Optimizing Outcomes for Patients With Anxiety

(page 303 in syllabus)

William M. Sauvé, MD
Clinical Director of Military Programs
Poplar Springs Hospital

Sponsored by the Neuroscience Education Institute
Additionally sponsored by the American Society for the Advancement of Pharmacotherapy

This activity is supported solely by the sponsor, Neuroscience Education Institute.
Individual Disclosure Statement

Faculty Editor / Presenter

William M. Sauvé, MD, is the clinical director of military programs at Poplar Springs Hospital in Petersburg, VA.

Speakers Bureau: Pfizer
Learning Objectives

• Explain the neurobiology of both normal and pathological stress and anxiety
• Identify the environmental and genetic factors that can contribute to the development of an anxiety disorder
• Identify new treatment options in development for PTSD
• Customize treatment regimens for patients with PTSD based on symptom profile, comorbidities, and life situations
Pretest Question 1

38y/o male with PTSD, alcohol dependence, and chronic back and knee pain presents on these medications: quetiapine (Seroquel) 50mg qHS, prazosin 3mg qHS, duloxetine (Cymbalta) 90mg daily, gabapentin 300mg TID, clonidine 0.1mg TID, zolpidem (Ambien) 10mg qHS and clonazepam (Klonopin) 1mg up to TID as needed. His complaints include ongoing nightmares, exaggerated startle, depressed mood, difficulty staying asleep and poor memory. What might you do FIRST to optimize this patient's medication regimen?

1. Increase quetiapine dose
2. Increase prazosin dose
3. Change the clonazepam to from PRN to BID
4. Discontinue the hypnotics (zolpidem) and the benzodiazepines (clonazepam)
The Path to PTSD: A Circuit’s Story
Normal Stress in Normal Circuits

normal circuit at rest → emotional trauma → normal circuit activated → emotional trauma withdrawn → normal circuit at rest

overactivation  normal  baseline  hypoactivation
The Path to PTSD: A Circuit’s Story
Stress Sensitization in Normal Circuits

- normal circuit at rest
- emotional trauma
- normal circuit activated
- sustained, repeated emotional trauma
- normal circuit continuously activated
- emotional trauma withdrawn
- irreversible stress sensitization

- overactivation
- normal
- baseline
- hypoactivation


Copyright © 2011 Neuroscience Education Institute. All rights reserved.
The Path to PTSD: A Circuit’s Story
Progression From Stress Sensitization

- Emotional trauma
- Irreversible stress sensitization
- Vulnerable but presymptomatic

- Lack of compensation
- Prodromal symptoms

- Emotional trauma continues
- Decompensation with either overactivation or breakdown
- Subsyndromal symptoms

- Emotional trauma withdrawn
- Decompensation is sustained
- Psychiatric symptoms

THE STRESS DIATHESIS MODEL

Trauma is necessary but not sufficient for the precipitation of anxiety disorders such as PTSD

Only 5-30% of trauma victims develop PTSD

Mahan, Ressler. TINS 2011;Epub ahead of print.
Stress Diathesis Model: A Tale of Two Influences, Part 1

normal genes

life events

bad childhood, divorce, virus or toxin

normal circuit

normal activation

overactivation, normal, baseline, hypoactivation

normal phenotype
Stress Diathesis Model: A Tale of Two Influences, Part 2

- risk gene
- divorce
- single life event stressor

“biased” circuit

- overactivation
- normal baseline
- hypoactivation

overactivation inefficient information processing

normal phenotype

Stress Diathesis Model: A Tale of Two Influences, Part 3

- risk gene
- multiple life events
- bad childhood
- divorce
- virus or toxin

-diathesis
- “biased” circuit
- hypoactivation with malfunction
- unsuccessful compensation
- psychiatric symptoms


Copyright © 2011 Neuroscience Education Institute. All rights reserved.
HPA Axis: A Critical Circuit for Stress Responses

I can’t believe that guy shot at me!
HPA Axis: A Critical Circuit for Stress Responses

