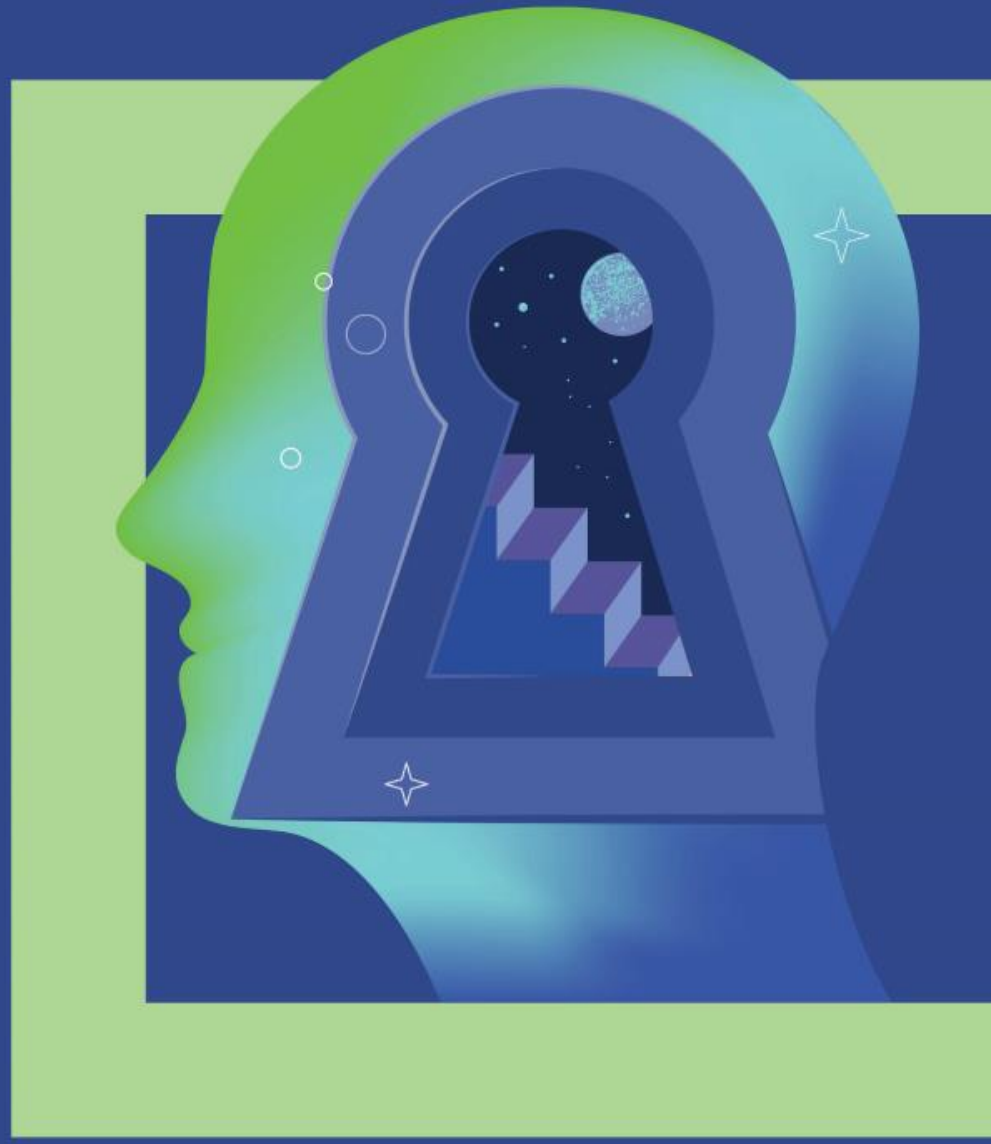
Unlocking Hope:
Novel Perspectives on PTSD Assessment and Treatment



Supported by an independent educational grant from Otsuka America Pharmaceutical, Inc.

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Faculty Disclosures

- **Rakesh Jain:** AbbVie (Allergan): Consultant (Ongoing)|AbbVie (Allergan): Grant/Research Support (Ongoing)|AbbVie (Allergan): Speaker's Bureau (Ongoing)|Acadia: Consultant (Ongoing)|Adamas: Advisory Board (Ongoing)|Adamas: Consultant (Ongoing)|Alfasigma: Consultant (Ongoing)|Alkermes: Advisory Board (Ongoing)|Alkermes: Consultant (Ongoing)|Alkermes: Speaker's Bureau (Ongoing)|Almatica: Consultant (Ongoing)|Almatica: Speaker's Bureau (Ongoing)|Axsome Therapeutics, Inc.: Consultant (Ongoing)|Axsome Therapeutics, Inc.: Speaker's Bureau (Ongoing)|Biogen: Consultant (Ongoing)|Boehringer Ingelheim: Consultant (Ongoing)|Cingulate Therapeutics: Consultant (Ongoing)|Corium: Advisory Board (Ongoing)|Corium: Consultant (Ongoing)|Corium: Speaker's Bureau (Ongoing)|Eisai: Advisory Board (Ongoing)|Eisai: Consultant (Ongoing)|Eisai: Speaker's Bureau (Ongoing)|Evidera: Consultant (Ongoing)|Impel: Consultant (Ongoing)|Indivior: Speaker's Bureau (Ongoing)|Intra-Cellular Therapies: Speaker's Bureau (Ongoing)|Ironshore: Speaker's Bureau (Ongoing)|Janssen: Advisory Board (Ongoing)|Janssen: Consultant (Ongoing)|Janssen: Speaker's Bureau (Ongoing)|Lilly: Advisory Board (Ongoing)|Lilly: Consultant (Ongoing)|Lilly: Grant/Research Support (Ongoing)|Lilly: Speaker's Bureau (Ongoing)|Lundbeck: Advisory Board (Ongoing)|Lundbeck: Consultant (Ongoing)|Lundbeck: Grant/Research Support (Ongoing)|Lundbeck: Speaker's Bureau (Ongoing)|Merck: Advisory Board (Ongoing)|Merck: Consultant (Ongoing)|Merck: Speaker's Bureau (Ongoing)|Neos Therapeutics: Advisory Board (Ongoing)|Neos Therapeutics: Consultant (Ongoing)|Neos Therapeutics: Speaker's Bureau (Ongoing)|Neurocrine Biosciences: Advisory Board (Ongoing)|Neurocrine Biosciences: Consultant (Ongoing)|Neurocrine Biosciences: Speaker's Bureau (Ongoing)|Osmotica: Consultant (Ongoing)|Otsuka: Advisory Board (Ongoing)|Otsuka: Consultant (Ongoing)|Otsuka: Grant/Research Support (Ongoing)|Otsuka: Speaker's Bureau (Ongoing)|Pamlab: Advisory Board (Ongoing)|Pamlab: Consultant (Ongoing)|Pamlab: Speaker's Bureau (Ongoing)|Pfizer, Inc.: Advisory Board (Ongoing)|Pfizer, Inc.: Consultant (Ongoing)|Pfizer, Inc.: Grant/Research Support (Ongoing)|Pfizer, Inc.: Speaker's Bureau (Ongoing)|Sage Therapeutics: Advisory Board (Ongoing)|Sage Therapeutics: Consultant (Ongoing)|Shire: Advisory Board (Ongoing)|Shire: Consultant (Ongoing)|Shire: Grant/Research Support (Ongoing)|Shire: Speaker's Bureau (Ongoing)|Sumitomo: Consultant (Ongoing)|Sumitomo: Speaker's Bureau (Ongoing)|Sunovion: Advisory Board (Ongoing)|Sunovion: Consultant (Ongoing)|Sunovion: Speaker's Bureau (Ongoing)|Supernus: Advisory Board (Ongoing)|Supernus: Consultant (Ongoing)|Takeda: Advisory Board (Ongoing)|Takeda: Consultant (Ongoing)|Takeda: Grant/Research Support (Ongoing)|Takeda: Speaker's Bureau (Ongoing)|Teva Pharmaceuticals: Advisory Board (Ongoing)|Teva Pharmaceuticals: Consultant (Ongoing)|Teva Pharmaceuticals: Speaker's Bureau (Ongoing)|Transcend Therapeutics: Consultant (Ongoing)|Tris Pharmaceuticals: Speaker's Bureau (Ongoing)|Usona: Advisory Board (Ongoing)|Viatris: Consultant (Ongoing)|Viatris: Speaker's Bureau (Ongoing)
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Disclosure

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- This activity has been independently reviewed for balance.

