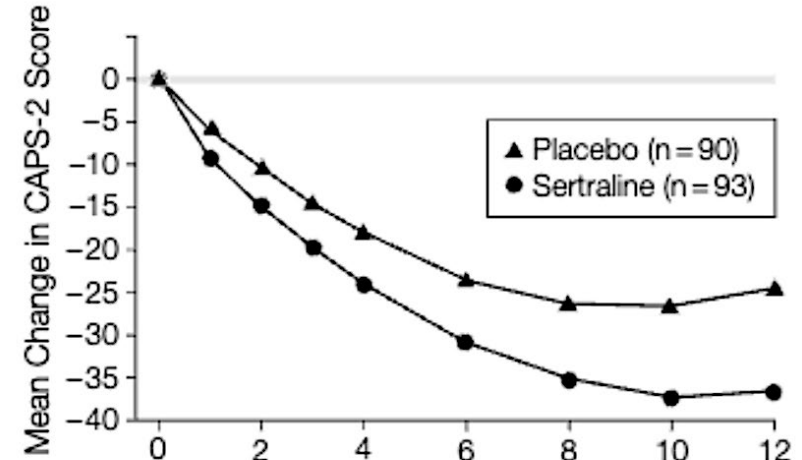
Sertraline in PTSD: An FDA Approved Treatment Option

12 weeks, double-blind, placebo-controlled study
Placebo (n=93) vs sertraline 50-200 mg (n=94)

Table 3. Effect of Study Treatment on Primary and Secondary Efficacy Measures*

Efficacy Measures (Adjusted Scores)	Mean Score		P Value
	Sertraline (n = 93)	Placebo (n = 90)	
CAPS-2 total score			
Baseline	76.6 (17.5)	75.1 (17.7)	.02
Change	-33.0 (2.8)	-23.2 (2.9)	
End point	43.4 (28.1)	51.9 (28.7)	
IES total score			
Baseline	37.7 (15.7)	36.7 (15.4)	.07
Change	-16.2 (1.6)	-12.1 (1.6)	
End point	21.0 (17.6)	24.5 (17.5)	
CGI-Severity			
Baseline	4.5 (0.73)	4.6 (0.72)	.01
Change	-1.2 (0.13)	-0.8 (0.13)	
End point	3.3 (1.3)	3.8 (1.2)	
CGI-Improvement	2.5 (0.13)	3.0 (0.14)	.02
HAM-D total score			
Baseline	21.5 (6.9)	20.2 (8.0)	.04
Change	-8.6 (1.3)	-5.0 (1.2)	
End point	13.7 (10.4)	15.8 (10.4)	
Davidson PTSD scale total score			
Baseline	71.9 (24.1)	68.5 (27.8)	.003
Change	-28.1 (2.8)	-16.1 (2.8)	
End point	43.2 (29.9)	52.2 (31.3)	

*CAPS-2 indicates Clinician Administered Posttraumatic Stress Disorder (PTSD) Scale Part 2; IES, Impact of Event Scale; CGI, Clinical Global Impression; and HAM-D, Hamilton Depression Rating Scale. A decreased CAPS-2 score represents improvement. Baseline and end point scores are mean (SD), and change scores are mean (SEM).



Examining the Challenge of Non-Recommended Treatments in PTSD



VA / DOD Guidelines for PTSD: Recommended Against / Insufficient Evidence

Treatment of PTSD: 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.
- Suggest against divalproex, guanfacine, ketamine, prazosin, risperidone, tiagabine, or vortioxetine for the treatment of PTSD.
- Recommend against benzodiazepines for the treatment of PTSD.
- Recommend against cannabis or cannabis derivatives for the treatment of PTSD.

Use of Non-Recommended Therapies

Benzodiazepines

- Not FDA Approved
- VA Guidelines discourage use
- Can worsen PTSD symptoms/reduce benefits of psychotherapy
- Addiction, dependence, disinhibition can be common

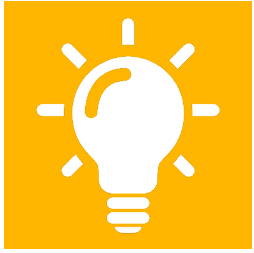
Prazosin

- Not FDA Approved
- Evidence for core PTSD symptoms limited/suboptimal
- Often used to suppress nightmares
- Twice daily dosing often needed

Unmet Needs in PTSD Treatments

- Less than 40% likelihood of patients responding adequately to FDA approved SSRIs compared to placebo with small effect sizes in 10-12 week RTC
- FDA approved treatments may not address all symptom clusters such as depressive or anxious symptoms
- Clinician and patient barriers to psychotherapy including
 - Mismatch between demand and availability of service
 - Client's may prefer treatment with medication
 - Client's may perceive therapy as not beneficial

Hoskins MD, et al. *Eur J Psychotraumatol*. 2021;12(1):1802920. Krystal JH, et al. *Biol Psychiatry*. 2017;82(7):e51–e59. Martin A, et al. *J Clin Med*. 2021;10(18):4175. Murray H, et al. *Cogn Behav Ther*. 2022;15(e33):1-15. Popiel A, et al. *J Behav Ther Exp Psychiatry*. 2015;48:17-26. Popiel A, et al. *J Behav Ther Exp Psychiatry*. 2015;48:17-26. U.S. Department of Veterans Affairs. 2023. Accessed March 11, 2025. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf. Williams T, et al. *Cochrane Database Syst Rev*. 2022;3:CD002795.



