Handout for the Neuroscience Education Institute (NEI) online activity:

The War At Home: Psychiatric Outcomes of Deployment
Learning Objectives

• Identify the mental health issues commonly encountered in the military population

• Understand the neurobiological, environmental, and genetic factors that increase the risk of mental illness in the military population

• Utilize best practices for the treatment of PTSD and comorbid conditions
I see patients who are Veterans of the recent Iraq/Afghanistan wars in my practice.

1. Frequently
2. Sometimes
3. Never
Pre-Poll Question 2

I feel competent treating patients from the military population, including Veterans.

1. strongly disagree

2.

3.

4.

5. strongly agree
Pretest Question 1

A 25-year-old man who is on active duty in the military has been on 4 combat deployments, including 1 in Iraq and 2 in Afghanistan. During 1 of his deployments, he suffered a blast injury with a level 2 concussion. He has been suffering from depressed mood, baseline anxiety, panic attacks, frequent combat-related nightmares and flashbacks, decreased appetite, and some irritability. He increased his alcohol use after his first deployment, and in the past few months, he has increased it even more, to about 15 or more drinks per day. His alcohol use has resulted in 3 DUIs. He has been abstinent from alcohol for the past 7 days. He first started treatment about 1 month ago, when he was diagnosed with PTSD and started on alprazolam 0.5 mg 3 times daily. This patient is new to you. What might you do first?

1. Increase the dose of alprazolam to 1 mg 3 times daily
2. Transition the patient from alprazolam to clonazepam
3. Transition the patient to quetiapine 100 mg 3 times daily
4. Begin prolonged exposure-based psychotherapy
You Will Probably Be Enlisted for The War At Home

- The "War at Home" is fought on many different fronts and is only just getting started
  - $350,000,000 \times 1\% = 3,500,000 \times 15\% = 525,000$
  - If all wars were to end tomorrow, we would likely see new cases for at least another decade
  - The VA and DOD would likely be unable to handle all the demand; private mental health must get comfortable with the idea of caring for patients with combat PTSD
Risks in the Military: More Than Just Combat

- Separation
- Destruction
- Combat
- Unpredictable threats
- Easy weapon access
- Readjustment

Posttraumatic Stress Disorder (PTSD)

• 3 main categories of symptoms
  – Physiological hyperarousal
  – Thought intrusion
  – Avoidance or emotional numbing in response to actual or threatened death or serious injury to oneself or others

• How common is PTSD?
  – Prevalence is 0.6-31% (after combat duty in Iraq or Afghanistan)

Prevalence of PTSD: It Depends WHO You Ask


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Prevalence of PTSD: It Depends HOW You Ask

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<th>Study</th>
<th>Percentage (95% CI)</th>
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Prevalence of PTSD: It Depends WHEN You Ask

PTSD Etiology

• Does combat-related PTSD differ from non-combat-related PTSD?
  – A combatant is not a victim
  – Treating combat PTSD can present some unique challenges
  – Patient may question your worthiness; how to establish rapport?
  – What if the would-be therapist has a very real fear regarding their patient?

• Killing vs. fear of being killed or harmed
  – Moral injury?
Grief

• A substantial number of veterans diagnosed with PTSD may actually be suffering from severe grief
  – Your patient's combat experience may not have been as traumatizing as you imagine
  – Is the source of distress:
    • The details of the firefight?
    • The fact that the patient's dearest friend was killed in the firefight?

• Grief does not seem to respond to treatments meant for PTSD
THE NEUROBIOLOGY OF PTSD
Stress Diathesis Model: A Tale of 2 Influences, Part 1

normal genes

bad childhood

divorce

virus or toxin

life events

normal circuit

overactivation
normal
baseline
hypoactivation

normal phenotype

Stress Diathesis Model: A Tale of 2 Influences, Part 2

- risk gene
- divorce
- single life event stressor
- "biased" circuit
- overactivation
- normal
- baseline
- hypoactivation
- normal phenotype

Stress Diathesis Model: A Tale of 2 Influences, Part 3

Diathesis

Risk gene

Bad childhood

Divorce

Multiple life events

Virus or toxin

Stress

"Biased" circuit

Hypoactivation with malfunction

Unsuccessful compensation

Psychiatric symptoms

Genetic Predisposition

• ADRA2B
  – Deletion causes reduction in alpha 2B autoreceptor
  – Leads to increased neurotransmission
  – May result in enhanced emotional memory

