Posttraumatic Stress Disorder (PTSD)

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Learning Objectives

1. Describe the epidemiology, etiology, diagnosis, comorbidity, course, and prognosis of PTSD.
2. Discuss the pharmacotherapeutic and psychotherapeutic options for PTSD.
3. Develop a medication treatment plan for a patient with PTSD, including selection of medication, dosing information, adverse effect monitoring, expected time course of response, and duration of treatment.
4. Discuss the treatment of PTSD in special populations.

Overview

- Traumatic events are extremely common
- Exposure to a traumatic event
  - Direct or indirect
  - Once or repeatedly
- It's normal to have some degree of psychological distress after exposure to a traumatic event
- In most cases, symptoms resolve within several weeks as people use coping skills and support networks to deal with the experience
Overview

- Sometimes though psychological distress persists and is intense enough to interfere with the person’s life
- PTSD develops in approximately 1 out of every 3 to 5 people who are exposed to traumatic events
- PTSD is rather distinctive among mental disorders in that it has an identifiable precipitating cause

Historical Perspective

- Long recognized -- “soldier’s heart”, “shell shock”, “battle fatigue”
- PTSD was included in DSM-III in 1980
- PTSD has been subject to considerable debate and controversy

Historical Perspective

- Changes with subsequent editions of DSM
  - Broadening the definition of the stressor
  - Altering symptoms and symptom clusters
  - Defining duration of symptoms
  - Adding the requirement for distress or impairment
  - Categorization of the illness
Historical Perspective

- Empirical data concerning treatment continue to accumulate; our understanding of the effectiveness of various therapies continues to evolve.
- Various psychotropics have been studied in PTSD, but no drug has been specifically developed for PTSD.

Epidemiology

- 12-month prevalence in U.S. = 3.5%.
- Lifetime prevalence in U.S. = 8.7%.
- Higher rates among those at greater risk of traumatic exposure (e.g., veterans, firefighters, and police).
- Very high rates among those who experience rape, military combat and captivity, and genocide.

Epidemiology

- More prevalent and longer lasting in females compared to males.
- Older adults are more likely to experience subthreshold presentations than full-threshold presentations.
- Race:
  - Asians < whites
  - African Americans > whites
  - Latinos = whites
Etiology/Pathophysiology

- Genetic influences
- Pre-, peri-, and post-trauma risk factors
- Pathophysiology

Examples of Risk Factors

- Pretrauma
  - History of depression or anxiety
  - Previous trauma exposure
  - Childhood adversity
  - Lower intelligence or education
- Peritrauma
  - Severity of the trauma
  - Perceived threat to life
- Posttrauma
  - Inappropriate coping strategies
  - Subsequent life stressors

Pathophysiology

- HPA axis
- Noradrenergic system
- Serotonergic system
- Glutamatergic system
- Other systems
  - Cannabinoid
  - Opioid
Clinical Features
• Many types of traumas can lead to development of PTSD
• Some exposed to trauma develop PTSD whereas others do not
• More problematic traumas
  – Interpersonal & intentional
  – Prolonged and/or repeated

Clinical Features
• Patients typically present with a variety of core PTSD symptoms from different clusters
• Some patients experience their most prominent symptoms in a particular symptom cluster while others exhibit combinations of symptom patterns
• Frequent associated symptoms include anger, guilt, and physical health problems

Diagnosis (DSM-5)
• Exposure to actual or threatened death, serious injury, or sexual violence
• Manner of exposure
  – Directly experiencing the event
  – Witnessing the event occur to someone else
  – Learning that the event occurred to a close family member or close friend (if violent or accidental)
  – Experiencing repeated or extreme exposure to aversive details of the event (e.g., first responders).
Diagnosis

• Symptoms: ≥ 1 intrusion; ≥ 1 avoidance; ≥ 2 cognition/mood; ≥ 2 arousal/reactivity
• Duration: ≥ 1 month
• Clinically significant distress or impairment in social, occupational, or other important areas of functioning