Key Learning Points

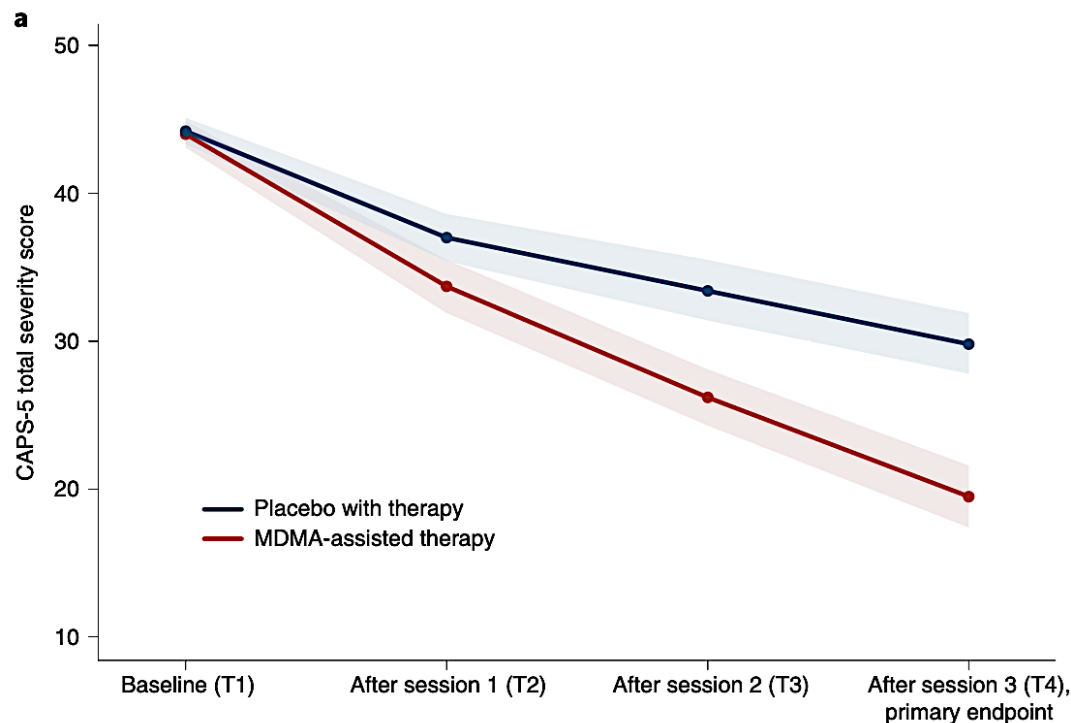
- ✓ PTSD is widely underdiagnosed and inadequately treated
- ✓ Guidelines recommend psychotherapy as first-line treatment (evidence-based, guideline-supported)
- ✓ Only two FDA-approved medications for PTSD: paroxetine and sertraline
- ✓ Avoid non-recommended treatments as these can have negative impacts
- ✓ Emerging pharmacologic treatments may soon improve unmet needs

Novel and Investigational Therapies for PTSD

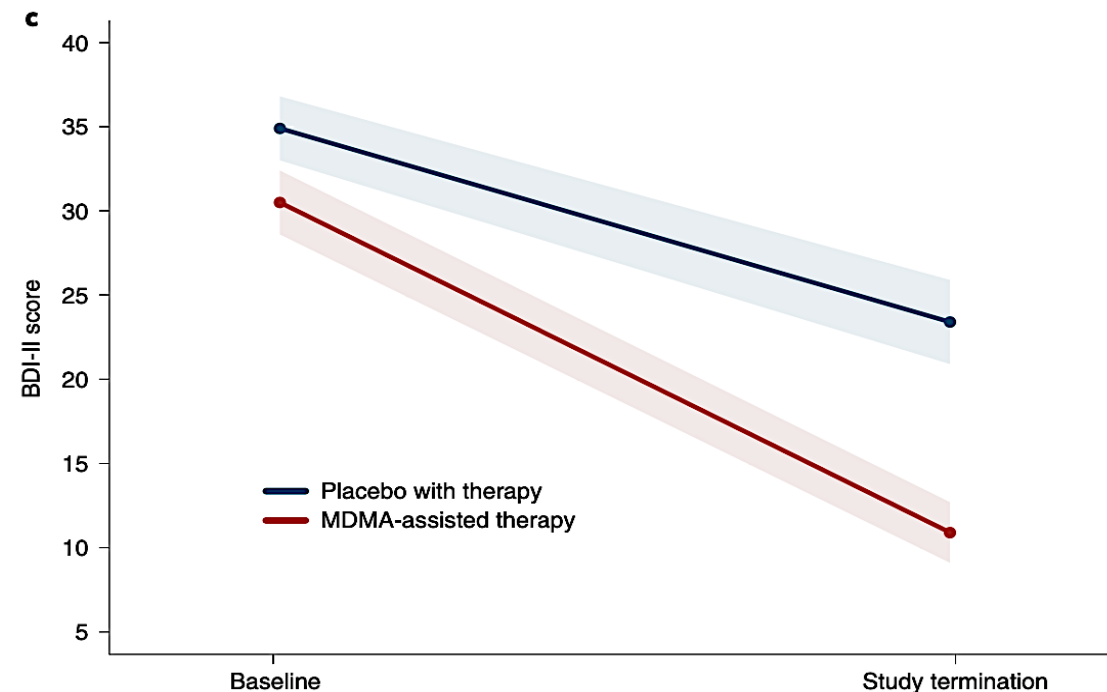


MDMA - Impressive Results from Phase 3 Study

Participants ($n = 90$) were randomized 1:1 to receive manualized therapy with MDMA or with a placebo, combined with three preparatory and nine integrative therapy sessions.



Clinician-Administered PTSD Scale for DSM-5
(CAPS-5, the primary endpoint)



The effect size of the MDMA-assisted therapy treatment compared with placebo with therapy was $d=0.91$

MDMA – Safety Signal Is Reassuring

	MDMA (n=46), n (%)	Placebo (n=44), n (%)
SAEs	-	2 (4.5)
Suicide attempts	-	1 (2.3)
Suicidal ideation resulting in self-hospitalization	-	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	-
Suicidal behavior (suicide attempts and preparatory acts) and self-harm	-	1 (2.3)
Suicidal behavior (preparatory acts), self-harm and suicidal ideation	-	1 (2.3)
Cardiac events that could indicate QT prolongation (total)	-	1 (2.3)
Irregular heartbeats and palpitations	-	1 (2.3)
Abuse potential for MDMA (total)	-	-

Safety Signal with MDMA Was Robust

Focus on Suicidality Treatment emergent adverse events (TEAEs, adverse events that occurred during the treatment period from the first experimental session to the last integration session) that were more prevalent in the MDMA study arm were typically transient, mild to moderate in severity, and included muscle tightness, decreased appetite, nausea, hyperhidrosis and feeling cold

MDMA Rx. did not induce adverse events of abuse potential, suicidality, or QT prolongation.

FDA Did Not Approve NDA for midomafetamine assisted therapy in PTSD based on data submitted.