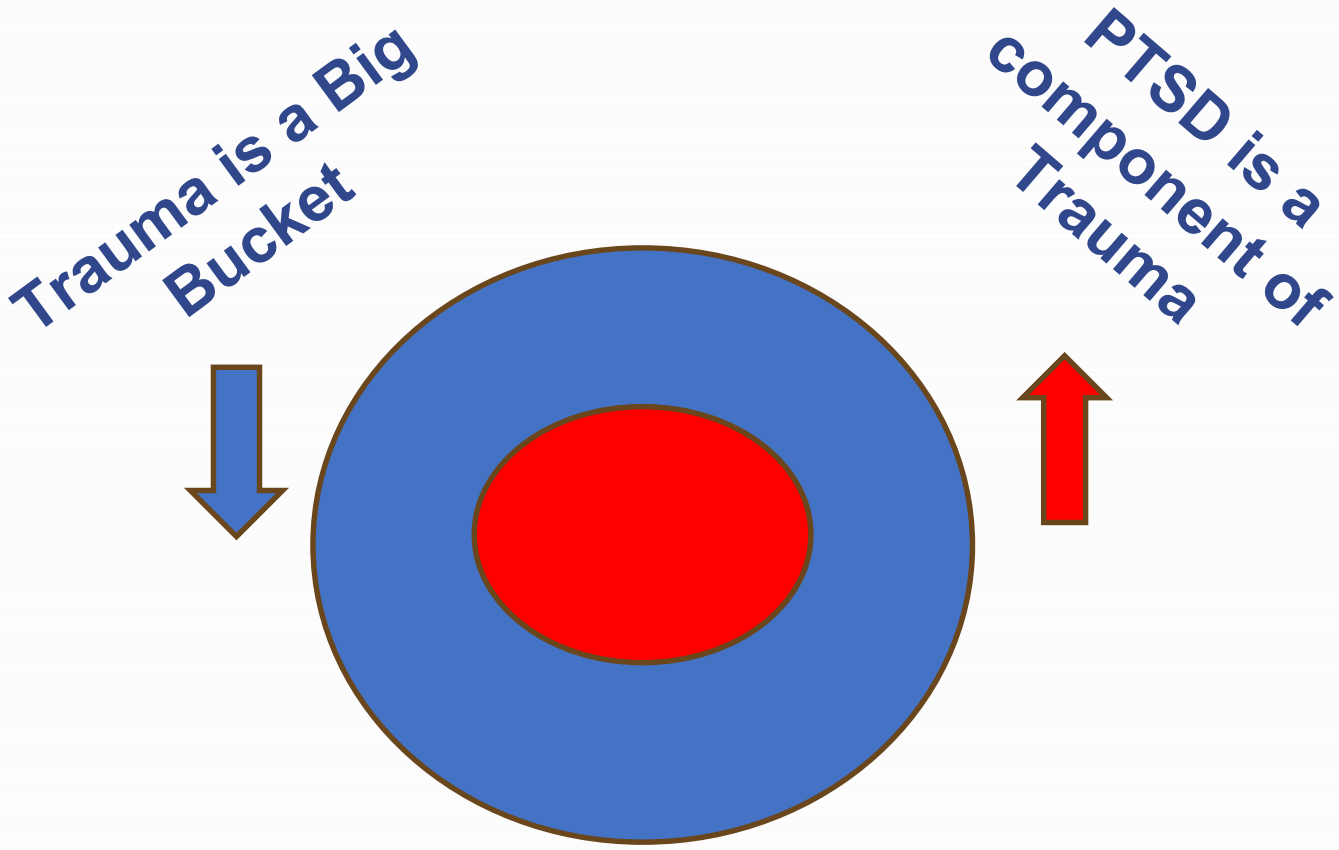
Learning Objectives

- Assess the prevalence and burden of PTSD, including its stigma, risk factors, and other drivers, and the scope of its presenting symptoms
- Identify PTSD using validated, guideline-recommended screening tool
- Evaluate the most recent data associated with current and emerging therapies for PTSD
- Implement strategies to ensure timely referral to specialty care for patients presenting with complex PTSD

Introduction to PTSD and the Role of Primary Care In Patient Identification and Support

What Is Trauma, and Where Does PTSD Fit into Its Ecosphere?

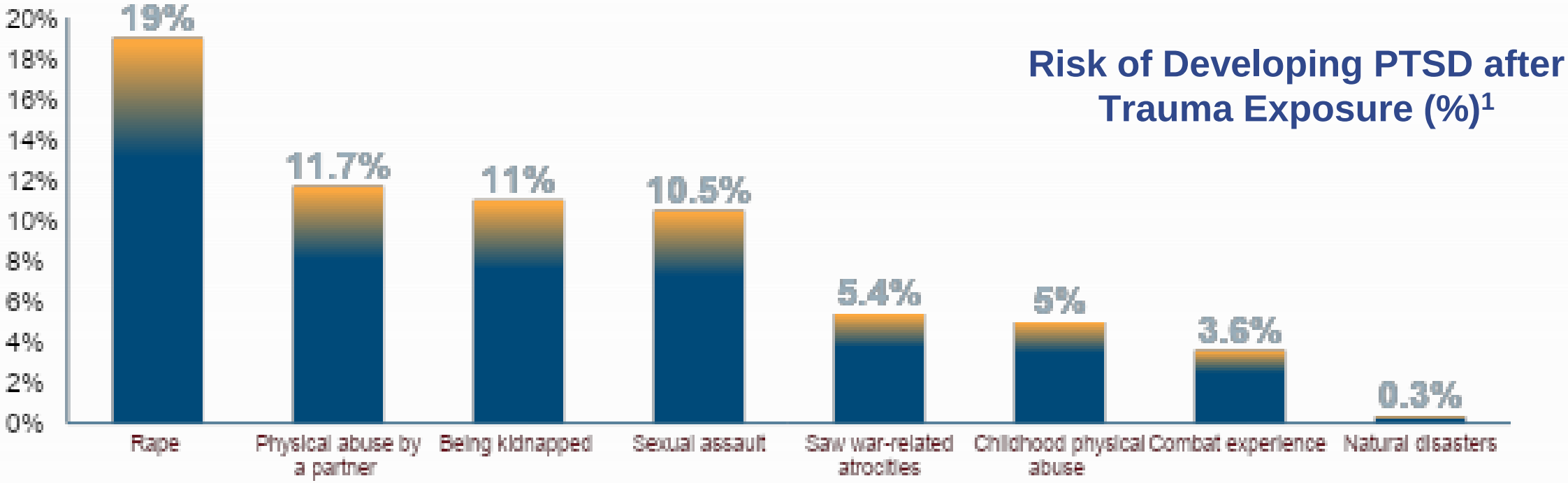
Definition of Trauma - Trauma is the lasting emotional response that often results from living through a distressing



COVID-19 = coronavirus disease 2019.

Kessler RC, et al. *Eur J Psychotraumatology*. 2017;8(suppl 5):1353383. Liu H, et al. *JAMA Psychiatry.* 2017;74(3):270-281. Luz MP, et al. *J Psychiatr Res*. 2016;72:51-57. Tortella-Feliu M, et al. *Neurosci Biobehav Rev.* 2019;10:154-165. Yunitri N, et al. *Int J Nurs Stud.* 2022;126:104136.

PTSD: Is It Common in Clinical Practice?



The average risk of developing PTSD after a traumatic exposure ranges from 4% to 30%, varying by trauma type

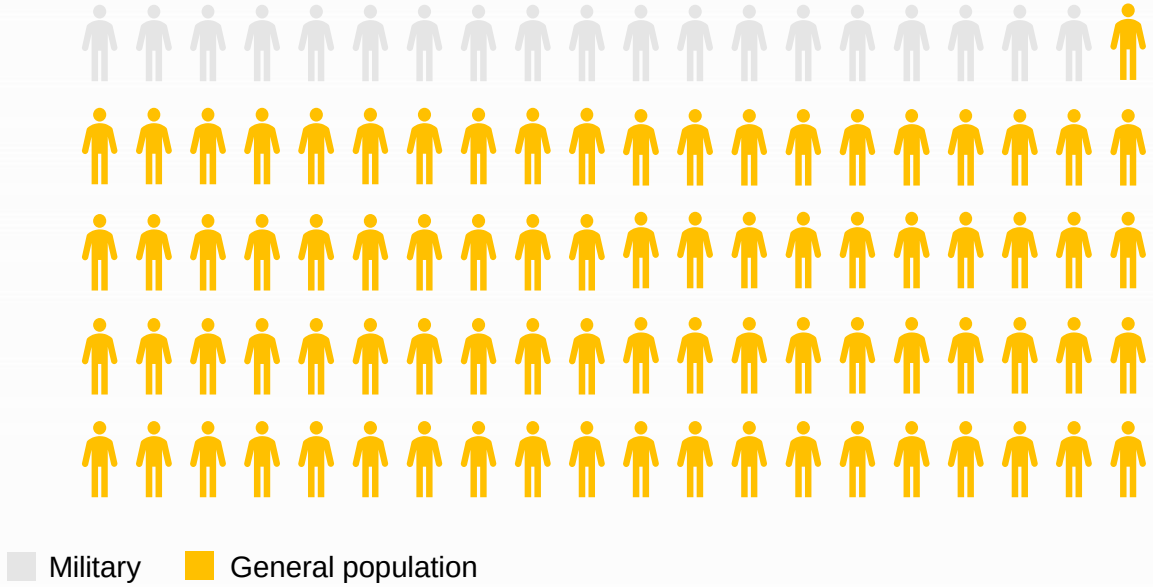
COVID-19=coronavirus disease 2019.

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

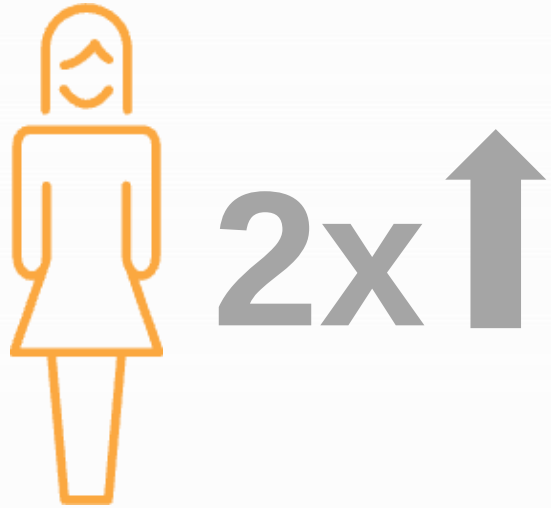
Liu H, et al. *JAMA Psychiatry.* 2017;74(3):270-281. Luz MP, et al. *J Psychiatr Res*. 2016;72:51-57. Tortella-Feliu M, et al. *Neurosci Biobehav Rev.* 2019;10:154-165. Yunitri N, et al. *Int J Nurs Stud.* 2022;126:104136.