Diagnosis: Intrusion Symptoms

• Distressing memories
• Distressing dreams
• Dissociative reactions (e.g., flashbacks)
• Psychological distress upon exposure to internal or external cues
• Marked physiological reactions to internal or external cues

Diagnosis: Avoidance Symptoms

• Avoidance of distressing memories, thoughts, or feelings about the trauma
• Avoidance of external reminders that arouse distressing memories, thoughts, or feelings about the trauma
### Diagnosis:
**Cognition/Mood Symptoms**
- Inability to remember an important aspect of the trauma
- Negative beliefs or expectations about oneself, others, or the world
- Distorted thoughts about the trauma that lead to blaming oneself or others
- Persistent negative emotional state
- Diminished interest or participation in activities
- Feelings of detachment or estrangement from others
- Persistent inability to experience positive emotions

### Diagnosis:
**Arousal/Reactivity Symptoms**
- Irritable behavior and angry outbursts
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle reflex
- Problems with concentration
- Sleep disturbance

### Differential Diagnosis
- Acute stress disorder
- Obsessive-compulsive disorder
- Panic disorder
- Generalized anxiety disorder
- Personality disorders
- Psychotic disorders
Comorbidity

- Major depressive disorder
- Anxiety disorders
- Substance use disorders
- TBI in combat veterans

Course

- Usually develops within the first 3 months post-trauma; there may be a delay of months or years
- Symptoms and symptom patterns may vary over time
- Symptoms resolve within 3 months in approx ½ cases; some patients can remain symptomatic for many years
- Recurrence may occur with such things as reminders of the trauma or ongoing life stressors

Prognosis

- Significant functional impairments
- Profound quality of life deficits
- Greater healthcare utilization and higher healthcare costs
- Increased risk of suicidality in war veterans and in civilians
Prevention: Psychotherapy

- Psychological debriefing
  - Single-session, individual or group crisis intervention
  - Meant to reduce and prevent psychological sequelae following traumatic events by promoting emotional processing
  - Focus is on the present reaction of individuals shortly after a traumatic experience
  - Use is no longer advocated; studies have revealed that it is ineffective -- or even potentially harmful

Prevention: Psychotherapy

- Cognitive-behavioral therapy (CBT)
  - Has shown considerable promise in cases involving acute stress disorder or high levels of distress
  - Early intervention CBT involves 60-90 minute weekly sessions over 5-12 weeks
  - Evidence for efficacy in preventing PTSD is strongest for those exposed to accidents (e.g., MVAs); less convincing for those exposed to interpersonal violence (e.g., rape)

Prevention: Pharmacotherapy

- Benzodiazepines have not been beneficial in studies examining prevention of PTSD
- While RCTs have not found that propranolol can reduce the rate of PTSD, a cohort study and a RCT revealed a reduction in PTSD symptom levels and reduced physiological activity to reminders of trauma
- Acute IV hydrocortisone was superior to placebo in preventing PTSD symptoms in medical patients with septic shock or those undergoing cardiac surgery
Prevention: Pharmacotherapy
- Escitalopram was ineffectual in a recent RCT, but sertraline therapy resulted in a greater decrease in parent-reported symptoms in a small, RCT in burned children
- No specific pharmacological intervention has been recommended for routine use as secondary prevention for PTSD; however, propranolol or sertraline can be considered

Treatment: Psychotherapy
- Cognitive-behavioral therapy (CBT)
- Eye movement desensitization and reprocessing (EMDR)
- Others
  - Group therapy
  - Psychodynamic psychotherapy
  - Hypnosis
  - Couple or family therapy

CBT
- Based on the relationship between thoughts, emotions, and behaviors
- Relatively brief form of psychotherapy that is problem-focused and action-oriented
- Typically averages 8-12 sessions administered once- or twice-weekly, with each session lasting 60-90 minutes each
- Patients complete homework assignments between sessions
Types of CBT