I can’t believe that guy shot at me!
I can’t believe that guy shot at me!
I can’t believe that guy shot at me!
HPA Axis: A Critical Circuit for Stress Responses

I can’t believe that guy shot at me!
HPA Axis: A Critical Circuit for Stress Responses

I can’t believe that guy shot at me!
HPA Axis: A Critical Circuit for Stress Responses

Hypothalamus

Hippocampus

Pituitary

Adrenal

Corticotropin (ACTH)

Glucocorticoid receptor

Cortisol

Corticotropin releasing factor (CRF)
I am so tired from working 60 hours per week, taking care of my small children and my elderly parents, and not being able to pay the bills.
I am so tired from working 60 hours per week, taking care of my small children and my elderly parents, and not being able to pay the bills.
I am so tired from working 60 hours per week, taking care of my small children and my elderly parents, and not being able to pay the bills.
Reduced Hippocampal Volume and Stress: Cause or Effect?

Most Common Mental Illnesses Associated With Trauma

MDD
- Depressed mood
- Loss of interest/pleasure
- Appetite/weight changes
- Suicidality
- Guilt/worthlessness

Anxiety Disorder
- Anxiety
- Worry
- Irritability
- Muscle tension
- Phobic avoidance
- Compulsions
- Panic attacks

Sleep
- Concentration

Fatigue
- Psychomotor
### Who Is At Risk?

<table>
<thead>
<tr>
<th>STRONG</th>
<th>MODERATE</th>
<th>???</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric history</td>
<td>Life stress</td>
<td>Trauma type</td>
</tr>
<tr>
<td>Childhood abuse</td>
<td>Lack of social support</td>
<td>Small hippocampus</td>
</tr>
<tr>
<td>Family psychiatric history</td>
<td>Other previous trauma</td>
<td>Genetic polymorphisms</td>
</tr>
<tr>
<td></td>
<td>Other adverse childhood experience</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trauma severity</td>
<td></td>
</tr>
</tbody>
</table>

Early Life Stress

early life stress  

stress sensitization  

adult trauma

Early Life Stress: Is It All Bad?

- **Amygdala**
  - **No stress in infancy**
  - **Mild stress in infancy**
  - **Child abuse**
  
- **No stress in infancy**
  - Normal stress activation

- **Mild stress in infancy**
  - Reduced reactivity to stress

- **Child abuse**
  - Stress sensitization but no symptoms of anxiety or depression

- **Multiple adult life stressors**
  - **No psychiatric disorder**
  - **MDD**
  - **Anxiety disorder**

Genetic Risk Factors Under Investigation

- **DA transporter gene** (SLC6A3 9 allele)
  - An excess of 9 tandem repeats found in patients who developed PTSD

- **5-HT transporter gene** (“s” allele)
  - Increased risk of PTSD in high-risk environments

- **BDNF gene** (Val66Met)
  - Met/Met carriers have greater recruitment of amygdala and PFC during memory formation and retrieval

- **Glucocorticoid receptor co-chaperone FKBP5 gene**
  - Interaction with childhood abuse
  - May contribute to increased sensitivity of the amygdala and HPA axis

Risks in the Military: More Than Just Combat

- Separation
- Destruction
- Readjustment
- Combat
- Unpredictable threats
- Easy weapon access
- Lack of public support

PTSD and the HPA Axis

- Increased sensitivity to negative cortisol feedback
- Low cortisol
- Reduced hippocampal volume
- Increased CRF
- Downregulated CRF receptors

Hippocampus
Hypothalamus
Pituitary
Adrenal
## Neuroimaging Findings in PTSD

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Functional</th>
<th>Structural</th>
<th>Potential Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>↑</td>
<td></td>
<td>Exaggerated fear response</td>
</tr>
<tr>
<td>rACC</td>
<td>↓</td>
<td>↓ volume</td>
<td>Deficits in extinction, emotion regulation, attention, contextual processing</td>
</tr>
<tr>
<td>dACC</td>
<td>↑</td>
<td></td>
<td>Exaggerated fear learning</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>↑↓</td>
<td>↓ volume</td>
<td>Deficits in contextual processing, Intrusive memories</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>↑↓</td>
<td>↓ volume</td>
<td>Increased anxiety proneness</td>
</tr>
</tbody>
</table>