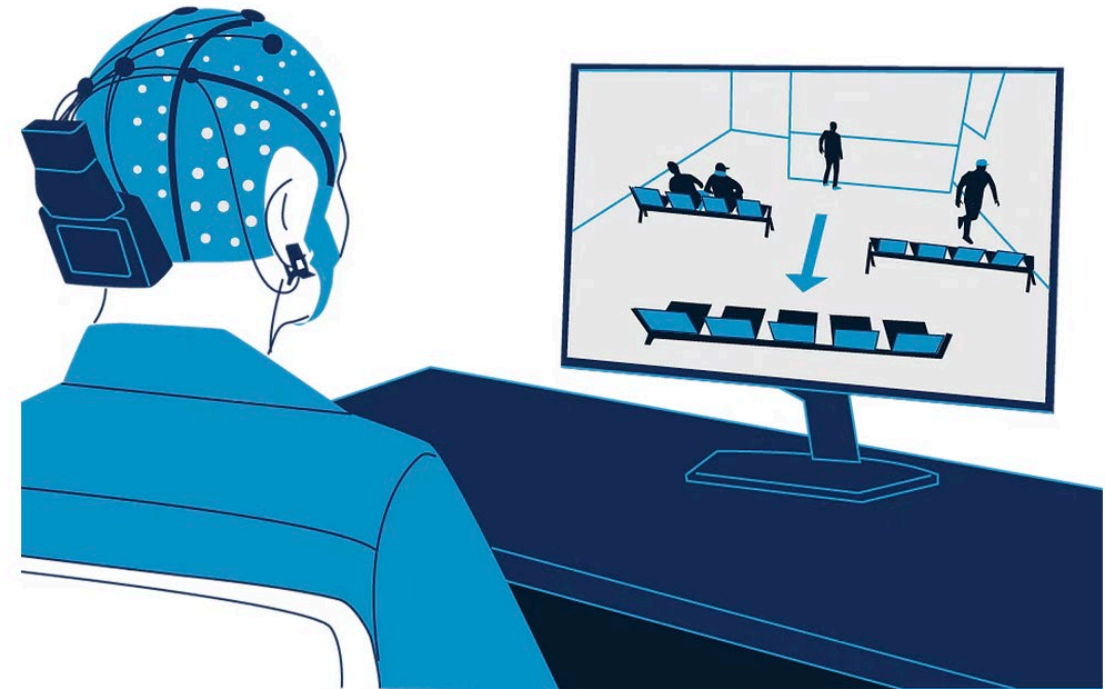
Prism Digital Biomarker-Based Neuromodulation Adjunct Dtx for PTSD

Mechanism of Action (MOA) and Rationale for Treatment of PTSD:

- **Amygdala-Based Biomarker:** Prism utilizes a proprietary amygdala-based biomarker to address PTSD symptoms. Research indicates that PTSD is associated with hyperactivity in the amygdala, the brain region involved in emotional responses. By targeting this hyperactivity, Prism aims to help patients regulate their emotional responses.
- **Self-Neuromodulation via Neurofeedback:** The device employs neurofeedback techniques, allowing patients to monitor and modulate their brain activity in real-time. During therapy sessions, patients wear an EEG headset and interact with a computer simulation. This setup enables them to learn strategies to control amygdala activity, thereby reducing PTSD symptoms.

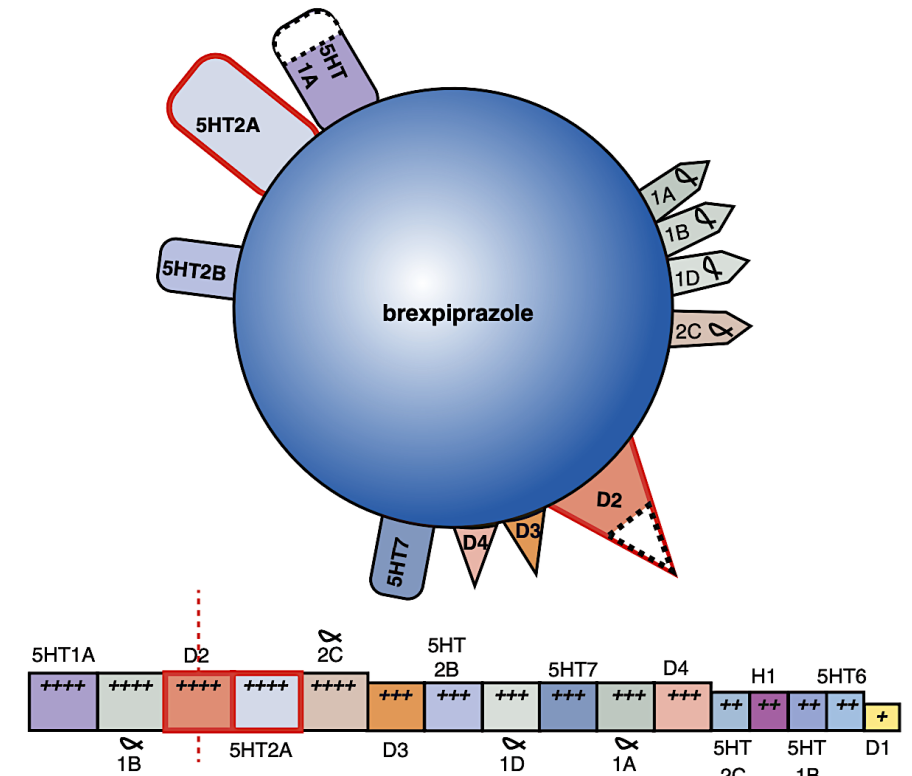
Prism Digital Biomarker-Based Device – FDA Cleared

- **Clinical Trial Outcomes:** In an open-label clinical trial involving 79 adults with chronic PTSD, participants underwent 15 neurofeedback sessions over eight weeks. The study reported that 67% of patients experienced clinically significant symptom improvement three months post-treatment, with minimal adverse effects. AE's fatigue/Headache, mild/transient and resolved without treatment
- **FDA 510(k) Clearance:** Based on the positive clinical trial results, Prism received FDA 510(k) clearance in 2023 as a prescribed adjunct therapy for PTSD.