• COMT
  – Catechol-O-methyltransferase is involved in the breakdown of dopamine
  – May impact prefrontal regulation of amygdala reactivity to adverse events
    • Impacting consolidation

Rasch et al. PNAS 2009;106(45):19191-6;
Todd et al. Neuropsychologia 2011;49(4):734-44.
I can't believe that guy shot at me!
HPA Axis: Chronic Stress

Will I be shot at today? Will I encounter an IED while on patrol? Are my pregnant wife and unborn child doing okay?
PTSD and the HPA Axis

increased sensitivity to negative cortisol feedback

low cortisol

increased CRF

downregulated CRF receptors

reduced hippocampal volume

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## Neuroimaging Findings in PTSD

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<th>Brain Region</th>
<th>Functional</th>
<th>Structural</th>
<th>Potential Implications</th>
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<td>rACC</td>
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<td>↓ volume</td>
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<tr>
<td>Hippocampus</td>
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<td>↓ volume</td>
<td>Deficits in contextual processing</td>
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<tr>
<td>Insular cortex</td>
<td>↑↓</td>
<td>↓ volume</td>
<td>Increased anxiety proneness</td>
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Brain Atrophy in PTSD is Ongoing

Resilience

• What is "resilience"?

• Is it modifiable?
  – Resilience may affect treatment response
  – Is it possible to entrain resilience in order to prevent PTSD?
    • Does incidence of PTSD reflect failure of training?
  – Stress Resilience in Virtual Environments (STRIVE)
  – Meditation training
    • Transcendental meditation, mindfulness, and progressive muscle relaxation have potential
  – Comprehensive Soldier Fitness (CSF)

PTSD "Pharmacy"

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

Recent Meta-analysis of PTSD Pharmacotherapy

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Random effects model 2425
Heterogeneity: I²=218%, τ²=4.209, p=0.1717

Novel PTSD Psychopharmacology

• Topiramate
  – Level D evidence (no evidence of benefit and possibly evidence of harm)
  – Still useful for headache prophylaxis, which you can expect to see often in patients with PTSD

• Eszopiclone
  – Some small studies have been positive (Duffy, Malloy)

• Gabapentin/pregabalin
  – No benefit for prevention
  – However, is useful for pain and possibly for alcohol relapse prevention

Novel PTSD Psychopharmacology

• Propranolol
  – Jury is still out, but some studies have indicated that it is not prophylactic

• Hydrocortisone may be beneficial

• D-cycloserine
  – A recent double-blind, placebo-controlled RCT showed some response in severe PTSD

• Endocannabinoids

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
• Nightmares tend to come back after prazosin is discontinued

Prazosin vs. Quetiapine

Propranolol (Inderal)

• Beta-blocker and antihypertensive drug

• Might block effects of stress from prior traumatic experiences

• Usual dosage 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

MDMA: Improvement on Clinician-Administered PTSD Scale (CAPS)

Atypical Antipsychotics for PTSD: Increasing Serious Side Effects Without Therapeutic Benefits?

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

Olanzapine Monotherapy

Mean CAPS Total Score

Baseline | Week 4 | Week 8
---|---|---
Olanzapine | Placebo

Aripiprazole

Pharmacotherapy Following Traumatic Injury May Prevent the 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

Cortisol Following Stress Increases BDNF in Hippocampus

PTSD "Non-Pharmacy"

- First-line treatment:
  - Exposure therapy
  - Cognitive restructuring

- Second-line treatment:
  - Acceptance and commitment therapy
  - Stress inoculation
  - Eye movement desensitization and reprocessing

- Adjunctive therapy:
  - Seeking safety therapy
  - Motivational interviewing
  - Dialectical behavior therapy

Virtual Exposure Therapy

McLay RN. Cyberpsychol Behav Soc Networking 2011;14(4):223-9;
Behavioral Activation and Therapeutic Exposure (BA-TE) Treatment

EMDR vs. Psychotherapy

Behavioral Sleep Intervention vs. Prazosin

Additional Nonpharmacological Options

• Yoga
• Acupuncture
• ECT
• rTMS
  – 1 Hz
  – 10 Hz
  – 20 Hz

Comorbid Conditions: Substance Use Disorders

- Approximately 75% of military personnel diagnosed with PTSD have a co-occurring substance abuse disorder
- 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
- Alcohol
- Prescription opiates