Brain Atrophy in PTSD is Ongoing

PTSD “Non-Pharmacy”

1st-line
- exposure therapy
- cognitive restructuring

2nd-line
- acceptance and commitment therapy
- stress inoculation

adjunctive
- motivational interviewing
- dialectical behavior therapy
- seeking safety therapy
- eye movement desensitization and reprocessing

Virtual Exposure Therapy


Copyright © 2011 Neuroscience Education Institute. All rights reserved.
PTSD “Pharmacy”

Only sertraline and paroxetine are FDA-approved to treat PTSD.

5-HT Signaling Increases BDNF Release, Which Modifies 5-HT Innervation

Sertraline

- SSRI
- FDA-approved for the treatment of PTSD
- Most common side effects are sexual dysfunction, gastrointestinal issues, and CNS problems
- Weight gain and sedation unusual
- Initial dosing at 25 mg/day increased to 50 mg/day after 1 week; maximum dose 200 mg/day single dose

- 169 outpatient veterans in randomized, double-blind comparison of sertraline vs placebo
  - 12 wks flexible dose (25-200 mg/day)
  - Scales: CAPS, Impact of Events, Clinical Global Impressions (CGI-I)
- No significant difference noted between sertraline and placebo

- 37 patients in randomized, double-blind comparison of sertraline vs nefazodone
  - 12 wks flexible dose (avg. 153 mg/day sertraline)
  - Scales: CAPS, CGI-I
- Both treatment groups showed improvement; no difference between groups in efficacy

Paroxetine for Non-Combat-Related PTSD

- SSRI
- FDA-approved for PTSD treatment
- Aids in treatment of re-experiencing, avoidance, and hyperarousal
- Effective antidepressant and anxiolytic

Other Medications

- Other SSRIs/SNRIs: rationale and some published data in support of efficacy
- Benzodiazepines: negative studies
- MAOIs: mixed data
- Atypical antipsychotics: mixed data
  - Possibly beneficial as adjuncts for psychotic symptoms, sleep

Pretest Question 2

38y/o male with PTSD, alcohol dependence, and chronic back and knee pain presents on these medications: quetiapine 50mg qHS, prazosin 3mg qHS, duloxetine 90mg daily, gabapentin 300mg TID, clonidine 0.1mg TID, zolpidem 10mg qHS. He has also recently started on clonazepam 1mg BID. His complaints include ongoing nightmares, depressed mood, difficulty staying asleep and poor memory. What might you do now to optimize this patient's medication regimen?

1. Increase quetiapine dose
2. Decrease quetiapine dose
Atypical Antipsychotics for PTSD: Increasing Serious Side Effects Without Therapeutic Benefits?

- Study investigating risperidone vs placebo in SSRI-resistant PTSD cases

![Graph showing CAPS total score and follow-up time](image)

No. of patients
- Placebo: 134, 122, 127, 124
- Risperidone: 133, 128, 122, 123

Noradrenergic Hyperactivity in Anxiety

- anxiety / panic attacks
- tremor
- sweating
- tachycardia
- hyperarousal
- nightmares

Alpha-1 Adrenergic Blockers to Treat Anxiety and Nightmares

- tremor
- sweating
- tachycardia
- hyperarousal
- nightmares

Pretest Question 3

38y/o male with PTSD, alcohol dependence, and chronic back and knee pain presents on these medications: quetiapine 50mg qHS, prazosin 3mg qHS, duloxetine 90mg daily, gabapentin 300mg TID, clonidine 0.1mg TID, zolpidem 10mg qHS. *He has also recently started on clonazepam 1mg BID and his quetiapine dose was increased to 300 mg/day. His is still complaining of ongoing nightmares, but his depression has improved. He also still has difficulty staying asleep, chronic knee and back pain, and poor memory. What might you do now to optimize this patient's medication regimen?*