The Case for Augmentive Brexpiprazole for PTSD

- As you recall from our previous conversation regarding the neurobiology of PTSD, all three monoamines are implicated in its pathophysiology
 - Serotonin
 - Dopamine
 - Norepinephrine



Based on the pathophysiology of PTSD, and brexpiprazole high potency, triple monoaminergic effects, there is logical reason to believe there might be synergetic effects in combining an SSRI with brexpiprazole.

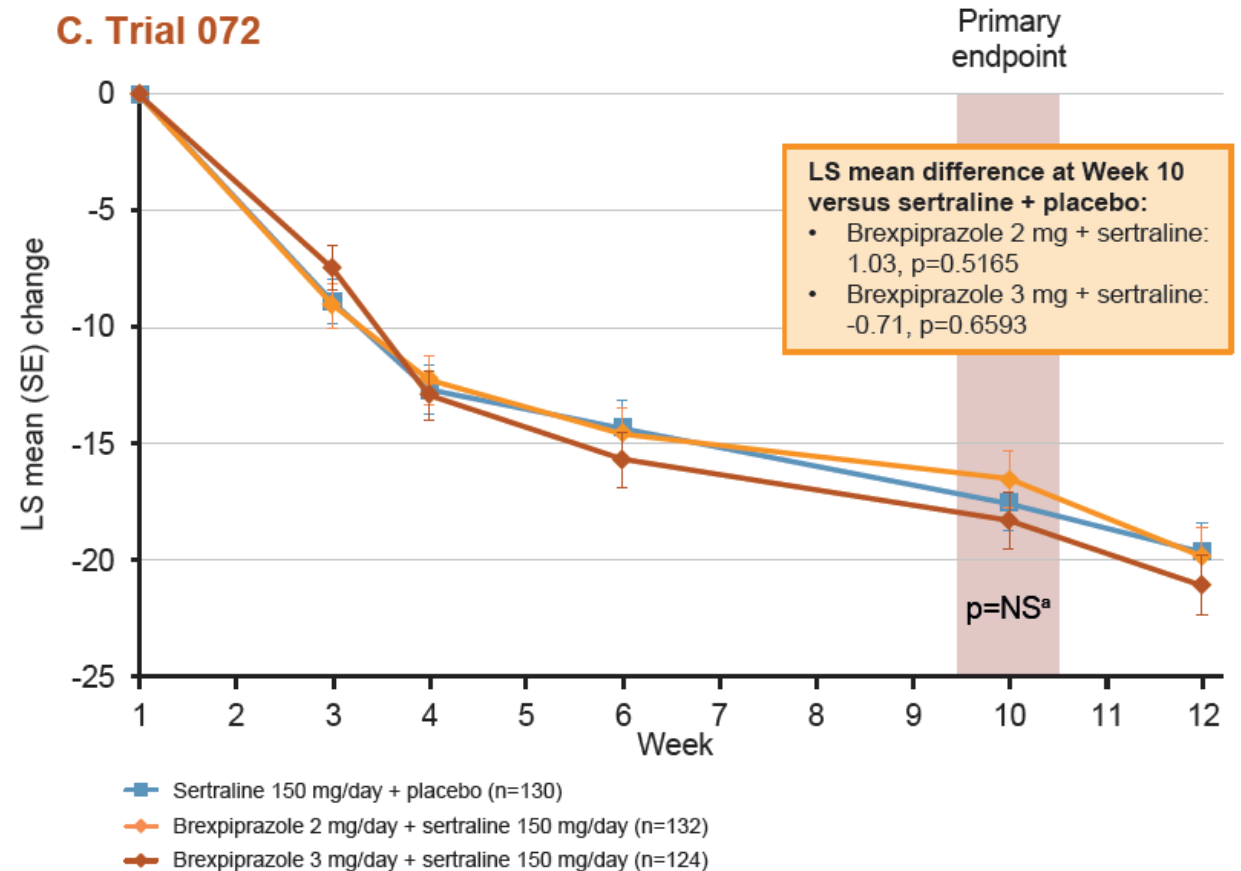
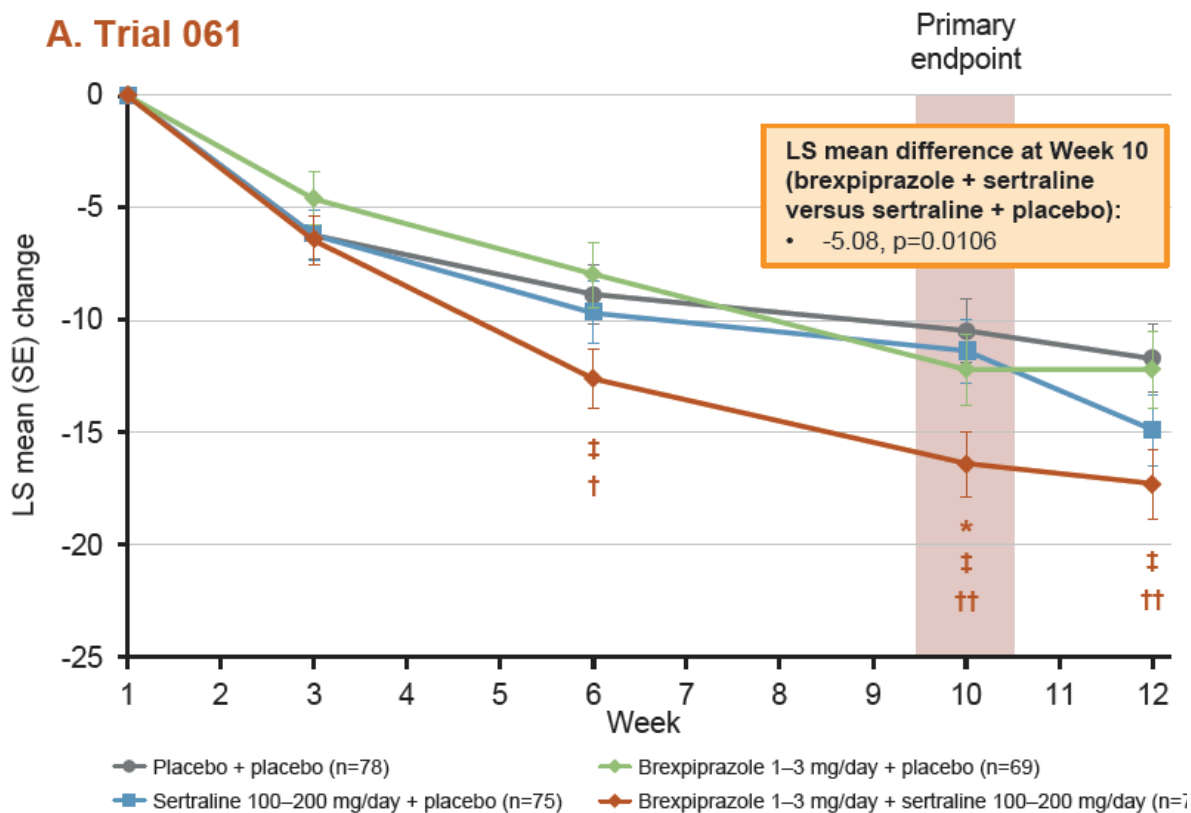
Could Adding an Atypical to an SSRI Help Treat PTSD?