Most Cases of PTSD Occur in the General (Non-Military) Population, and more Frequently in Women

More than 80% of patients with PTSD are in the general population[1-3]



Incidence of PTSD is 2x higher in women than men[1,4]



~13 million adults in the United States will experience PTSD during a given year (~4.9%)*[4-8]

*In 2022[7]

1. Davis LL, et al. *J Clin Psychiatry*. 2022;83(3):21m14116; 2. United Nations Department of Economic and Social Affairs. 2019. Accessed October 9, 2023. https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf; 3. Kessler RC, et al. *Arch Gen Psychiatry*. 2005;62(6):617-627; 4. Kilpatrick DG, et al. *J Trauma Stress*. 2013;26:537-547. 5. Lehavot K, et al. *Am J Pre Med.* 2018;54(1):e1-e9. 6. US Census Bureau. (2022). National Population by Characteristics: 2020-2022. Accessed September 28, 2024. https://www.census.gov/data/tables/time-series/demo/popest/2020s-national-detail.html. Data on file; 7. Data on file (Prevalence Estimate); 8. U.S. Department of Veterans Affairs. 2023. Accessed October 9, 2023. www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf

There Are Many Risk Factors for the Development of Trauma-Related Psychiatric Challenges

Demographic Risk Factors

Female Sex

Women are 2–4 times more likely than men to develop PTSD, after adjusting for the traumatic event [1,2,7,10]

Low Socioeconomic Status

Individuals with a lower socioeconomic status have an increased risk of PTSD[1,2,4]

LGBTQ+

Some studies suggest higher rates of PTSD many such individuals

Other Risk Factors

Personal Trauma

Prior history of trauma and overall volume of traumatic events are predictive of future trauma exposure and PTSD development[1,3,4,7,9]

Occupational Risk

Military personnel, particularly those in active combat, and first responders have a greater likelihood of exposure to traumatic events and PTSD development.[1,2,9]

Genetics[a]

SNP-based heritability for PTSD has been estimated as 5-20%, with some variance by sex.[1,8]

Substance Abuse

Reciprocal risk[2,9]

CNS = central nervous system; SNP = single nucleotide polymorphisms.
A = **Potential epigenetic modifications associated with PTSD are also under exploration**

1. Sareen J. PTSD in Adults: Epidemiology, pathophysiology, clinical manifestations, course, assessment, and diagnosis. Accessed August 2023. www.uptodate.com/contents/posttraumatic -stress-disorder-in-adults-epidemiology-pathophysiology-clinical-manifestations-course-assessment-and-diagnosis; 2. Vieweg WV, et al. *Am J Med* 2006; 119:383; 3. Kroll J. *JAMA* 2003;290:667; 4. Ayazi T, et al. *BMC Psychiatry* 2012;12:175; 5. Roberts AL, et al. *Psychological Med* 2011;41(1), 71–83; 6. Spoont M, McClendon J. Accessed August, 2023. www.ptsd.va.gov/publications/rq_docs/V31N4.pdf; 7. Kessler RC, et al. *Eur J Psychotraumatol.* 2017;8(sup5): 1353383; 8. Nievergelt CM, et al. *Nature Commun.* 2019;10(1):1-16; 9. Mayo Clinic. Post-Traumatic Stress Disorder (PTSD) Overview. Accessed August, 2023. www.mayoclinic.org/diseases-conditions/post-traumatic-stress-disorder/symptoms-causes/syc-20355967; 10. Goldstein RB, et al. *Soc Psychiatry Psychiatr Epidemiol.* 2016;51:1137-1148.

Mind-Body Ramifications of Trauma Related Disorders

Nervous system

- Memory
- Cognition
- Stress symptoms

Immune system

- Suppression of pro-inflammatory cytokines
- Regulation of immune cell maturation, migration, and apoptosis

Cardiovascular system

- Cardiovascular and metabolic disease

Reproductive system

- Epigenetic transmission

Take Home Message: Trauma and Trauma related disorders are true Mind-Body disorders. Keeping this in mind is an imperative for every clinician encountering patients with such disorders.

Yehuda, et al. *Nat Rev Dis Primers.* 2015;1:15057.

Psychiatric Comorbidities Are Common Among Individuals with PTSD

As Demonstrated by National Surveys Data:

~80-90%

Meet criteria for at least one other psychiatric disorder

~40-60%

Have three or more other psychiatric diagnoses

Most Common Comorbidities:

Affective Disorders (Depression)

- **~50% individuals had comorbid major depressive disorder**

Anxiety Disorders

- **Individuals have 2.4 -7.1 higher odds of having an anxiety disorder**

Substance Use Disorder

- **~46% met criteria for a substance use disorder**

Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues Clin Neurosci.* 2015;17(2):141-150. Nijdam MJ, et al. The role of major depression in neurocognitive functioning in patients with posttraumatic stress disorder. *Eur J Psychotraumatol.* 2013;4:10.3402/ejpt.v4i0.19979. Dutra SJ, et al. Reward ameliorates posttraumatic stress disorder-related impairment in sustained attention. *Chronic Stress (Thousand Oaks).* 2018;2: 2470547018812400. Brady KT, et al. Comorbidity of psychiatric disorders and posttraumatic stress disorder. *J Clin Psychiatry*. 2000;61(suppl 7):22-32.

PTSD Is Characterized by Four Symptom Clusters and Diagnosed Using DSM-5 Criteria

A. Exposure to trauma

B. ≥1 Intrusion (re-experiencing) symptoms

- Recurrent, involuntary, and intrusive distressing memories
- Recurrent distressing dreams
- Dissociative reactions (eg, flashbacks)
- Intense or prolonged psychological distress to external/internal cues
- Marked physiological reactions to external/internal cues

+

C. ≥1 Persistent avoidance of stimuli

- Avoidance of or efforts to avoid distressing memories, thoughts, or feelings
- Avoidance of or efforts to avoid external reminders that arouse distressing memories, thoughts, or feelings

+

D. ≥2 Negative alterations in cognition and mood

- Inability to remember
- Persistent or exaggerated bad feelings
- Persistent, distorted cognitions
- Persistent negative emotional state
- Marked diminished interest
- Feelings of detachment or estrangement from others
- Persistent inability to experience positive emotions

+

E. ≥2 Marked alterations in arousal and reactivity

- Irritable behavior and angry outbursts
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle response
- Problems with concentration
- Sleep disturbance

F. Duration of symptoms ≥1 month

G. Symptoms cause clinically significant distress or functional impairment

H. Symptoms are not attributable to another medical condition

***DSM-5 = Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.**

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. APA Publishing; 2013. Mann SK, Marwaha R. Posttraumatic Stress Disorder. In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 30, 2023.

Screening for PTSD

PC-PTSD-5 Screening Tool

What type of trauma have you experienced?

In the past month, have you …

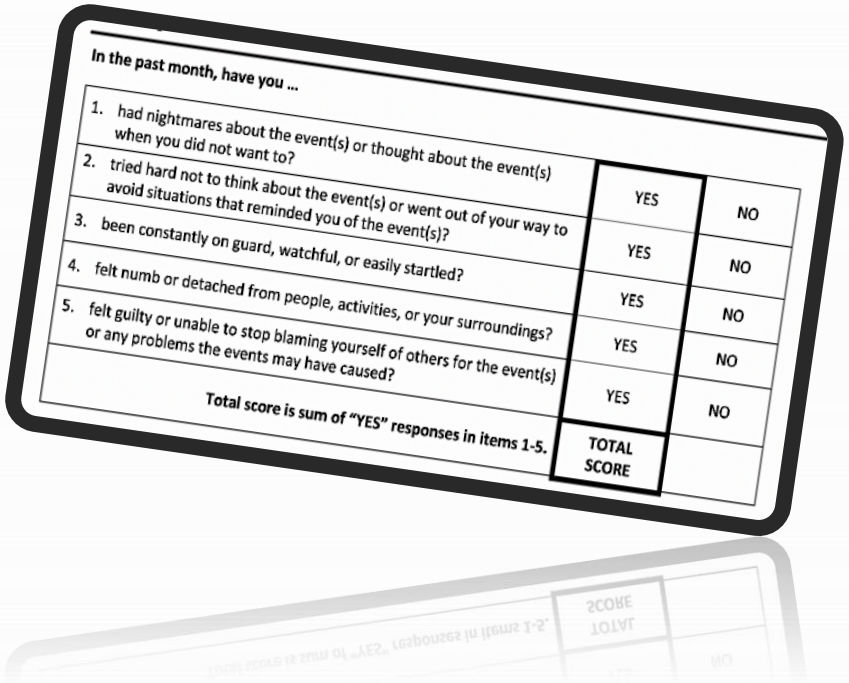
1. Had nightmares above the event(s) or thought about the event(s) when you did not want to?	YES	NO
2. Tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)?	YES	NO
3. Been constantly on guard, watchful, or easily startled?	YES	NO
4. 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**	

PC-PTSD-5 = Primary Care PTSD Screen for DSM-5.

National Center for PTSD. Primary Care PTSD Screen for DSM-5 (PC-PTSD-5). 2022. Accessed July 7, 2024. https://www.ptsd.va.gov/ professional/assessment/documents/pc-ptsd5-screen.pdf. Prins A, et al. *J Gen Int Med.* 2016;31(10):1206-11.

How Is PC-PTSD-5 Scored?

- Respondents can score a 0-5, which is a count of "yes" responses to the 5 questions below.
- Research in a large sample of VA primary care patients found that a cut-point of 4 ideally balanced false negatives and false positives for the overall sample and for men.
- However, for women, a cut-point of 4 resulted in high numbers of false negatives.
- Practitioners may consider a lower cut-point for women in some settings if evaluation resources are available.