- Exposure therapy
  - Generally combines imaginal exposure to memories of the trauma and in vivo exposure to reminders of the trauma or triggers for trauma-related fear and avoidance

- Stress inoculation training (SIT)
  - Multifaceted approach that can include such things as education, muscle relaxation training, breathing retraining, self-talk, thought stopping, and role playing

- Cognitive therapy (CT)
  - Focused on thoughts related to safety, trust, and views of oneself

- Cognitive processing therapy (CPT)
  - Combines writing a trauma narrative and reading it repeatedly along with CT that is focused on safety, trust, control, esteem, and intimacy

EMDR

- Based on the theory that the improper storage of the traumatic event in implicit memory causes dysfunctional intrusions, emotions, and physical sensations

- Procedures are meant to stimulate the patient’s information processing in order to help incorporate the targeted event as an adaptive memory
EMDR Procedure

• Patient focuses on image, sensations, and negative cognition while simultaneously moving his/her eyes back and forth (e.g., watching light bars or therapist's fingers) for approximately 20-30 seconds
• Eye movement episodes are repeated until the target and any new associations have resolved (“desensitization”)

EMDR Procedure

• Subsequent eye movement episodes are administered with the patient focused on the alternate positive cognition in order to replace the negative cognition (“installation”)
• Thought that the dual attention serves to move the targeted event from implicit to explicit memory, which no longer contains the disturbing thoughts, emotions, and sensations

EMDR

• Single-episode traumas may respond more favorably
• Established efficacy in adult patients; not as well studied in children and adolescents
• Generally well tolerated
• Duration of treatment is highly patient-dependent
Treatment: Pharmacotherapy

- SSRIs
- Venlafaxine
- Other antidepressants
- Anticonvulsants
- Second generation antipsychotics (SGAs)
- Antiadrenergics
- Benzodiazepines
- Other medications

SSRIs

- Well-established treatments for PTSD; sertraline and paroxetine are FDA-approved
- By far the most extensively studied medications in PTSD
- Fluoxetine, paroxetine, and sertraline have demonstrated efficacy for acute treatment of PTSD in many RCTs
- Fluoxetine and sertraline have shown efficacy in placebo-controlled long-term relapse prevention studies
- Useful across the various PTSD symptom clusters and for co-occurring depression and disability

SSRIs

- Efficacy shortcomings
  - Little is known about the efficacy of some SSRIs; citalopram has a single RCT with negative results
  - SSRIs may have differential treatment effects
  - Despite overall evidence for efficacy, there have been negative trials
  - Results of more recent studies have cast doubts on the usefulness of SSRIs for treatment of combat-related PTSD
SSRIs

- Usual dosage
  - Fluoxetine 20-60 mg/day
  - Paroxetine 20-60 mg/day
  - Sertraline 50-200 mg/day
- May have relatively flat dose-response curves

SSRIs

- Adverse effects
  - Sexual dysfunction
  - Nausea, diarrhea
  - Dizziness
  - Nervousness/anxiety
  - Hyponatremia/SIADH
  - Serotonin syndrome
- Drug interactions are more common with fluoxetine, fluvoxamine, and paroxetine

Venlafaxine

- More effective than placebo, in contrast to sertraline, in a 12-week study
- More effective than placebo in a 6-month study in terms of improving both PTSD symptom severity and remission rates
- Potentially efficacious in improving PTSD symptoms in both men and women, and across all trauma types
Venlafaxine

- Usual dosage is 150-375 mg/day
- Adverse effects
  - Increased blood pressure
  - Sexual dysfunction
  - Nausea
  - Insomnia or somnolence
  - Nervousness
  - Dizziness

Other Antidepressants

- Mirtazapine
  - Resulted in a greater number of treatment responders vs. placebo in a small study
- TCAs
  - Amitriptyline and imipramine – but not desipramine – were efficacious in RCTs
  - Problematic adverse effects, lower adherence rates, and greater toxicity