Two Phase 3 clinical trials of brexpiprazole as combination therapy with sertraline for the treatment of post-traumatic stress disorder (PTSD):

- The first trial was a Phase 3, randomized, double-blind, 2-arm, flexible dose trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (2 - 3 mg/day) as combination therapy with sertraline in 416 randomized adult subjects with PTSD. (Study is positive and met the $p < 0.05$ threshold)
- The second trial was a Phase 3, randomized, double-blind, 3-arm, fixed dose trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (2 or 3 mg/day) as combination therapy with sertraline in 553 randomized adult subjects with PTSD. (Study failed to meet $p < 0.05$)
- A phase II study was also positive.

Brexpiprazole + Sertraline (Efficacy)

Three separate trials in PTSD. Primary endpoint: Change from randomization (Week 1) to Week 10 in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total score.

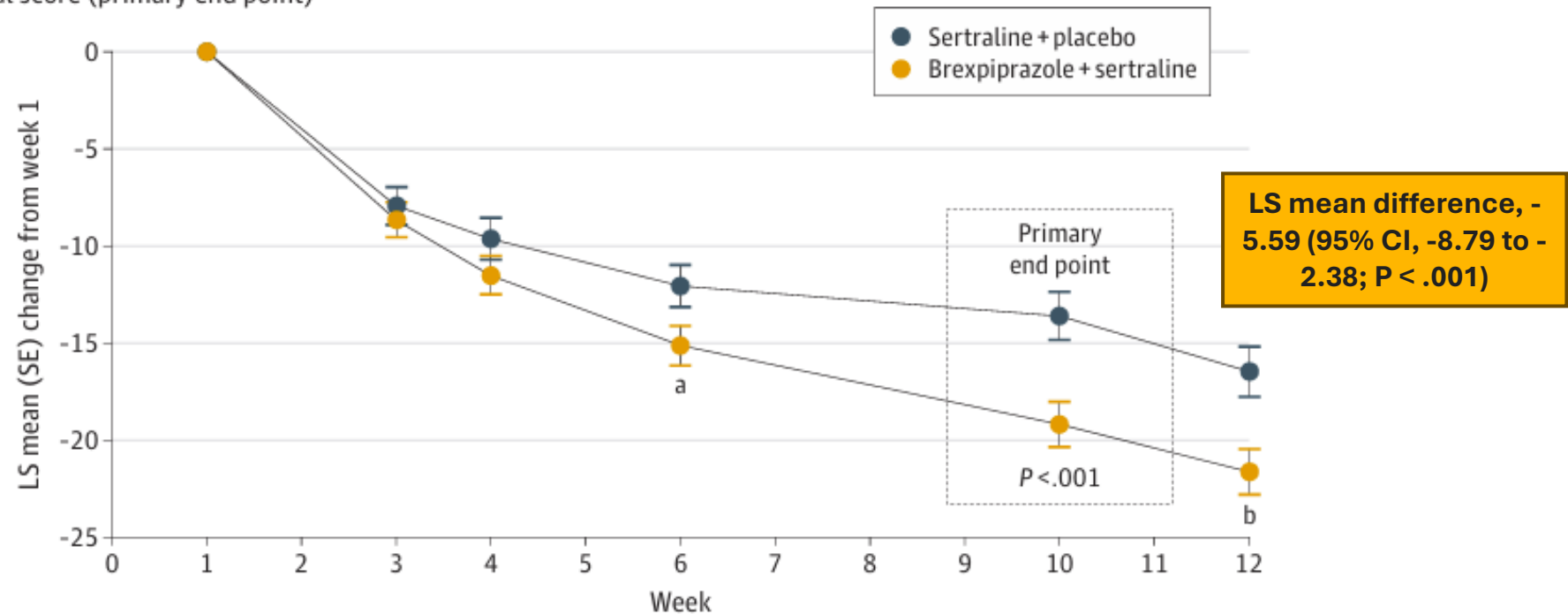


Brexpiprazole + Sertraline Showed Statistically Significant Greater Improvement vs Placebo + Sertraline in Phase 3 Trial

Change in CAPS-5 total score

A CAPS-5 total score (primary end point)

