The Evolution of Post-traumatic Stress Disorder: Focus on Diagnostic, Evaluation, and Treatment Advances

Steven T. Szabo, MD, PhD
Assistant Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine
Durham, North Carolina

William M. Sauvé, MD
Regional Medical Director
Greenbrook TMS NeuroHealth Centers
Glen Allen, Virginia
Today’s Speakers

Steven T. Szabo, MD, PhD
Duke University Medical Center
Dr. Szabo is an assistant professor of psychiatry and behavioral sciences at Duke University School of Medicine. He received his PhD in neurosciences from McGill University. Dr. Szabo completed postdoctoral training in psychopharmacology at the University of Florida and in mood and anxiety disorders at the National Institutes of Mental Health. He received his medical degree from the Medical University of the Americas and completed a residency in psychiatry at Duke University Medical Center in Durham, North Carolina.

William M. Sauvé, MD
Greenbrook TMS NeuroHealth Centers
Dr. Sauvé is the regional medical director at Greenbrook TMS NeuroHealth Centers in Glen Allen, Virginia. He was previously the clinical director of the military program at the Poplar Springs Hospital in Petersburg, Virginia. He received his medical degree from Uniformed Services University in Bethesda, Maryland, and completed his psychiatry residency at the National Capitol Consortium in Washington, DC. Dr. Sauvé is certified by the American Board of Psychiatry and Neurology.
This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC.

Speakers are paid consultants for Otsuka Pharmaceutical Development & Commercialization, Inc.
PsychU Virtual Forum Rules Of Engagement:

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC. have entered into collaboration with OPEN MINDS, to explore new ways of bringing/increasing awareness around serious mental illness.

OPDC/Lundbeck’s interaction with OPEN MINDS is through PsychU, an online, non-branded portal dedicated to providing information and resources on important disease state and care delivery topics related to mental illness. One of the methods employed for the sharing of information will be the hosting of virtual fora. Virtual fora conducted by OPDC/Lundbeck are based on the following parameters:

When conducting medical dialogue, whether by presentation or debate, OPDC/Lundbeck and/or its paid consultants aim to provide the viewer with information that is accurate, not misleading, scientifically rigorous, and does not promote OPDC/Lundbeck products.

No continuing medical education (CME) credits are available for any PsychU program.

OPDC/Lundbeck and/or their paid consultants do not expect to be able to answer every question or comment during a PsychU Virtual Forum; however, they will do their best to address important topics and themes that arise.

OPDC/Lundbeck and/or their paid consultants are not able to provide clinical advice or answer questions relating to specific patient’s condition.

Otsuka and Lundbeck employees and contractors should not participate in this program (e.g., submit questions or comments) unless they have received express approval to do so from Otsuka Legal Affairs.

OPDC/Lundbeck operate in a highly regulated and scrutinized industry. Therefore, we may not be able to discuss every issue or topic that you are interested in, but we will do our best to communicate openly and directly. The lack of response to certain questions or comments should not be taken as an agreement with the view posed or an admission of any kind.

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other healthcare professional.
Objectives

• Review some of the basics about post-traumatic stress disorder (PTSD)
• Consider how perceptions of the disease, PTSD diagnostics, and assessment of symptoms have changed over time
• Discuss advances in the understanding of PTSD neurobiology
• Provide an overview of select treatments for PTSD and an update on the identification of potential biomarkers
The Basics of PTSD
PTSD: Did You Know?

In the general population, women are 2x as likely as men to experience PTSD at some point in their lives. Of those who have experienced trauma, about 1 in 10 men and 2 in 10 women will develop PTSD.\(^1,2\)

Sexual assault is more likely to result in symptoms of PTSD than are other types of trauma, including combat.\(^1\)

Social support is a resilience factor against developing PTSD after trauma; research suggests it is more protective for women than men.\(^1\)

Many people with PTSD also experience chronic pain or other physical health problems.\(^1\)

PTSD often co-occurs with depression or other mental health conditions.\(^1\)

---

PTSD, post-traumatic stress disorder.


*The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other healthcare professional.*
PTSD: Why Does It Matter?

A study of male veterans who served in the Vietnam War reported that those with PTSD had 2x the risk of death from heart disease*; each 5-point increase in symptom score corresponded to a 20% increase in risk of heart disease mortality¹.