In the past month, have you ...		
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 of others for the event(s) or any problems the events may have caused?	YES	NO
Total score is sum of "YES" responses in items 1-5.	TOTAL SCORE	

Prins A, et al. *J Gen Int Med.* 2016;31(10):1206-11.

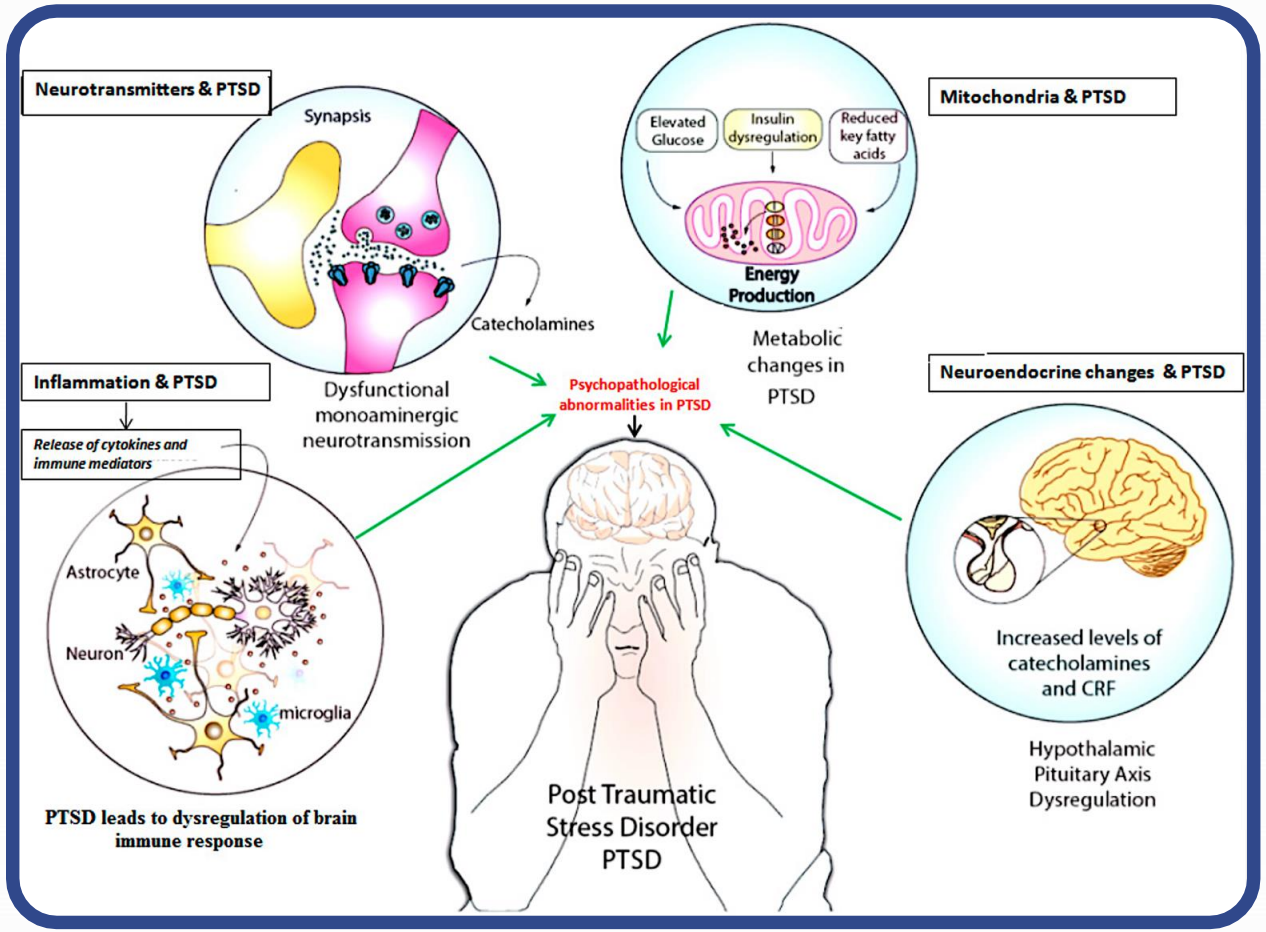
Section 1:
Conclusion & Key Learning Points

- ✓ PTSD is common in primary care practices
- ✓ PTSD is often missed, perhaps mostly because it often presents with common co-morbidities of major depression, anxiety disorders, insomnia, substance misuse, etc.
- ✓ PTSD is hugely impairing and its early diagnosis – facilitated by routine screening – is warranted
- ✓ PTSD is a very disabling condition, and majority of cases are in the non-combat populations, in ‘regular’ civilian life

General Pathophysiology of PTSD

PTSD 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.

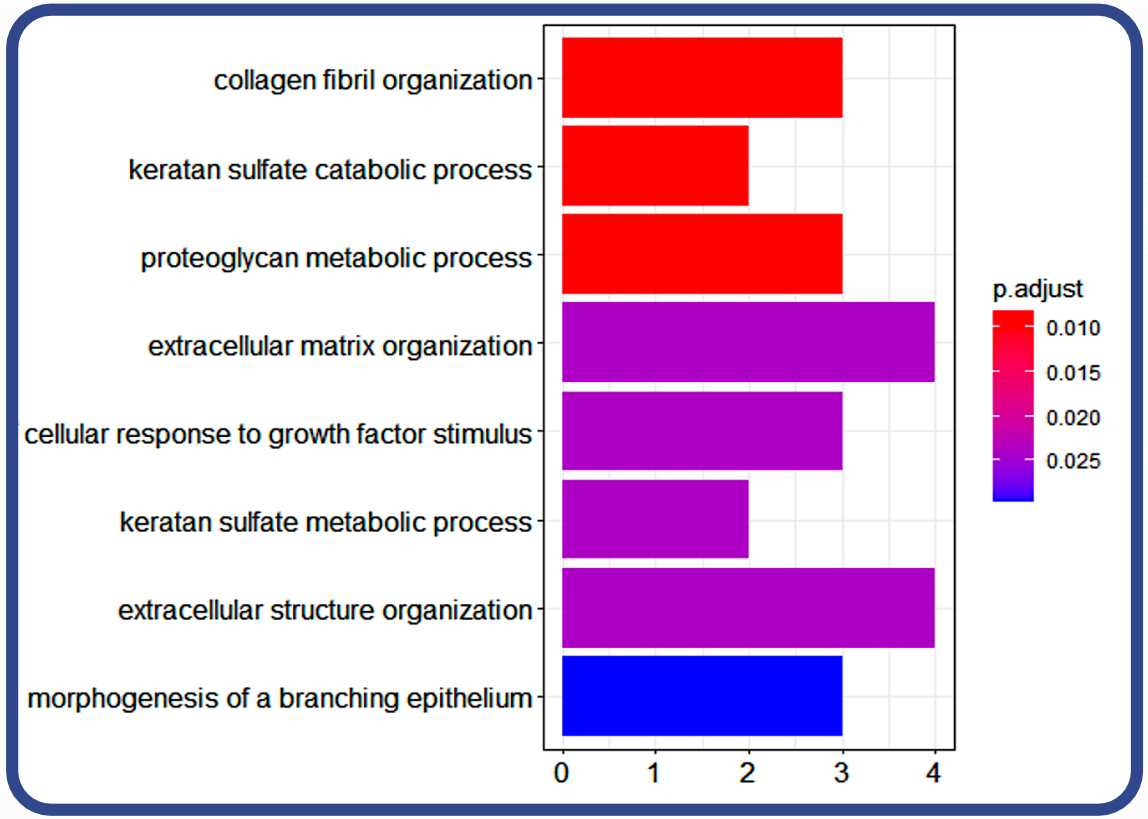


Aliev G, et al. *J. Clin. Med.* **2020;***9:*2951. doi:10.3390/jcm9092951.

PTSD Changes Gene Expression and Literally Borrows into Our Very Cellular Organization and Functioning

The study participants (n=72,21 of which eventually developed PTSD) are a subsample of participants enrolled in a longitudinal and prospective cohort study of adults living in Detroit, Michigan called Detroit Neighborhood Health Study.

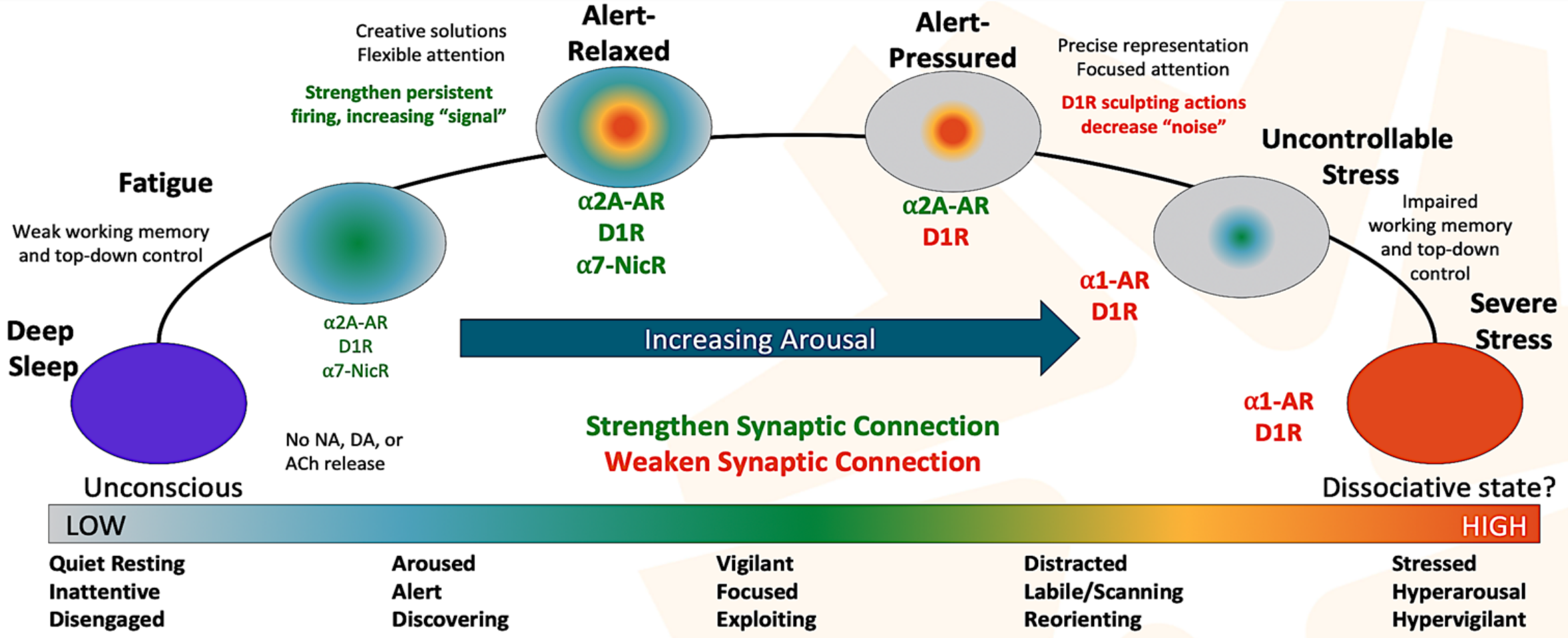
The top genes associated with PTSD development regarding the PTSD measure were found to be involved in cellular organization and functioning.