Trial 071

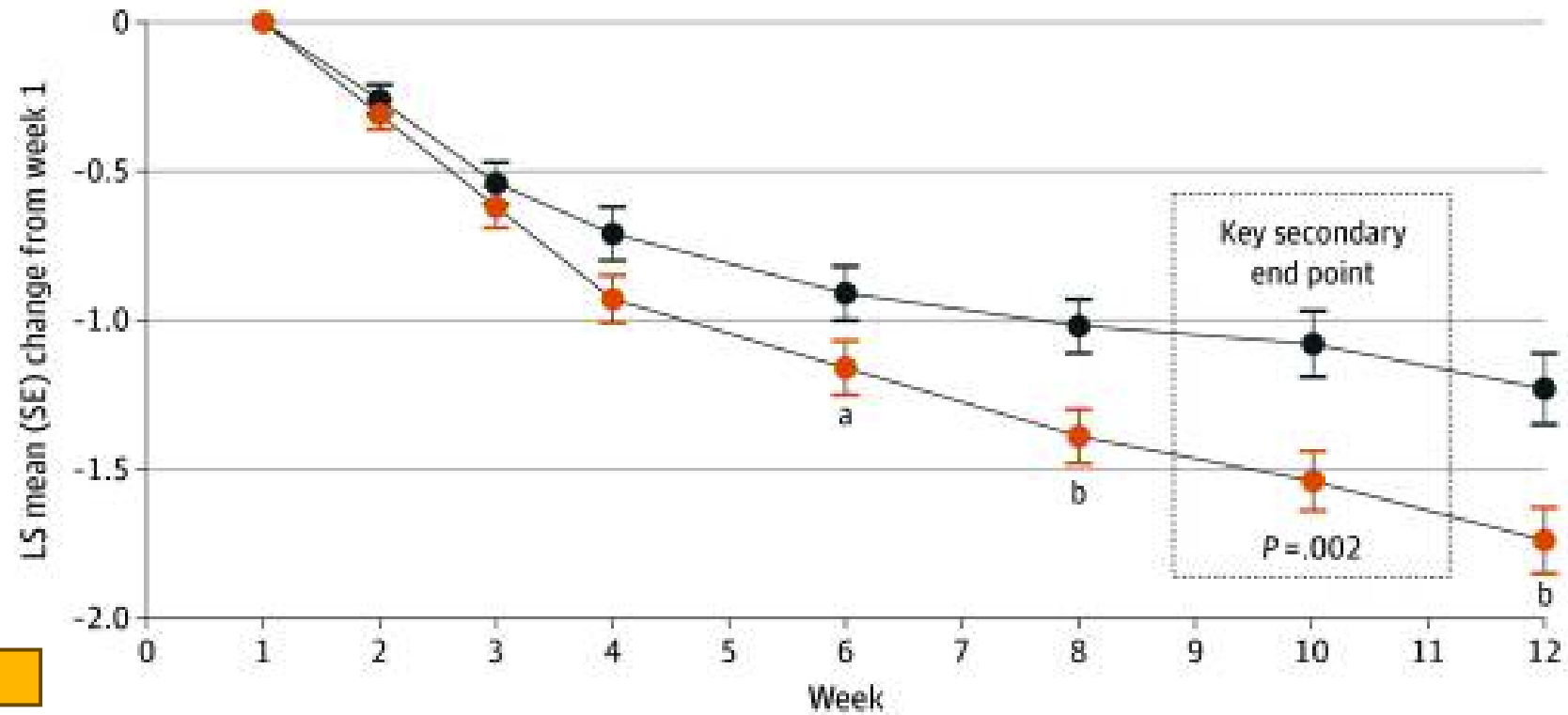


LS mean difference, -5.59 (95% CI, -8.79 to -2.38; P < .001)

No. of patients						
Sertraline + placebo	134	125	125	109	87	81
Brexpiprazole + sertraline	148	140	141	126	95	99

Key Secondary End Points

B CGI-S score (key secondary end point)

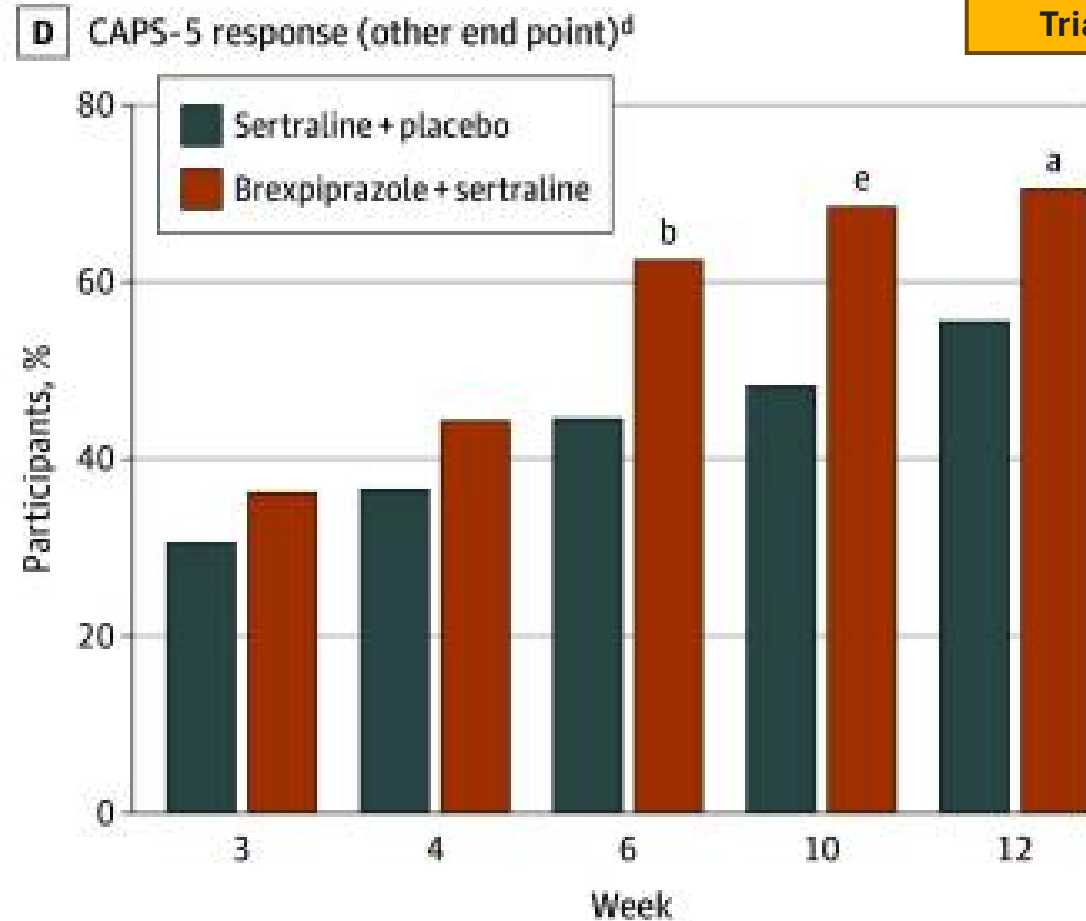
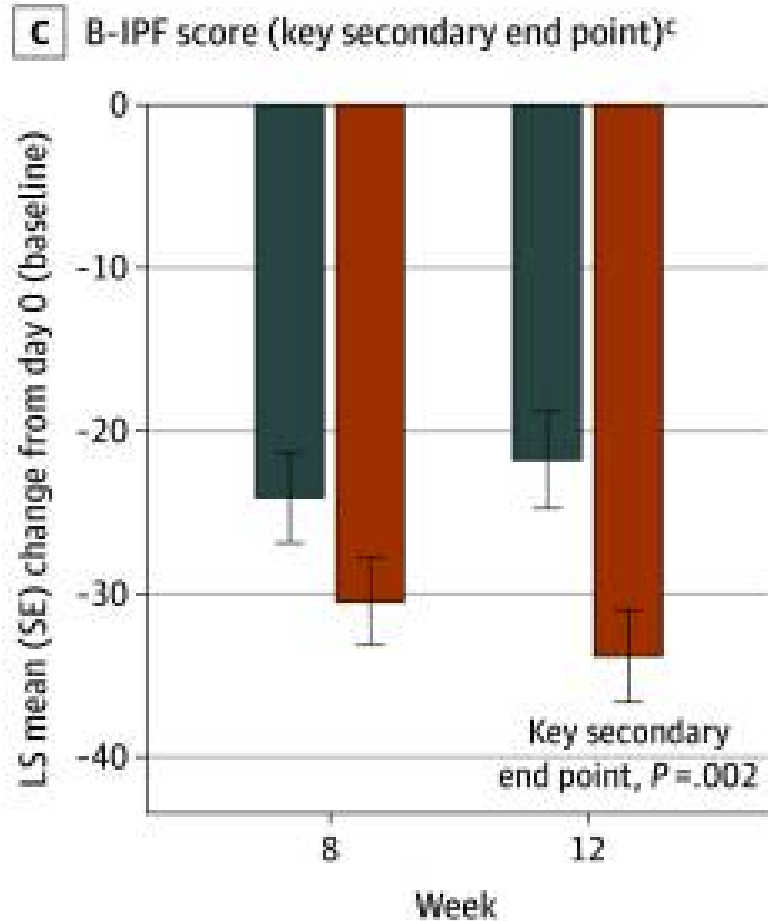