Other Antidepressants

- Phenelzine
  - Mixed results in RCTs
  - Highly problematic drug-drug & drug-food interactions
- Nefazodone
  - Effective in a single RCT; however, problems with tolerability
- Bupropion
  - No significant effect vs. placebo in an 8-week trial
Anticonvulsants

- RCTs of anticonvulsants for treatment of PTSD are relatively limited in number; results are largely mixed
- Lamotrigine was successful in a 12-week trial that involved men and women with combat-related as well as civilian traumas
- Topiramate demonstrated limited benefits in a 12-week trial that involved civilian patients with PTSD
- Tiagabine did not differ from placebo in two different trials

- Divalproex has demonstrated beneficial effects as adjunctive therapy or monotherapy in several open trials, but it was not found to be efficacious in a well-designed trial that involved male veteran patients
- Gabapentin, carbamazepine, phenytoin, and levetiracetam have limited data suggesting their usefulness; need RCTs

- In general, high incidence of adverse effects
- Some agents have various monitoring parameters that should be followed
- Not first-line therapy for PTSD; but may have a role
  - Alternative treatment in patients intolerant to first-line therapies
  - Augmentation for partial responders
  - Treatment of refractory patients
SGAs

- Studied in at least a dozen prospective, controlled trials
- Risperidone demonstrated efficacy in multiple trials as adjunctive therapy and also in a monotherapy trial; two adjunctive therapy trials involving patients with SSRI-resistant PTSD failed to show efficacy
- Olanzapine demonstrated mixed results in a few monotherapy trials, and it was effective in an adjunctive therapy trial

Mixed efficacy results, but might be useful in treating anxiety, depression, and psychosis
- One of the key concerns is the potential for significant adverse effects, including sedation, weight gain, and EPS
- Quetiapine has been studied in open-label trials; might improve sleep disturbances
- On the whole, SGAs may have a role as adjunctive treatment in cases of partial response to SSRI/SNRI therapy

Antiadrenergics

- Prazosin
  - Used for management of PTSD-related nightmares and sleep disturbances; might reduce total PTSD symptoms
  - Typically added to ongoing first-line treatment
  - Onset of action as soon as 1 week in some patients
  - Generally well-tolerated; most frequent adverse effect is orthostatic hypotension
  - Start at 1 mg qhs & slowly titrate; usual dosage is 3-15 mg qhs
Antiadrenergics

- Other alpha-1 adrenergic antagonists have not been as well studied
- Guanfacine showed no effect on PTSD symptoms, subjective sleep quality, or general mood disturbances in a RCT of veterans with chronic PTSD
- Propranolol and clonidine have shown some promise in open-label studies

Benzodiazepines

- No evidence of efficacy vs. core symptoms
- Risk of abuse
- Worsened PTSD symptoms after withdrawal
- Nevertheless, used for sleep and anxiety very frequently
- Not recommended as monotherapy in PTSD

Other Medications

- Ketamine
- D-cycloserine
- MDMA
Therapeutic Goals

- Acute: reduction in core symptoms
- Continuation: prevention of relapse
- Prevention or reduction of comorbid conditions
- Improve quality of life and psychosocial functioning

Efficacy of Treatment

- Response: approx 60%
- Remission: approx 30%
- Systematic review in 2006
  - Mean decrease of 5.76 points on CAPS vs. placebo
  - Response rate 59.1% meds vs. 38.5% placebo
  - NNT = 4.85

Efficacy of Treatment

- AHRQ in 2013
  - Psychotherapies had large effect sizes; NNT loss diagnosis = 2 exposure, 4 for CPT, CT, EMDR
  - Pharmacotherapies had small-medium effect sizes; paroxetine and venlafaxine also had evidence of efficacy for inducing remission (NNT = 8)
  - Not enough head-to-head evidence for comparative effectiveness
Selection of Treatment Intervention