1. Increase prazosin dose
2. Increase neurontin dose
3. Both of the above
Prazosin (Minipress)

- Alpha-1 adrenergic blocker
- Antihypertensive drug
- Used to prevent nightmares in patients with PTSD; normalizes slow-wave sleep
- Not extensively studied in PTSD
- Dose not established; studied at 1–20 mg/day at bedtime or in divided doses
- Side effects include orthostatic hypotension, insomnia/fatigue, depression, nervousness, dizziness, syncope, headache, gastrointestinal effects
- Side effects generally decrease with time
- Notable interactions: diuretics, other antihypertensive drugs

Prazosin vs. Quetiapine

Beta Adrenergic Blockers to Treat Anxiety

- anxiety / panic attacks
- tremor
- sweating
- tachycardia
- hyperarousal
- nightmares

Preemptive Treatment: Blocking Fear Conditioning With Beta Blockers

Preemptive Treatment: Blocking Fear Conditioning With Beta Blockers

VMPFC

hippocampus

ß1 blocker

no fear response

locus coeruleus
Propranolol (Inderal)

• Beta blocker and antihypertensive drug
• Might block effects of stress from prior traumatic experiences
• Usual dose range: up to 240 mg/day; effective dose varies greatly
• Side effects include insomnia/fatigue, depression, vivid dreams, gastrointestinal effects
• Notable interactions: most atypical antipsychotics, alcohol, ibuprofen/NSAIDs, SSRIs, duloxetine
• A recent study showed that propranolol was ineffective for reducing PTSD-like onset in a rat model

Pharmacotherapy Following Traumatic Injury May Prevent Development of PTSD

- 696 injured U.S. military personnel
- Intravenous administration of morphine during resuscitation and trauma care

Odds Ratio Adjusted for Injury Severity Score (95% CI): 0.48 (0.34–0.68) p<0.001

Prophylactic Use of Cortisol

- PTSD may develop as a result of subadequate cortisol response
- High dose hydrocortisone treatment given in first few hours immediately following trauma

Cortisol Following Stress Increases BDNF in Hippocampus

Fear Conditioning vs Fear Extinction


Copyright © 2011 Neuroscience Education Institute. All rights reserved.
Fear Conditioning vs Fear Extinction

VMPFC
hippocampus

VMPFC
hippocampus
sensory cortex
thalamus

no fear response

learning

fear conditioning

fear response!!!

fear extinction

new learning

no fear response

= glutamate

= GABA

Facilitating Fear Extinction: Enhancing Inhibitory Learning With the NMDA Agonist D-Cycloserine

Potential Sites of Action for Novel Treatments for PTSD

**Adrenal**

**Hippocampus**

**Hypothalamus**

**Pituitary**

- **glucocorticoid antagonist**
- **CRF-1 antagonist**
- **vasopressin 1B antagonist**

- **Corticotropin (ACTH)**
- **Glucocorticoid receptor**
- **Cortisol**
- **Corticotropin releasing factor (CRF)**
Common Comorbidities and Complications

- PTSD
  - Anxiety/Re-experiencing
    - Worry
    - Sleep
    - Irritability
    - Avoidance/Numbing
    - Concentration problems
    - Arousal
  - Suicidality
  - Alcohol and drug dependence
  - Traumatic brain injury
  - Depression
  - Other anxiety disorders

Copyright © 2011 Neuroscience Education Institute. All rights reserved.
## Suicide Risk Factors