Trial 071

No. of patients

Sertraline + placebo	137	135	126	127	109	99	89	83
Brexpiprazole + sertraline	148	141	137	142	124	119	99	99

Key Secondary End Points



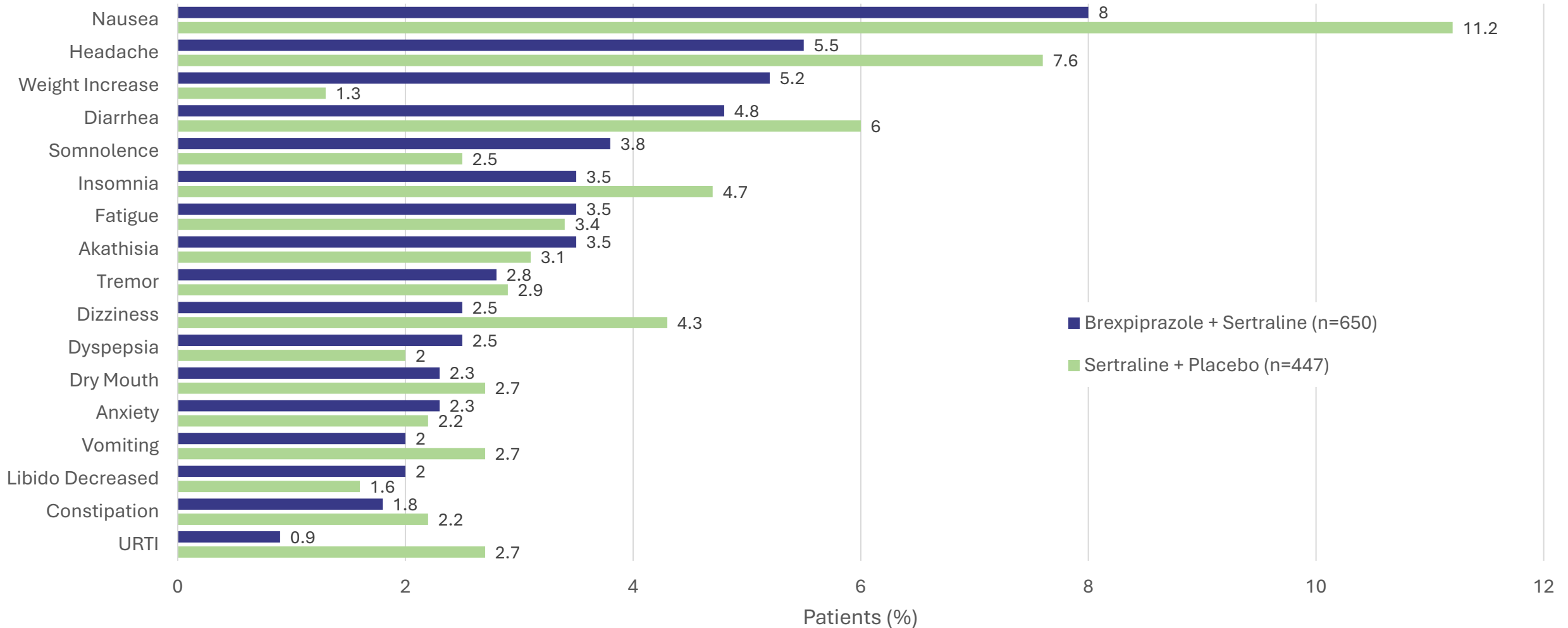
Brexpiprazole + Sertraline (Safety)

Three separate trials in PTSD. Primary endpoint: Change from randomization (Week 1) to Week 10 in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total score.

	Pooled Data (Trials 061, 071, 072)	
	Sertraline + Placebo (n=447)	Brexpiprazole + Sertraline (n=650)
Patients with at least one TEAE	251(56.2%)	361(55.5%)
Serious TEAEs	7(1.6%)	5(0.8%)
Severe TEAEs	13(2.9%)	15(2.3%)
Discontinuation due to AEs	31(6.9%)	26(4.0%)
Deaths	1(0.2%)	1(0.2%)

Brexpiprazole + Sertraline (Safety)

Most Frequent TEAEs in Trials 061, 071, and 072 Pooled



Current Status of Brexpiprazole+Sertraline

- The sNDA for brexpiprazole + sertraline for the indication of PTSD was accepted by the FDA on April 8th, 2024
- PDUFA Date: Pending FDA review and advisory committee input, possibly later half of 2025.