- Patient preferences
- Evidence for efficacy
- Access to treatment
- Choosing between medications
  - Adverse effect profiles
  - Cost
  - Other psychiatric diagnoses
  - Concurrent medical conditions & medications

Treatment Guidelines

- There are numerous practice guidelines for the treatment of PTSD; several have been updated since 2010
- In general, high level of consensus between guidelines
- Differences due to various methodologies, levels of evidence, and recommendation grading systems

Treatment Guidelines

- Trauma-focused psychotherapies are always emphasized
- What about pharmacotherapy?
  - Some guidelines consider medications as alternative first-line treatments
  - Others consider medications as options when psychotherapy is unavailable, unacceptable, or unsuccessful
- SSRIs and venlafaxine are preferred medications
### Treatment Guidelines: BAP 2014

- **First-line:**
  - Paroxetine, sertraline, venlafaxine, trauma-focused individual CBT or EMDR
  
- **When initial treatments fail:**
  - Combination evidence-based medication and psychotherapy; augmentation with olanzapine, risperidone, or prazosin

### Treatment Guidelines: ACPMH 2013

- **First-line:**
  - Trauma-focused CBT or EMDR

- **Other:**
  - Medications should not be routine first treatment
  - SSRIs are medications of first choice

### Treatment Guidelines: VA 2010

- **First-line:**
  - Psychotherapy (exposure therapy, CT, SIT, EMDR) and/or SSRI (fluoxetine, paroxetine, sertraline) or SNRI (venlafaxine)

- **Other:**
  - Mirtazapine, nefazodone, amitriptyline, imipramine, phenelzine are potential monotherapies
  - Augmentation therapy includes risperidone, olanzapine; prazosin can be added for sleep/nightmares
Treatment Algorithm: VA 2013

- Initial treatment
  - Psychotherapy or
  - SSRI or SNRI or
  - Psychotherapy + SSRI or SNRI
- Step 1
  - Switch to another SSRI or SNRI or
  - Add psychotherapy or
  - Switch to another SSRI or SNRI + Add psychotherapy

Treatment Algorithm: VA 2013

- Step 2
  - Switch to mirtazapine or
  - Add psychotherapy or
  - Switch to mirtazapine + Add psychotherapy

Treatment Algorithm: VA 2013

- Step 3
  - Switch to alternative Step 2 or
  - Switch to TCA or
  - Switch to nefazodone or
  - Switch to phenelzine
  - Add psychotherapy
- Add prazosin at any time for sleep/nightmares
Assessment of Response

- **When?**
  - At least every three months, but more frequently initially
- **What?**
  - PTSD symptom severity
  - Comorbid mental disorders
  - Suicide risk
  - Functioning and quality of life
  - Treatment adherence
  - Adverse effects
  - Patient satisfaction

Assessment of Response

- **How?**
  - Clinical interview
  - Validated PTSD scales

PTSD Scales

- Numerous scales are available
- Uses
  - Screen for PTSD
  - Aid in diagnostic workup
  - Evaluate response to therapy
- Self-report vs. clinician-rated
PTSD Scales

- There is no “best” scale; depends on a given clinical situation
- Some considerations
  - Time required to administer the measure
  - Need to correspond to DSM criteria for PTSD
  - Literacy level of the patient population

PTSD Scales: Examples

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<th>Screen</th>
<th>Clinician-rated</th>
<th>Self-report</th>
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<td></td>
<td>*Clinician Administered PTSD Scale (CAPS)</td>
<td>*PTSD Checklist (PCL)</td>
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<td>*PTSD Symptom Scale – Interview (PSS-I)</td>
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<td>*Structured Interview for PTSD (SIP)</td>
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<td>*Posttraumatic Diagnostic Scale (PDS)</td>
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Course of Pharmacotherapy

- Dosing
  - Initiate at low dose
  - Titrate gradually within the usual dosage range according to efficacy and tolerability
- Time course of response
  - Effects may be evident within the first 2-4 weeks
  - Adequate trial length is considered approx 8-12 weeks
  - Optimal results may not be realized until after 6-9 months of treatment
Course of Pharmacotherapy