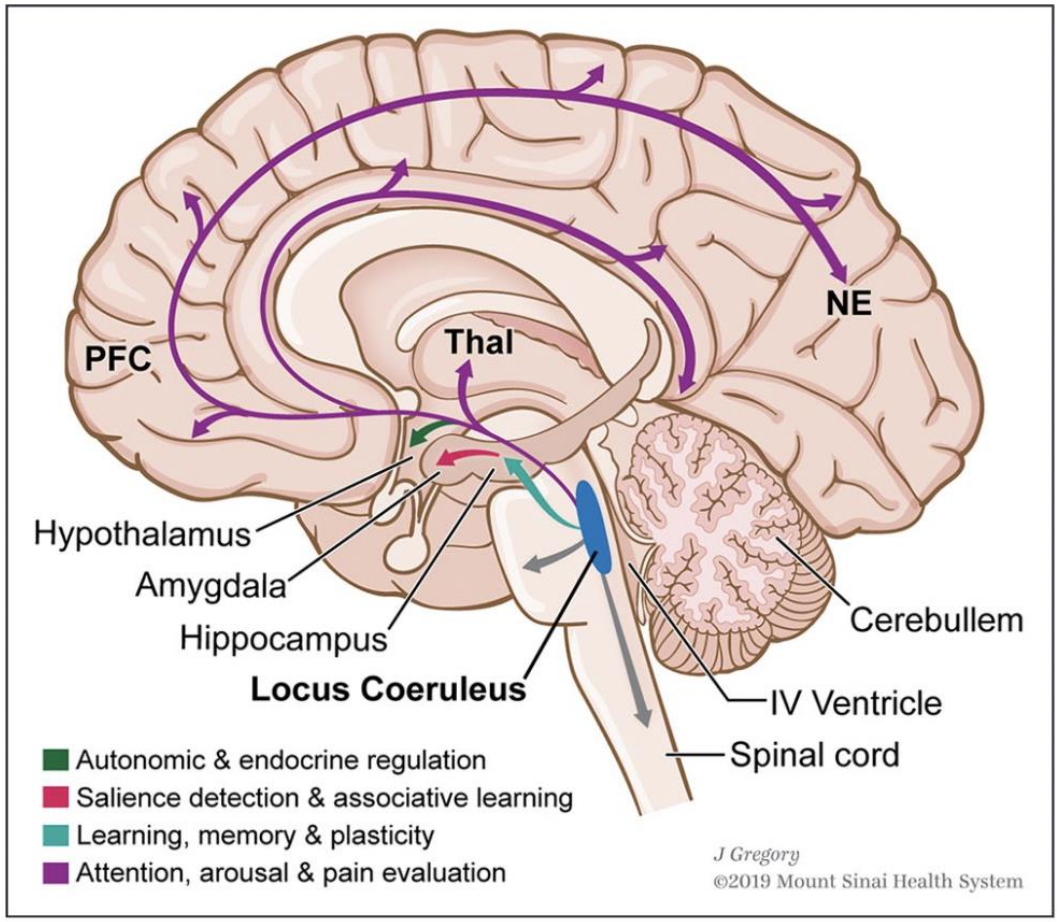
Dahrendorff J. USF Tampa Graduate Theses and Dissertations. 2021. Accessed July 1, 2024. https://digitalcommons.usf.edu/etd/9095

Norepinephrine Is also a Prominent Player in the Pathogenesis of PTSD

Norepinephrine: Spectrum in Heath and Disease



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



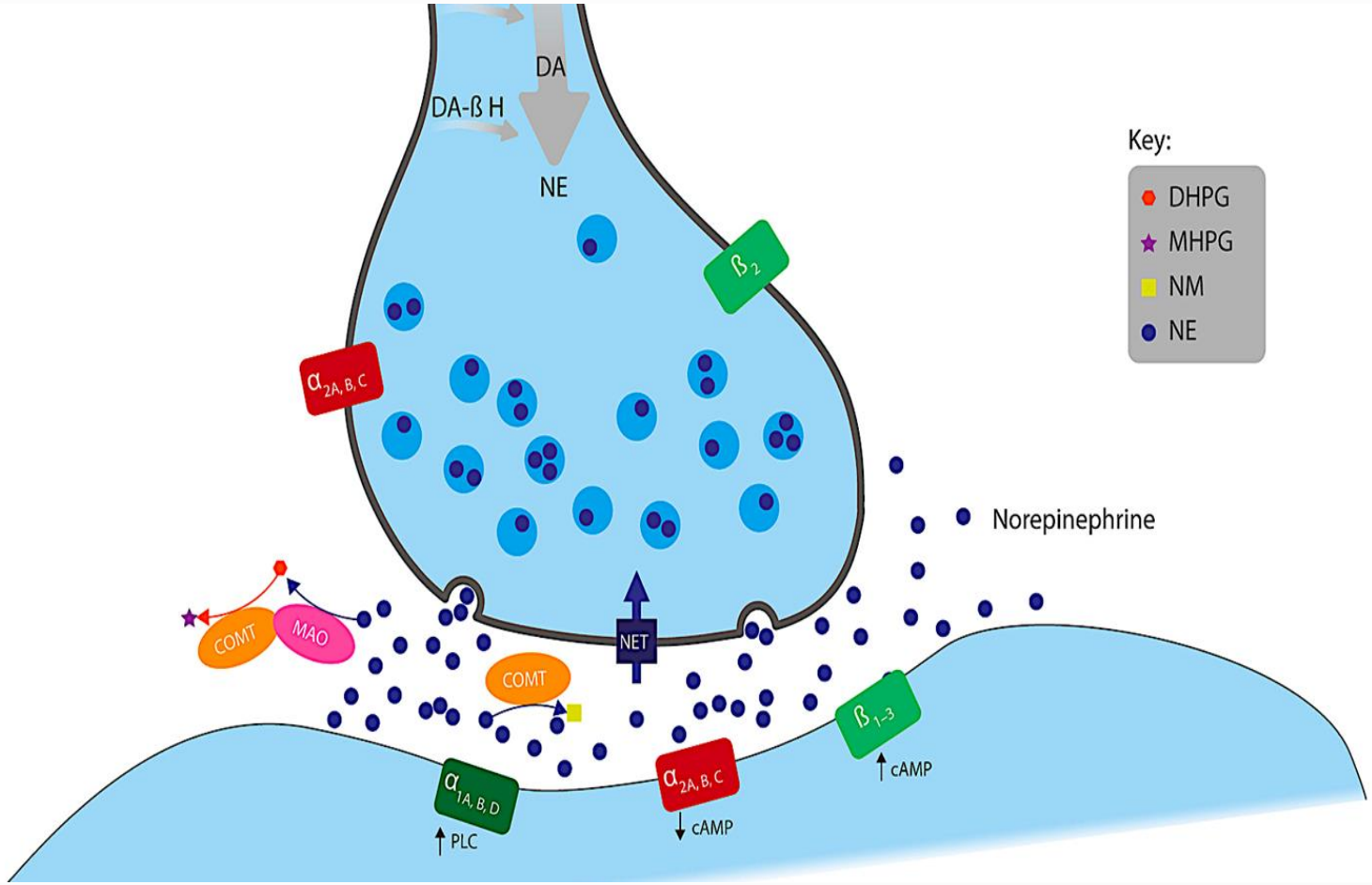
Major locus coeruleus (LC) projections throughout the central nervous system play distinct functional roles. Ascending LC projections innervate the **hypothalamus** for **autonomic** and **endocrine** regulation; the **amygdala** for salience detection and associative learning; the **hippocampus** to 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.**

Morris LS, et al. *Brain and Neuroscience Advances*. 2020;4. doi:10.1177/2398212820930321

NE Exerts Its Effects via Its Army of Receptors

α1- and β-ARs have a stimulatory effect on cell signaling, whereas α2-ARs inhibit signaling.