Current Status Investigational; not FDA-approved for PTSD.

sNDA = supplemental New Drug Application. PDUFA = Prescription Drug User Fee Act. Otsuka Pharmaceutical Co., Ltd., & Lundbeck. June 2024. Otsuka and Lundbeck announce FDA acceptance of sNDA filing for brexpiprazole in combination with sertraline for the treatment of adults with PTSD. Lundbeck. [<https://www.lundbeck.com/us/newsroom/2024/otsuka-and-lundbeck-announce-fda-acceptance-of-snda-filing-for-brexiprazole>].



Key Learning Points

- ✓ Atypicals – e.g. brexpiprazole, have evidence for helping in addressing PTSD symptoms
 - ✓ In Trial 071, sertraline + brexpiprazole led to significantly greater improvements than sertraline + placebo in total PTSD symptoms measured with the CAPS-5, overall PTSD severity (measured with the CGI-S), and psychosocial functioning (measured with the B-IPF)
- ✓ Both efficacy and side-effects of treatment options should be equally addressed by the thoughtful, trauma informed care provider.
- ✓ Novel digital therapies such as Prism offers an adjunct to standard of care in PTSD.

Optimizing Treatment for Patients with PTSD



Tailoring and Monitoring Treatment in PTSD

- PTSD varies by **symptom clusters**, allowing for **more individualized treatment**
- Understanding **neurobiology** guides personalized care
- Aligning treatment with **patient preferences** (psychotherapy, psychopharmacology) improves outcomes

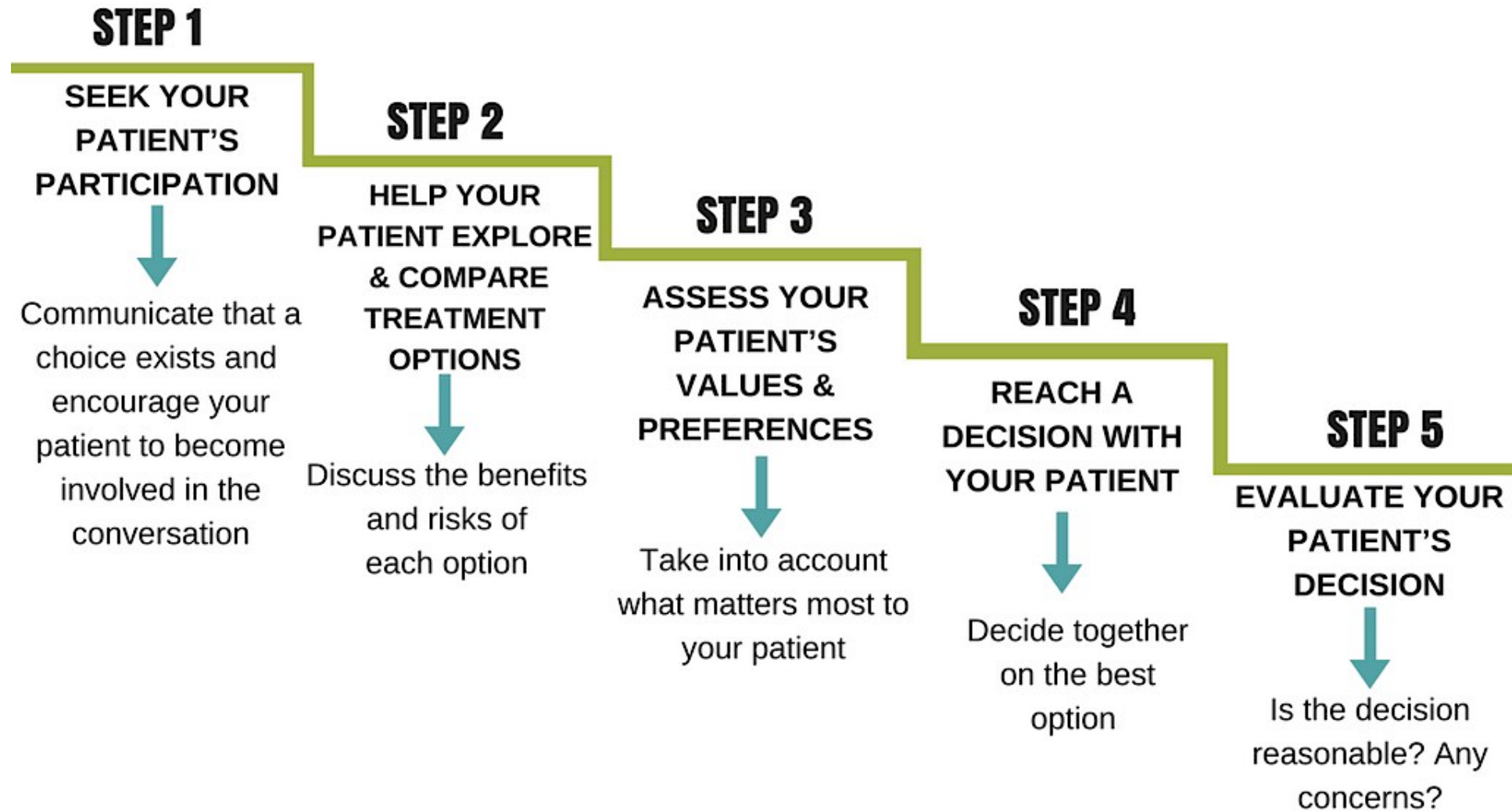


Shared Decision-Making

Shared Decision-Making (SDM) is a collaborative process in which clinicians and patients jointly select treatments, integrating the patient's preferences and values with the best available clinical evidence. This approach emphasizes patient autonomy and active participation in their own care.



Essential Steps of Shared Decision-Making



Patient Advocate Perspectives



Practical Takeaways



PTSD is a Mind-Body disorder associated with multiple comorbidities, including both psychiatric disorders and physical conditions such as cardiovascular disease



Shared decision-making is more likely to result in patients choosing evidence-based treatment options



Screening tools help clinicians identify PTSD, enabling a more accurate assessment and diagnostic process



Tailoring and monitoring treatment outcomes better addresses individual treatment needs

Questions?