Sleep problems, beyond being a defining symptom of PTSD, often develop into independent disorders in patients with PTSD and are associated with significant distress and impairment, including increased risk for suicidality².³

Patients with PTSD have a higher risk of substance use disorders, and often have comorbid physical and/or mental health disorders³.

Studies examining an association between PTSD and suicide among civilian populations have reported consistent evidence of a strong association, even after accounting for preexisting psychiatric comorbidity⁴.

---

¹During a 15-year follow-up period. PTSD, post-traumatic stress disorder.

PTSD: Overview

- PTSD is a psychiatric disorder that can affect individuals exposed to psychological trauma.\(^1\)
- Studies of the US general population have reported a lifetime PTSD prevalence of 6.8%–7.8% (highly variable across studies\(^*\))\(^2\)
  - Most prevalence studies have evaluated the general population or military veterans.
- The highest rates of PTSD (33%–≥50% of those exposed) are reported among survivors of rape, military combat and captivity, and ethnically or politically motivated internment and genocide\(^3\)

\(^*\)Variability is likely due to population type assessed and/or methodology of assessment.

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

PTSD and Traumatic Events

- PTSD is one of the few psychiatric disorders requiring an identifiable causal external event.\(^1\)
- The most studied traumatic events leading to PTSD include:\(^2\):
  - Combat exposure and injuries (among men) and rape, childhood sexual abuse, and domestic violence (among women)
- The severity and duration of a traumatic event and the risk for development of PTSD have a dose–response relationship.\(^2\)

*Not an exhaustive list.

PTSD, post-traumatic stress disorder.

• PTSD is heterogeneous and often presents across several symptom domains, including¹:
  – Re-experiencing, avoidance/numbing, and hyperarousal symptoms
• Common symptom presentation may differ by specialty:²
  – Primary care (eg, headaches, sleep disturbances, pain)
  – Mental health clinics (eg, depression, substance use, self-harm)
• Recognition of the condition is important, as even patients with subthreshold PTSD may have significant impairment that requires intervention²,³
Potential Symptoms of PTSD in Adults*

- Dysphoric or negative mood states (e.g., anger, guilt, shame)
- Recurrent, involuntary, intrusive, fear-based reexperiencing of event
- Anhedonic mood states (e.g., disinterest, detachment, lack of positive emotion)
- Concentration difficulties
- Difficulty remembering
- Reckless or self-destructive behavior
- Negative alterations in cognition (e.g., negative beliefs/expectations, distorted blame)
- Hyperarousal
- Sleep problems and/or nightmares
- Hallucinations; paranoid ideation
- Reactive to unexpected stimuli
- Dissociative symptoms (e.g., dissociative amnesia) Subtype specifier
- Avoidance of trauma-related thoughts or reminders
- Difficulty regulating emotion (e.g., short temper, aggressive behavior with little provocation)
- Heightened sensitivity to potential threats (hypervigilance)

*Not an exhaustive list. PTSD, post-traumatic stress disorder.

Mental Health Comorbidities: A Common Occurrence

• PTSD is highly comorbid with other mental disorders¹
  – >90% of patients with PTSD have 1 or more lifetime comorbid mental disorders¹
    • The most prevalent conditions include MDD, alcohol abuse/dependence, and anxiety disorders¹

• Many symptoms of PTSD overlap with those of other mental disorders¹,²
  – For example, many numbing and hyperarousal symptoms overlap with depressive symptoms, including loss of interest, detachment, difficulty concentrating, sleep impairment, and irritability²

• PTSD is differentiated from other mental disorders by the re-experiencing of symptoms (eg, nightmares, flashbacks)¹

MDD, major depressive disorder; PTSD, post-traumatic stress disorder.
Evolution of Perceptions of PTSD, PTSD Diagnostics, and Symptom Assessment
The Introduction and Evolution of PTSD

- Although PTSD has been observed throughout history, it was first officially introduced in DSM-III (1980)
- The definition of PTSD has varied across DSM editions, but 4 core features have remained throughout
  1. Experiencing or witnessing a stressful event;
  2. Re-experiencing symptoms of the event, including nightmares and/or flashbacks;
  3. Efforts to avoid situations, places, and people that are reminders of the traumatic event; and
  4. Hyperarousal symptoms, such as irritability, concentration problems, and sleep disturbances