- Results of therapy
  - Failed trial (inefficacy and/or intolerability)
    - Switch to another agent
  - Insufficient response
    - Longer-term treatment
    - Dosage optimization
    - Augmentation
    - Good response
      - Continuation treatment

- Duration of therapy
  - Successful treatment should be continued for at least 1 year
  - Considerations in regards to discontinuation
    - Persisting residual symptoms
    - Presence of ongoing stressors
    - Tolerability of therapy
    - Patient preference
    - Discontinuation should be via slow taper over at least 1 month

Special Populations: Women

- Disease characteristics
  - Higher lifetime risk
  - Greater symptom burden
  - Longer duration of illness
  - Worse quality of life
- Women may have better response rates to pharmacotherapy
Special Populations: Women

- Must consider pregnancy
  - Antidepressants: almost all are category C; paroxetine and nortriptyline are category D
  - Mood stabilizers: some are category C; CBZ & VPA are category D
  - SGAs: category C
  - Benzodiazepines: category D
- Must consider breastfeeding

Special Populations: Children & Adolescents

- Approximately 25% experience a significant traumatic event; estimated lifetime prevalence rate is approx 5% (females > males)
- PTSD can present differently
  - School-aged children may exhibit posttraumatic play or reenactment
  - Adolescents may exhibit impulsive and aggressive behaviors.

Special Populations: Children & Adolescents

- AACAP 2010
  - Trauma-focused psychotherapies recommended as first-line treatments; trauma-focused CBT has the most empirical support
  - SSRIs can be considered as treatment options; not recommended as sole therapy (i.e., without psychotherapy)
Special Populations: Children & Adolescents

- SSRIs have not performed well in RCTs
- SSRIs can have activating effects (e.g., irritability, poor sleep) that mimic hyperarousal symptoms
- Limited empirical evidence for other medications
- Low initial dosages; eventual dosages may resemble those of adults

Special Populations: Older Adults

- In general, PTSD is less prevalent and less severe vs. younger adults
- Concept of early-life vs. late-life trauma
  - Early-life trauma
    - Symptom severity and symptom pattern changes over time
    - Higher PTSD prevalence rates in older adults compared to late-life trauma
    - Causes much disability in areas such as role functioning, mobility, cognition, and social functioning
- Relatively sparse data concerning treatment
  - In general, older adults should be treated in a similar manner as younger adults
  - Pharmacotherapy considerations
    - Drug interactions
    - Medical disease states
    - Changes in clearance
    - Pre-existing cognitive impairment
Patient Education
- Psychoeducation
- Lifestyle changes/coping
- Medication counseling

Patient Education: Psychoeducation
- PTSD symptoms
  - Identify/label symptoms
  - Role of triggers
- Recovery process
  - Ongoing & gradual
  - Realistic expectations
- Treatment options

Patient Education: Psychoeducation
- Online resources
  - U.S. Department of Veterans Affairs National Center for PTSD
  - National Institute of Mental Health
  - National Alliance on Mental Illness
**Patient Education: Lifestyle Changes/Coping**

- PTSD support group
- Moderate physical exercise
- Community volunteerism
- Avoidance of drugs/alcohol
- Relationships with family and friends
- Relaxation methods
- Good sleep hygiene
- Positive distracting activities

**Patient Education: Lifestyle Changes/Coping**

- Negative coping mechanisms to be avoided
  - Substance abuse
  - Social isolation
  - Continuous avoidance of thinking about the trauma
  - Anger and aggression
  - Dangerous behavior
  - Working too much

**Patient Education: Medication Counseling**

- Purposes of treatment
- How/when to take medications
- Onset of response; expected duration
- Common/serious adverse effects
- Need for treatment adherence
- Discuss concerns/problems vs. unilaterally alter treatment