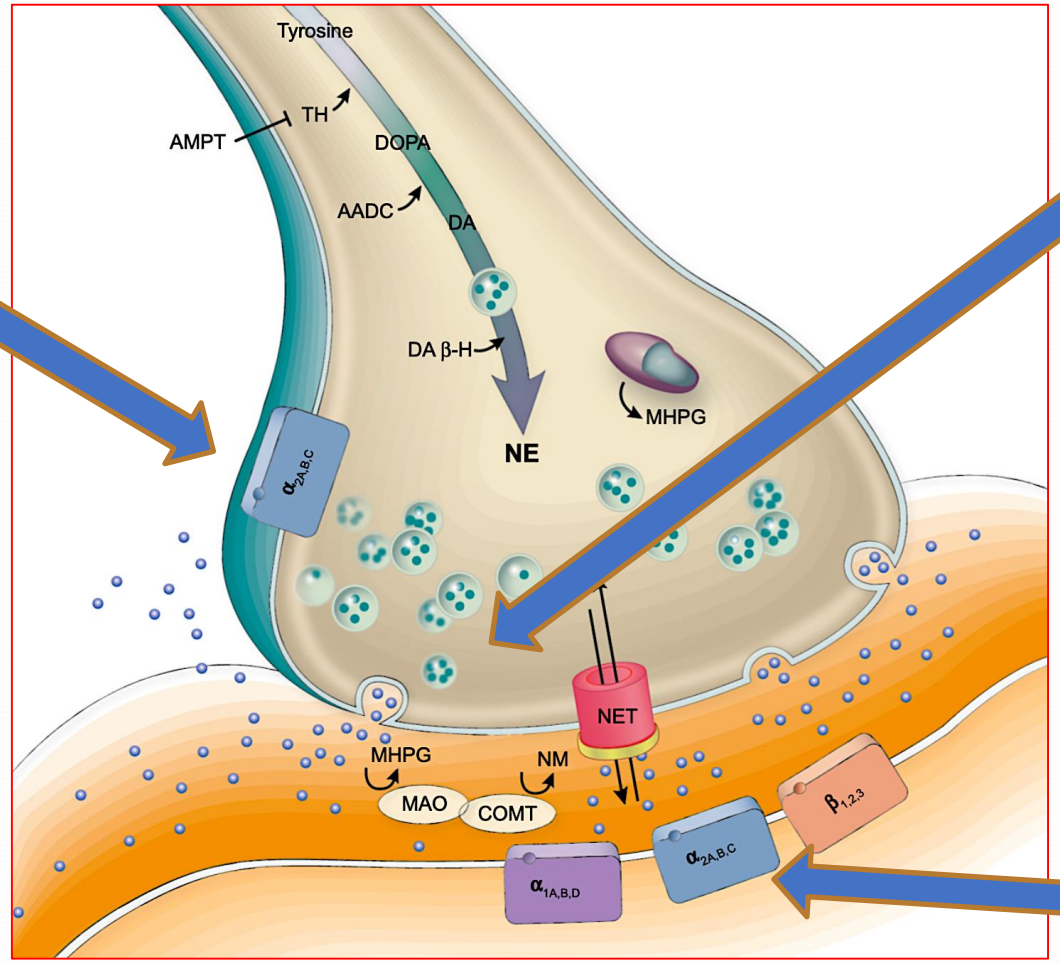
ARs are mainly located post-synaptically, α2- and β2-AR subtypes can also be localized pre-synaptically



Maletic V, et al. The Role of Norepinephrine and Its α-Adrenergic Receptors in the Pathophysiology and Treatment of Major Depressive Disorder and Schizophrenia: A Systematic Review. Front. Psychiatry. 2017;8:42. doi: 10.3389/fpsyt.2017.00042

While NE Reuptake Inhibition Has Been the Primary Tool For Intervention, Conversation Is Moving Rapidly Towards NE Receptor Activity Modulators

Direct Pre-synaptic Receptor Interventions



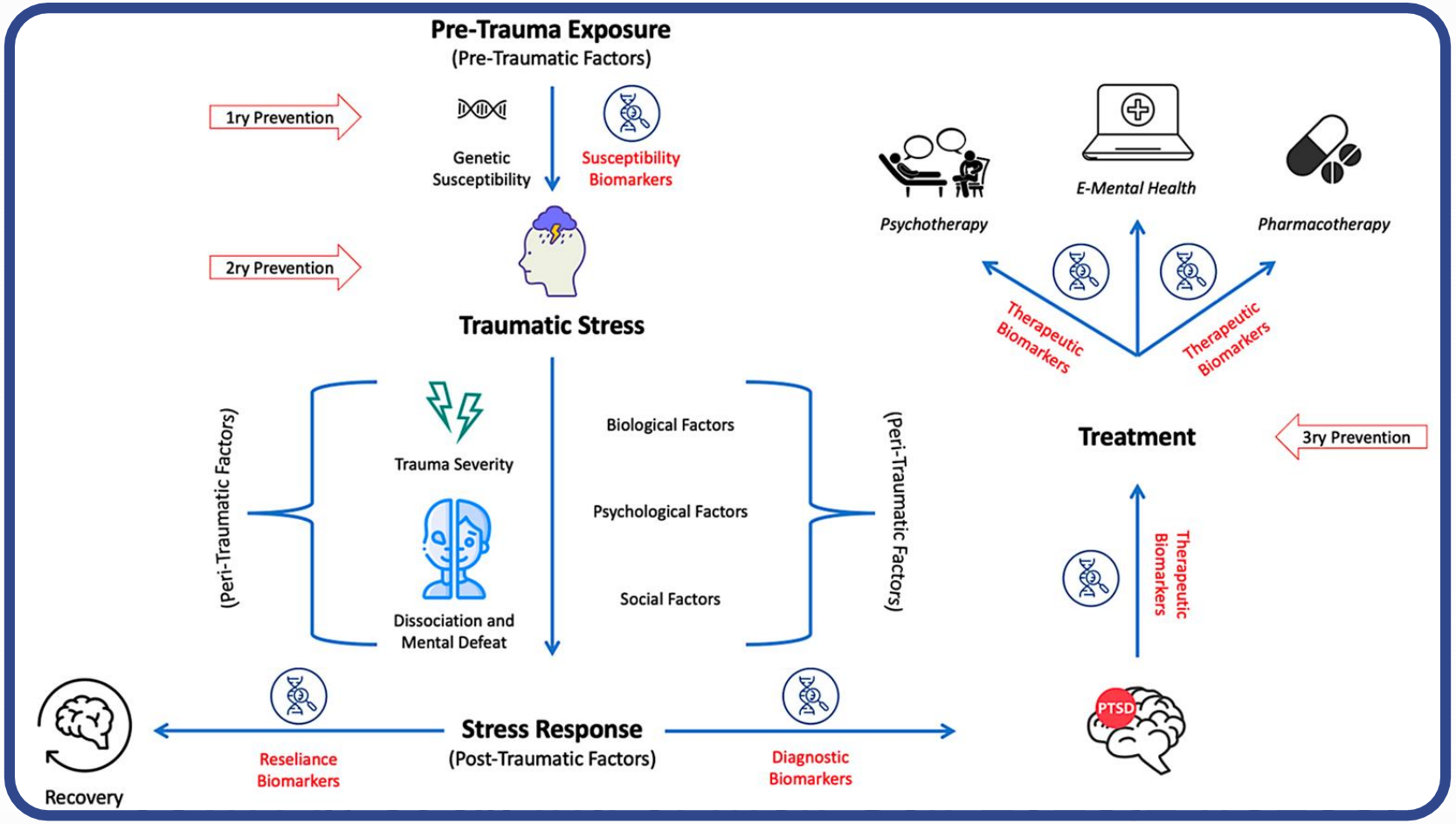
Norepinephrine Reuptake Inhibitors

(Non-selective, Non-specific NE Interventions)

Direct Post-synaptic Receptor Modulators

Montoya A, et al. *Neuropsychiatric Disease and Treatment*. 2016;12:541-557.

Biopsychosocial Model Applies to PTSD



The entirety of the pre-, peri- and post-traumatic factors can be biological, psychological, or social, according to the biopsychosocial model

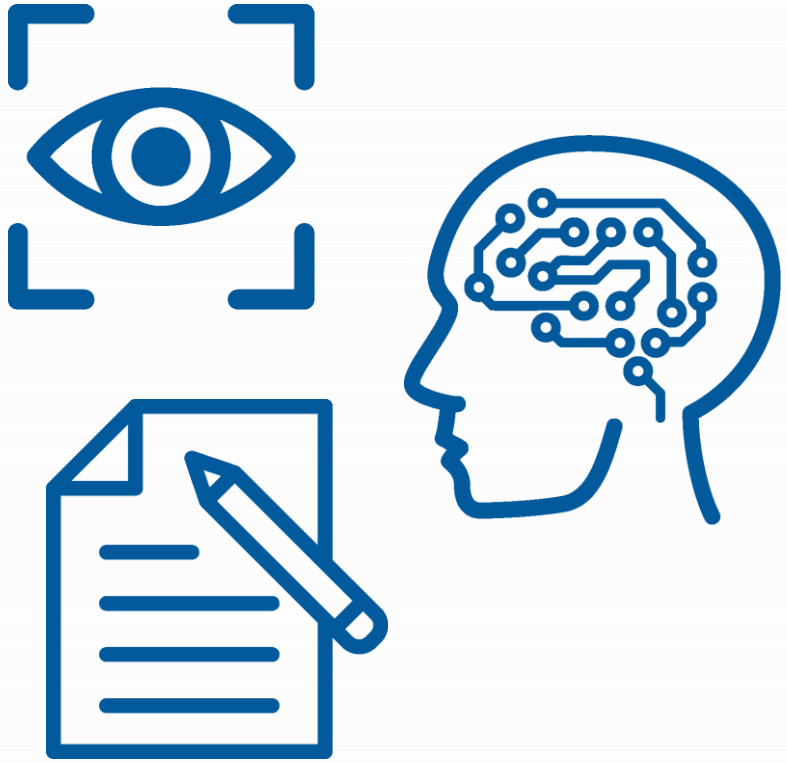
Section 2:
Conclusion & Key Learning Points