Evolution of the Diagnosis of PTSD\textsuperscript{1,2}

**Early names:**
- Nostalgia
- Soldier's heart

**World War I:**
- Combat stress
- Combat fatigue
- Traumatic neurosis

**World War II:**
- Transient situational personality disorders:
  - gross stress reaction

**DSM-I:**
- Transient situational disturbances

**DSM-II:**
- Transient situational disturbances

**Vietnam War:**
- Post-Vietnam syndrome
- Traumatic war neurosis

**World War I:**
- Shell shock
- War neurosis

**World War II:**
- Combat stress
- Combat fatigue
- Traumatic neurosis

**DSM-I:**
- Transient situational personality disorders:
  - gross stress reaction

**DSM-II:**
- Transient situational disturbances

**DSM-III:**
- Personality disorders:
  - gross stress reaction

**DSM-III-R:**
- Personality disorders:
  - gross stress reaction

**DSM-IV:**
- Personality disorders:
  - gross stress reaction

**DSM-IV-TR:**
- Personality disorders:
  - gross stress reaction

**DSM-5:**
- Personality disorders:
  - gross stress reaction

---

**Definition of Trauma (Criterion A):**

Experiencing or witnessed an event involving actual or threatened death or serious injury, or a threat to the physical integrity of self or others; the person's response involved intense fear, helplessness, or horror

---

**Selected Differences:**

- PTSD is no longer clustered within Anxiety Disorder, but within Trauma and Stressor Related Disorders
- Removal of the subjective component (emotional response) from the definition of trauma
- Addition of "negative alterations in cognitions and mood" as a criterion
- Diagnostic symptoms expanded from 12 to 17
- Identified age-specific features
- PTSD emerged as a separate diagnostic entity, placed among anxiety disorders

---

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

Heterogeneity of PTSD

According to DSM-5 criteria, there are ~636,120 different ways in which an individual can be diagnosed with PTSD.
Evolution of the Clinician-Administered PTSD Scale (CAPS)

- CAPS: A structured interview developed to measure the core set of PTSD symptoms, as outlined in the DSM-IV
  - 22-item scale that has frequency and intensity rating scales for symptoms
  - Demonstrated solid psychometric properties in trauma populations
  - Considered the gold standard in PTSD assessment
- With the release of DSM-5, the CAPS was updated (CAPS-5)
  - 30-item scale that assesses 20 DSM-5-identified PTSD symptoms
  - Can be used to assess PTSD symptoms over the past week or to make current (past month) or lifetime diagnosis of PTSD

Key Changes to CAPS-5 From Previous Version

- Identify a single (vs ≤3) traumatic event to serve as the basis of symptom inquiry
- Change from 22-item to 30-item questionnaire, corresponding to the DSM-5 (rather than the DSM-IV)
- Language reflects changes to existing symptoms, addition of new symptoms, and addition of dissociative subtype of PTSD
- Symptom items are rated with a single severity score (vs separate frequency and intensity scores)

PTSD, post-traumatic stress disorder.

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other healthcare professional.
Discussion
Recent Advances in the Understanding of PTSD Neurobiology
The Amygdala: A Critical Role in Fear Processing

• The amygdala plays a critical role in fear\(^1\)
• It consists of a group of interconnected nuclei, with differing functions, including\(^1\):
  – Computation of possible danger and emotional salience\(^2\)
  – Control of expression of behavioral, autonomic, and endocrine fear responses\(^1\)
  – Activation of amine modulatory systems (ie, adrenergic, serotonergic, dopaminergic, and cholinergic systems)\(^1\)
  – GABA-ergic signaling\(^1\)

Ach, acetylcholine; ANS, autonomic nervous system; B, basal; CE, central; DA, dopamine; GABA, gamma-aminobutyric acid; ITCs, intercalated cells; LA, lateral; NE, norepinephrine; 5-HT, serotonin.

Direct and Indirect Fear Detection Pathways

- Sensory information reaches lateral nucleus through 2 sensory inputs\(^1\)
  - Thalamic pathway ("low road") conveys a rapid and imprecise signal
  - Cortical pathway ("high road") delivers more refined and detailed representation, but includes additional synaptic connections, making transmission longer

- Evidence exists for 4 parallel pathways from inferior temporal cortex to amygdala ("high roads"), each having different correlated behavioral characteristics and propagation times\(^2\)


Triggering Fear and Anxiety Symptoms and Resulting Behavioral Responses

Outputs of the Central Nucleus or Lateral Division of the BNST to Various Target Structures and Possible Functions of These Connections