Treating Comorbid SUD in Patients With PTSD

- Methadone
- Buprenorphine
- Bupropion
- Varenicline
- Acamprosate
- Naltrexone
- SUD pharmacy

- Opiate
- Nicotine
- Alcohol
- Nonpharmacological

- Seeking safety therapy
- Motivational interviewing
- Support groups
Comorbid Conditions: Mild Traumatic Brain Injury (mTBI)

- Increased risk for pseudobulbar affect (PBA)?
- PBA is meant to encompass both pathological laughter and crying as well as affective lability
- PBA is characterized as an affective display that occurs without voluntary control or modulation and is not meaningfully related to the stimulus that provokes it
- Affective lability is characterized as paroxysms that are excessive but related to the stimuli that provokes them
- PBA is thought to involve a disconnection syndrome that disinhibits brainstem centers, depriving them of cortical constraints on bulbar control of the motor expression of emotional state
Neurobiology of PBA

- Dysregulation of affect is produced by impairments in a large-scale set of parallel-distributed circuits in a cortico-limbic-subcortico-thalamo-ponto-cerebellar network.
- Lesions in brainstem, bilateral inferior parietal and medial inferior frontal lobes, and right medial superior frontal lobe.

PTSD Polypharmacy

- A major problem that is increasingly trumpeted in the media
- Polypharmacy can be defined as any case in which more than 1 medication is used
- Irrational vs. rational polypharmacy
PTSD Polypharmacy (cont.)

• PTSD is an illness that likely must be treated with polypharmacy and raises the risk for irrational polypharmacy

• There is probably no drug that is very effective for PTSD

• By virtue of their occupation, psychopharmacologists will find themselves choosing medications to treat the symptoms of PTSD, which can include affective lability, anxiety, irritability, insomnia, and nightmares

• Making things worse, the PTSD sufferer is often in a considerable amount of acute distress; all drugs in the antidepressant class take weeks to work, leading to patients presenting week after week complaining that the meds "aren't working;" it is extraordinarily hard to say no
PTSD Polypharmacy (cont.)

• It is critical to avoid the cycle of piling meds on top of meds

• It is OK not to write another script

• Consider a more controlled environment while anxiety/distress remains high
PTSD Polypharmacy (cont.)

• A very large number of military veterans with PTSD also suffer from musculoskeletal injuries and possibly mTBI

• Chronic pain leads to opiates!

• mTBI often includes chronic headaches, which can also lead to escalating pain meds; mTBI presents with many symptoms that overlap with PTSD

• Patients may appear even more acute or unresponsive to treatment, leading to even more escalation of meds

• Complaints of poor concentration may result in the prescription of stimulants (in patients who suffer from insomnia and anxiety!)

• Patients with mTBI may also react to medications in unexpected ways
What To Do About Irrational Polypharmacy?

• Be the one to break the cycle of reactivity
  – Quetiapine was just removed from the "approved" list at the DOD (hint: irrational)
  – Develop the strength to refuse to prescribe away every complaint (is "zero" anxiety really a logical goal?)

• Be able to explain the rationale for each medication choice

• Review the list of medications OFTEN
  – Look for redundancy
  – Look for inadequate dosing
  – Look for contradictions (stimulants + sedatives?)
What To Do About Irrational Polypharmacy?

• Look for ways to treat without medication
  - Psychotherapy remains the best long-term treatment for PTSD
  - Cognitive therapy for sleep
  - Non-medication treatments for pain
  - Exercise
  - Physical therapy
  - TENS units, etc.
  - Acupuncture can be promising
  - Think about medications for PTSD symptoms that may also be beneficial for pain (duloxetine, etc.)
Summary

• Although the prevalence of psychiatric issues in the military may be difficult to assess, it is likely that most mental health clinicians will encounter the military population at some point in their practices.

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

• PTSD is a disorder with significant impact on functioning and quality of life; it should be diagnosed and treated according to the best available evidence.

• The treatment of common comorbid conditions, including substance abuse, need to be addressed in order to optimize treatment outcomes and improve quality of life.

• Maximizing treatment outcomes may require an integrated approach that encompasses both pharmacological and nonpharmacological interventions.