<table>
<thead>
<tr>
<th>Immutable</th>
<th>Circumstantial</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s history (experience of trauma/loss, previous attempt, psychiatric illness)</td>
<td>Unemployment (reserves)</td>
<td>Drinking/drug use</td>
</tr>
<tr>
<td>Family history</td>
<td>Financial difficulties</td>
<td>Nicotine use</td>
</tr>
<tr>
<td>Demographics (male, unmarried, early 20s)</td>
<td>Relationship difficulties</td>
<td>Unstructured time</td>
</tr>
<tr>
<td>Cultural/religious belief about suicide</td>
<td>Physical injury/illness, chronic physical pain</td>
<td>Perceived stress</td>
</tr>
<tr>
<td>Personality traits (impulsive, aggressive)</td>
<td>Life transitions</td>
<td>Current psychiatric illness (depression, alcohol abuse)</td>
</tr>
<tr>
<td></td>
<td>Access to lethal means</td>
<td>Hopelessness, helplessness</td>
</tr>
<tr>
<td></td>
<td>Disciplinary action</td>
<td>Anxiety, panic attacks, agitation, insomnia*</td>
</tr>
</tbody>
</table>

*Often precede suicide within hours/days/weeks*
Are Some Symptoms Precursors to Suicidality?

- Anxiety
- Agitation
- Panic attacks
- Insomnia
- Irritability
- Hostility
- Aggressiveness
- Impulsivity
- Restlessness
- Hypomania and mania
Suicide Risk Is Highest When:

- The person sees no way out and fears things may get worse
- The predominant emotions are hopelessness and helplessness
- The person is anxious, agitated, and has insomnia
- Thinking is constricted with a tendency to perceive his or her situation as all bad
- Judgment is impaired by use of alcohol or other substances
- There is a lack of future orientation
Suicide Assessment

• Conduct a thorough assessment and reassessment of suicide risk

• Involve patient and family in treatment plan

• Choose appropriate treatment setting and means of monitoring patient based on risk assessment

• Document your thinking about suicide risk and your decision-making based on your assessment

• Remember: 3 out of 4 suicide victims had contact with their primary care provider within 90 days of their suicide
PTSD and Substance Abuse

- Trauma memories may elicit cravings
- Childhood trauma can increase the risk of PTSD in substance abuse patients, especially if multiple traumas have been witnessed as an adult
- Unresolved PTSD can result in a higher risk of substance abuse
- Childhood traumas are a better predictor of adulthood substance abuse cravings than adolescent traumatic events

Treating Comorbid SUD in Patients With PTSD

- Methadone
- Buprenorphine
- Bupropion
- Varenicline
- Acamprosate
- Naltrexone
- Opiate
- Nicotine
- Alcohol
- Non-pharmacological
- Seeking safety therapy
- Motivational interviewing
- Support groups

SUD pharmacy
Gabapentin + Naltrexone

PTSD, Chronic Pain, and Depression

• 80% rate of chronic pain in sample of Vietnam vets with PTSD

• PTSD more influential than depression and other disorders in leading to poor physical health

• Depression found to mediate the relationship between PTSD and pain

• Treatment for PTSD and pain should take potential depressive symptoms into account

Persistent Postconcussive Syndrome (PPCS) and PTSD: Symptom Overlap

PTSD
- Nightmares
- Flashbacks
- Guilt

Emotional lability
- Depression
- Irritability/anger
- Concentration/attention problems
- Fatigue
- Hyperarousal
- Avoidance
- Apathy

PPCS
- Headaches
- Sensitivity to light/sound
- Memory deficit
- Dizziness
- Disinhibition

Brain Regions Vulnerable to TBI: Overlap With PTSD?

TBI

TBI and PTSD

DLPFC

OFC

subcortical white matter

hippocampus

PTSD and Comorbid TBI “Pharmacy”

Kennedy et al. JRRD 2007;44:895-920.

Copyright © 2011 Neuroscience Education Institute. All rights reserved.
Summary

• Many factors, both environmental and genetic, may contribute to whether one develops mental illness following trauma

• PTSD is a disorder with significant impact on functioning and quality of life

• Anxiety disorders, including PTSD, should be diagnosed and treated according to the best available evidence

• Maximizing treatment outcomes may require an integrated approach that encompasses both pharmacological and non-pharmacological interventions