BLA, basolateral nucleus of the amygdala; BNST, bed nucleus of the stria terminalis; CER, conditional emotional response; EEG, electroencephalogram; hypothal, hypothalamus; N, nucleus. Berlant JL. Primary Psychiatry. 2003;10(10):41-49.
Neural Regions Implicated in PTSD: The Prefrontal Cortex and Its Role in Contextualization

- PTSD has been conceptualized as a state of heightened responsivity to threatening stimuli or insufficient inhibitory control over exaggerated threat-sensitivity
  - Roles have been identified for mPFC, amygdala, extended amygdala, and hippocampus in mediating PTSD symptom formation
- Such models have been unable to fully explain the complexity of PTSD
  - Other processes are relevant, including fear conditioning, habituation, and extinction; cognitive–emotional interactions; and self-related and social emotional processing
- mPFC may play a role in contextualization, which could be dysregulated in PTSD
  - Process by which key dimensions of situational context are appraised, represented, and used to guide actions

### Categories of Contextual Variables in the mPFC

- **Cognitive**: Judges relevance of stimuli to memories and goals
- **Social**: Judges extent to which stimuli are self-related
- **Internal**: Judges overall homeostatic state of the internal milieu

ACC, anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; HPA, hypothalamic pituitary adrenal; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; PTSD, post-traumatic stress disorder; rmPFC, rostral medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

Discussion
PTSD Treatments and Biomarkers
Treatment of PTSD: Psychological and Pharmacological

• Treatment generally requires a combination of psychological and pharmacological approaches

• Psychological treatments are considered first-line
  – Treatments include CBT, prolonged exposure, and eye movement desensitization and reprocessing therapy
  – A potential barrier is the limited number of available trained therapists

• SSRIs have demonstrated efficacy in reducing symptoms and are considered first-line

• Other medications may be required to alleviate insomnia and nightmares
  – Alpha 1-adrenergic blockers, atypical antipsychotics, hypnotics, nonbenzodiazepines, and antihistaminergic drugs have been used to impact sleep, nightmares, and hyperarousal

CBT, cognitive behavioral therapy; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitors.
# Selected Therapies That Have Demonstrated Efficacy in Treating PTSD

<table>
<thead>
<tr>
<th>Psychotherapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Behavioral Therapy (CBT)</strong></td>
<td>CBT comprises a group of therapeutic methods that usually include relaxation and exposure techniques and cognitive restructuring techniques that aim to change dysfunctional beliefs¹</td>
</tr>
<tr>
<td><strong>Prolonged exposure or exposure therapy (ET)</strong></td>
<td>In exposure therapy a patient is asked to vividly recount a traumatic event repeatedly until his or her emotional response decreases. The patient is also asked to gradually confront safe but fear-evoking trauma reminders²</td>
</tr>
<tr>
<td><strong>Eye movement desensitization and reprocessing (EMDR)</strong></td>
<td>EMDR uses eye movements or other forms of bilateral stimulation to desensitize patients to anxiety and integrate information processing³,⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmaceutical therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td>SSRI antidepressants are considered first-line medication treatments for PTSD; however, SSRIs alone are not usually effective in treating insomnia and nightmares associated with PTSD⁵,⁶</td>
</tr>
<tr>
<td><strong>Alpha 1-adrenergic blocker</strong></td>
<td>Alpha 1-adrenergic blockers have demonstrated efficacy in reducing nightmares and hyperarousal related to PTSD⁵,⁷</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other therapies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcranial magnetic stimulation (TMS)</strong></td>
<td>TMS uses a pulsed magnetic field to noninvasively modulate neuronal activity⁸</td>
</tr>
</tbody>
</table>

---

PTSD, post-traumatic stress disorder.

Many patients do not adequately respond to traditional therapies
- Intense emotions triggered by exposure therapy may be intolerable and can lead to discontinuation; such therapies can also be labor-intensive and require training to administer
- Treatment with pharmacotherapy can be limited by intolerance, side effects, noncompliance, and contribution to polypharmacy

TMS uses a pulsed magnetic field to noninvasively modulate neuronal activity; when delivered repeatedly, it is referred to as repetitive TMS
- Variables modulating the interaction between the device and the brain include type of coil utilized, frequency of stimulus delivery, duration of pulse sequence, interstimulation rest periods, strength of magnetic field, total number of pulses in each session, and regularity of administered treatments

While optimal treatment parameters remain to be defined, evidence suggests 2 promising targets: the right dorsolateral prefrontal cortex and the mPFC
- Functional imaging studies have implicated alterations in the activity of these regions in PTSD