- ✓ PTSD is truly a Biopsychosocial disorder
- ✓ PTSD has genetic underpinnings, and this area of research is finally emerging
- ✓ PTSD and Norepinephrine dysregulation have an intimate relationship, and hyper-noradrenergic states are thought to be a source of significant symptomatology and impairment
- ✓ Norepinephrine exerts its effects through its excitatory receptors (usually Alpha 2) and inhibitory receptors (usually Alpha 1)

Current Therapies for PTSD

Nonpharmacologic Therapies

- Individual trauma-focused therapies are preferred
  - Prolonged Exposure (PE)
  - Cognitive Processing Therapy (CPT)
  - Eye Movement Desensitization and Reprocessing (EMDR)
- Cognitive Behavioral Therapy (CBT)
- Written Exposure Therapy (WET)
- Present Centered Therapy (PCT)



Pharmacologic Interventions

- SSRIs – Specifically sertraline and paroxetine
  - Only agents with FDA indication to date
- Other classes of antidepressants
- Atypical antipsychotics
- Mood stabilizers
- Alpha-1 blockers
  - Used for nightmares and sleep
- Benzodiazepines
  - Use with caution due to risk of dependence and addiction/abuse

Combination Therapies

- Psychotherapy + Medication
- Combination medication
  - ADT + Antipsychotic
  - ADT + Alpha-blocker
  - ADT + Mood stabilizer
  - ADT + Anxiolytic

- Monitor for Bipolar Disorder before prescribing ADT
- Sometimes combination medication regimens include more than 2 medications (ie, ADT + Mood stabilizer + Alpha-blocker)

Guidelines for Treatment of PTSD

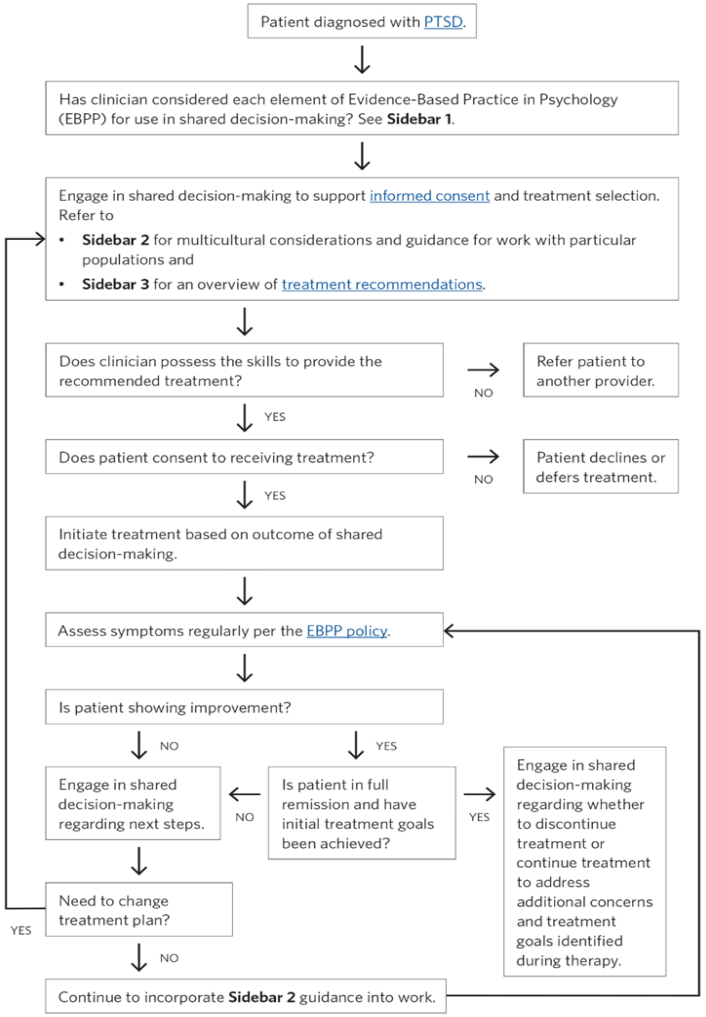
- APA (2017)
  - Recommends intervention in adults
  - Must consider benefits & harms of interventions
  - Consider pt values and preferences
  - Consider applicability of the evidence across demographic groups and settings

•**American Psychological Association (APA).** Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults (2017). Accessed October 1, 2024. https://www.apa.org/ptsd-guideline.

AMERICAN PSYCHOLOGICAL ASSOCIATION

Decision-Making Within Evidence-Based Practice in Psychology

Using the APA Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults



SIDEBAR 1

EVIDENCE-BASED PRACTICE IN PSYCHOLOGY (EBPP) ELEMENTS

1. Best available research (See Recommendations section as starting point).
2. Clinical expertise.
3. Patients' characteristics, values, and context.

SIDEBAR 2

ADDITIONAL GUIDANCE FROM APA'S GUIDELINES FOR PARTICULAR POPULATIONS

- EBPP Policy
- Multicultural guidelines
- Race and Ethnicity
- Boys and men
- Girls and women
- Sexual Minority Persons
- Transgender and gender nonconforming
- Persons with disabilities
- Persons with low-income and economic marginalization
- Additional guidance

SIDEBAR 3

EMPIRICALLY SUPPORTED TREATMENT RECOMMENDATIONS

Psychotherapy

- **Strong recommendation** for cognitive-behavioral therapy, cognitive processing therapy, cognitive therapy, and prolonged exposure therapy.
- **Conditional recommendation** for brief eclectic psychotherapy, eye movement desensitization and reprocessing therapy, and narrative exposure therapy.

Pharmacotherapy

- **Conditional recommendation** for fluoxetine, paroxetine, sertraline, and venlafaxine.

To view the full set of recommendations, including ones where there was insufficient evidence to recommend for or against the treatment, please refer to Table 1 of the full guideline document.

American Psychological Association (APA). Using the APA Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. Accessed October 1, 2024.

Section 3:
Conclusion & Key Learning Points

- ✓ There are multiple evidence-based therapy strategies
- ✓ Various medications can be used to target symptoms of PTSD
- ✓ Many Patients require a combination of psychotherapy and medication
- ✓ When in doubt, refer to APA Clinical Practice Guidelines

Newer and Emerging Therapies for PTSD

Unmet Need

- Currently only two medications (sertraline and paroxetine) FDA approved for the treatment of PTSD
- BOTH treatments are SSRIs
  - **This limits key areas implicated in pathophysiology of the illness**
- Not all patients are willing to engage in psychotherapy
- Psychotherapy is sometimes not adequate to address physical symptoms of PTSD

S = sertraline; P = paroxetine.

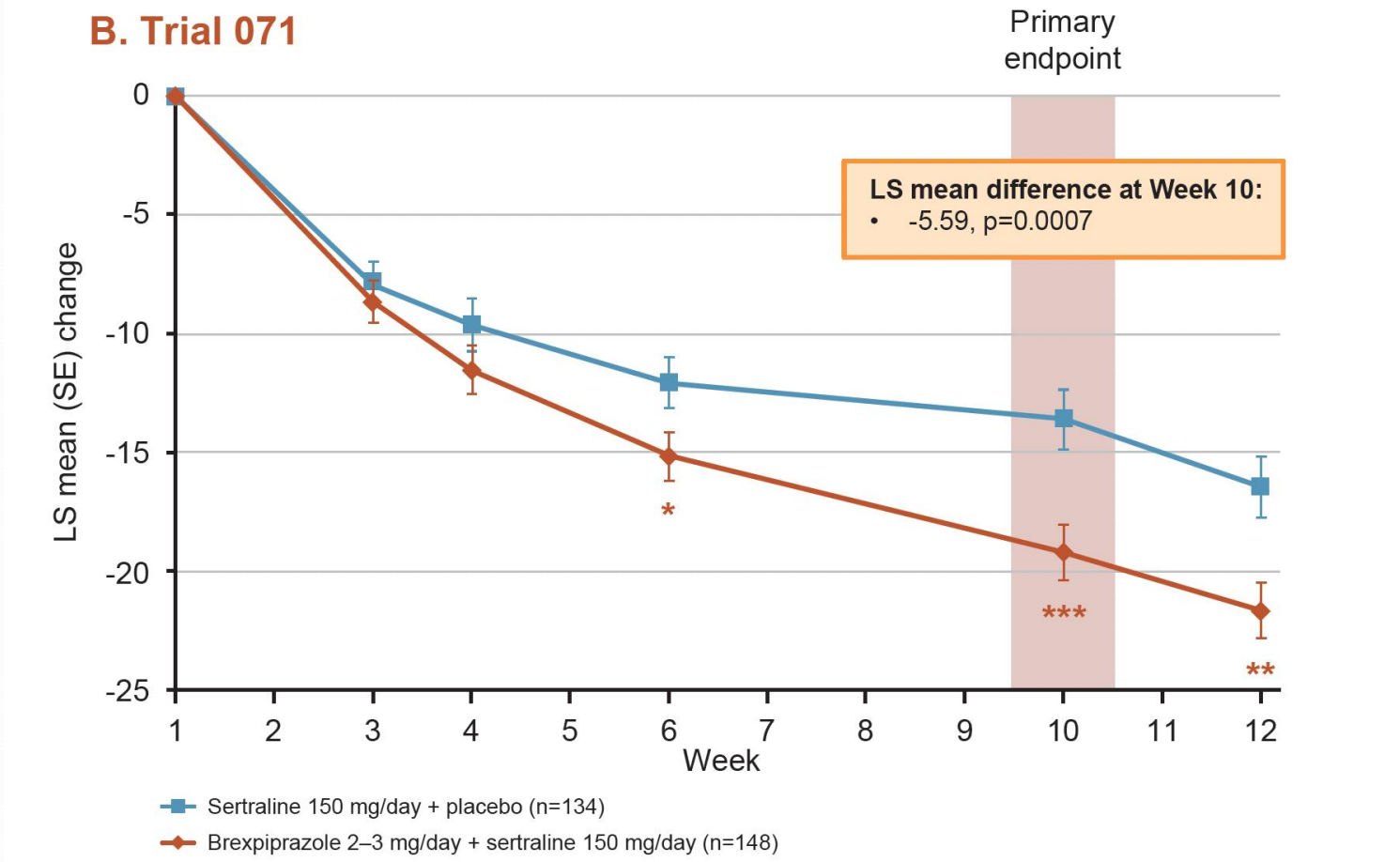
Novel and Emerging Therapies

- Brexpiprazole + Sertraline
  - Positive Phase III clinical trials
  - Awaiting FDA approval
- BNC210 – Bionomics
  - Announced in March 2024 advancing to Phase III
  - Negative allosteric modulation of alpha7-nicotinic acetylcholine receptor
- Denied FDA approval
  - MDMA assisted psychotherapy
- No further advancement in clinical trials
  - NYX-783 – NMDAR modulator
  - JZP150 – highly selective inhibitor of the enzyme fatty acid amide hydrolase (FAAH)

•BNC210 = negative allosteric modulator of the alpha 7 nicotinic acetylcholine receptor (α7 nAChR); MDMA = 3,4-methylenedioxy-methamphetamine;NYX-783 = a novel NMDA receptor modulator ; NMDAR = N-methyl-D-aspartate receptor.

Emerging Therapies: Brexpiprazole/Sertraline vs Sertraline/Placebo

Primary Endpoint Measure in both trials: Change from Week 1 to Week 10 in the Clinician-Administered PTSD Scale (CAPS-5) total score for brexpiprazole/sertraline combination vs sertraline/placebo in patients diagnosed with PTSD*



* Diagnosed per criteria from Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Otsuka Pharmaceutical Co. Ltd, Lundbeck US. Press Release: Otsuka and Lundbeck submit sNDA for FDA review of brexpiprazole and sertraline combination as potential treatment for PTSD. April 10, 2024. Accessed October 8, 2024. https://otsuka-us.com/news/otsuka-and-lundbeck-submit-snda-fda-review-brexpiprazole-and-sertraline-combination-potential.

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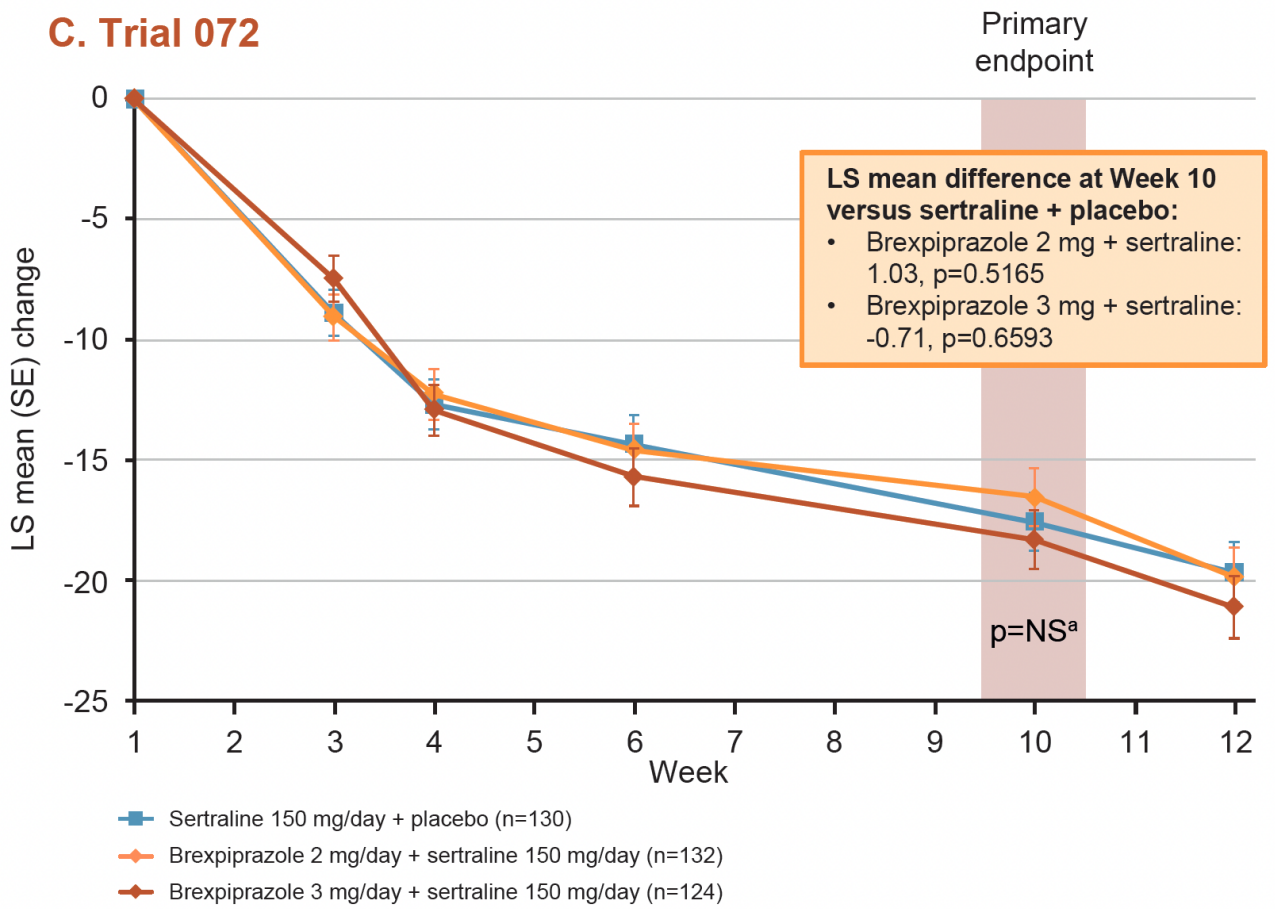

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Emerging Therapies: Brexpiprazole/Sertraline vs Sertraline/Placebo – Clinical Trials Results

- Trial #071 (phase 3) and trial #061 (phase 2) demonstrated that the combination treatment of brexpiprazole and sertraline was superior to treatment with sertraline plus placebo.
- Although trial #072 (phase 2) did not demonstrate superiority of the combination treatment of brexpiprazole and sertraline compared to treatment with sertraline plus placebo, the change from baseline observed in the brexpiprazole/sertraline combination group was consistent with the reductions observed in Trials #071 and #061.
- Brexpiprazole/sertraline combination was observed to be generally well-tolerated
- Safety results of the three trials were consistent with the known safety profile of brexpiprazole

Otsuka Pharmaceutical Co. Ltd, Lundbeck US. Press Release: Otsuka and Lundbeck submit sNDA for FDA review of brexpiprazole and sertraline combination as potential treatment for PTSD. April 10, 2024. Accessed October 8, 2024. https://otsuka-us.com/news/otsuka-and-lundbeck-submit-snda-fda-review-brexpiprazole-and-sertraline-combination-potential.

Section 4:
Conclusion & Key Learning Points

- ✓ There remains unmet needs pharmacologically in PTSD
- ✓ Brexpiprazole + Sertraline offered hope in Phase III clinical trials
- ✓ Additional pharmacologic interventions need to be studied to provide additional treatment options for patients in need

Essential Strategies for Optimal Patient-Centered Care

When To Refer To a Specialist?

- It is ALWAYS a good idea for Primary Care Clinicians to refer ALL patients with a dx. of PTSD for psychotherapy – whether or not they receive medication treatment or not
- If the patient is significantly suicidal, or psychotic, or manic
- If the patient has failed to respond to 2-3 different medication trials
- If dissociative symptoms are prominent
- When the diagnosis/ diagnoses is uncertain or confusing

PTSD and Shared Decision-Making:
An Essential Step to Optimize Outcomes

***Q:** What is Shared Decision Making?"*

***A:** "…a **process** in which clinicians and patients **work together** to select tests, treatments, management or support packages, based on clinical evidence and the patient's informed preferences; it involves the provision of evidence-based information about **options, outcomes, and uncertainties**, together with decision support counselling and a system for recording and implementing patients' informed preferences."*

Slade M. Implementing shared decision making in routine mental health care. *World Psychiatry*. 2017;16(2):146-153.

Expert Tips on Monitoring Patients with a Dx of PTSD

- ✓ Psychotherapy is always first line treatment. Pharmacotherapy is to be utilized as needed
- ✓ See such patients more frequently
- ✓ Use a ‘trauma informed’ interviewing approach
- ✓ Be gentle, kind, and unhurried
- ✓ Use measurement-based care, and don’t ignore any and all co-morbidities
- ✓ Be positive and optimistic! Most patients with a dx of PTSD improve and go on to lead healthy and productive lives

Section 5:
Conclusion & Key Learning Points

- ✓ Most patients with PTSD can be successfully treatment in the primary care setting
- ✓ Always attempt to engage the patient with a trauma informed therapist, and seek specialty psychiatry care in specific clinical scenarios
- ✓ Shared decision making (SDM) is highly recommend to ensure short and long-term success in patient suffering from PTSD
- ✓ Regular and close monitoring is indicated, Remaining positive and optimistic is also warranted as most patients can be successfully treated

Practical Take-Aways

Q&A