PTSD, post-traumatic stress disorder; mPFC, medial prefrontal cortex; TMS, transcranial magnetic stimulation.
Early Intervention in PTSD: Considering Genetic Risk

Methodology

• A study evaluated the effects of early intervention on the development of PTSD
  – 65 ED patients exposed to trauma were randomized to receive either 3 sessions of an exposure intervention, beginning shortly after trauma exposure, or assessment only, and PTSD symptoms were assessed*
  – Patients were genotyped for 10 genes previously associated with stress-response and assigned an additive risk score

Results

• Number of risk alleles was significantly associated with the likelihood of PTSD diagnosis (both groups)
• In patients with higher risk scores, early intervention was associated with significantly fewer symptoms of PTSD at 12 weeks compared to assessment only

*PTSD symptoms were assessed with the PSS-I Interview at weeks 4 and 12 post-assessment.
ED, emergency department; PSS-I, PTSD Symptom Scale-Interview; PTSD, post-traumatic stress disorder.
**Potential Biomarkers for PTSD**

<table>
<thead>
<tr>
<th>Neurotransmitters, peptides, and hormones</th>
<th>Neuroimaging and physiology</th>
<th>Cardiac Physiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Serotonin receptor 1A ↓ Serotonin Transporter ↓ Neuropeptide Y ↑ Norepinephrine ↑ Cannabinoid 1 receptors ↓ Allopregnanolone ↑ Arginine vasopressin</td>
<td>↓ Hippocampal volume ↑ Amygdala reactivity ↓ ACC activity during emotion processing</td>
<td>↑ Heart rate reactivity in response to loud tones</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPA Axis</th>
<th>Lymphatic and Immune System</th>
<th>Genetic and Epigenetic Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Glucocorticoid negative feedback ↑ Corticotropin releasing hormone ↑ Glucocorticoid receptors ↑ FKBP5</td>
<td>↑ Immune cell sensitivity to glucocorticoids ↑ Inflammatory cytokines ↑ NFκB ↑ C-reactive protein</td>
<td>Polymorphisms in genes for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PACAP • FKBP5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNA methylation at genes for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Glucocorticoid receptor • Corticotropin-releasing hormone • Arginine vasopressin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenals</th>
<th>Reproductive Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Baseline cortisol ↑ DHEA ↑ DHEA-S</td>
<td>↓ Testosterone in men ↓ Estradiol in women</td>
</tr>
</tbody>
</table>

---

*Causal relationships for these markers have not been established. Many are associated with other psychiatric conditions, some of which are often comorbid with PTSD (ie, not exclusive to PTSD).

ACC, anterior cingulate cortex; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; FKBP5, FK506 (tacrolimus) binding protein 5; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PACAP, pituitary adenylate cyclase-activating polypeptide.

Discussion
Questions
Closing
### Upcoming Virtual Fora*

<table>
<thead>
<tr>
<th>Event</th>
<th>Speaker(s)</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
</table>
| Neuromodulation Techniques: State Of The Science                      | • Philip G. Janicak, MD  
• Michael Thase, MD                                                  | July 11, 2018   | 12:00 pm ET     |
| Measurement-Based Care in Psychiatry: Clinical & Administrative Perspectives | • Charlotte Ostman, BA, MSW  
• James Greer, MD                                                      | July 25, 2018   | 12:00 pm ET     |
| Introducing RASP: Relapse Assessment in Schizophrenia Patients       | • Heidi Waters, MBA, PhD                         | August 8, 2018  | 12:00 pm ET     |
| An Update from NCQA©: Focusing on HEDIS® Behavioral Health Measures  | • Junqing Liu, PhD, MSW  
• Lauren Niles, MPH  
• Nora Fritz, BA                                                        | August 22, 2018 | 12:00 pm ET     |

*Register for these programs at [https://www.PsychU.org/events](https://www.PsychU.org/events)

---

The information provided by PsychU is intended for your educational benefit only. It is not intended as, nor is it a substitute for medical care or advice or professional diagnosis. Users seeking medical advice should consult with their physician or other healthcare professional.
The Evolution of Post-traumatic Stress Disorder: Focus on Diagnostic, Evaluation, and Treatment Advances

Steven T. Szabo, MD, PhD
Assistant Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine
Durham, North Carolina

William M. Sauvé, MD
Regional Medical Director
Greenbrook TMS NeuroHealth Centers
Glen Allen, Virginia