PTSD Overview and Psychopharmacology Update

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Disclosures

- I am employed by the U.S. Department of Veterans Affairs
- Except where clearly stated, this presentation reflects my opinions and not the VA
- Off-label use of medication will be discussed
- If we discuss TBI, I am listed as a co-inventor for a patent application disclosing a novel device for head acceleration and impact measurement, and co-founder and stockholder in a startup company to develop it

Objectives

- Review PTSD epidemiology
- Distinguish between first line and second line medications in treating PTSD
- Learn which medications do not have evidence to support use in PTSD

PTSD: Changes from DSM-IV to DSM5

	DSM5	DSM-IV
Total Symptoms	20	17
Symptom Clusters	5	4
	Stressor (1+) Intrusion (1+) Avoidance (1+) Altered Cognition & Mood (2+) Arousal (2+)	Stressor Intrusion Avoidance Arousal
New Symptoms	Beck's Triad Persistent Negative Emotions Self-Destructive Behavior	

PTSD Epidemiology

Epidemiology

- US adult population lifetime prevalence: 6.4 – 6.8%
  - Stable over two studies 5 years apart
  - Point prevalence 4-5%
- OEF/OIF Veterans lifetime prevalence: 7.3 – 8.6%
  - Expect higher figures with greater combat exposure
- Military Veterans overall lifetime prevalence: 8%
- Active-duty DoD prevalence: 2.2% in FY15
  - About one-half of the US population point prevalence
  - Almost certainly under-reported due to concerns about career, security clearance, or peer opinions

Epidemiology by Veteran Service Era

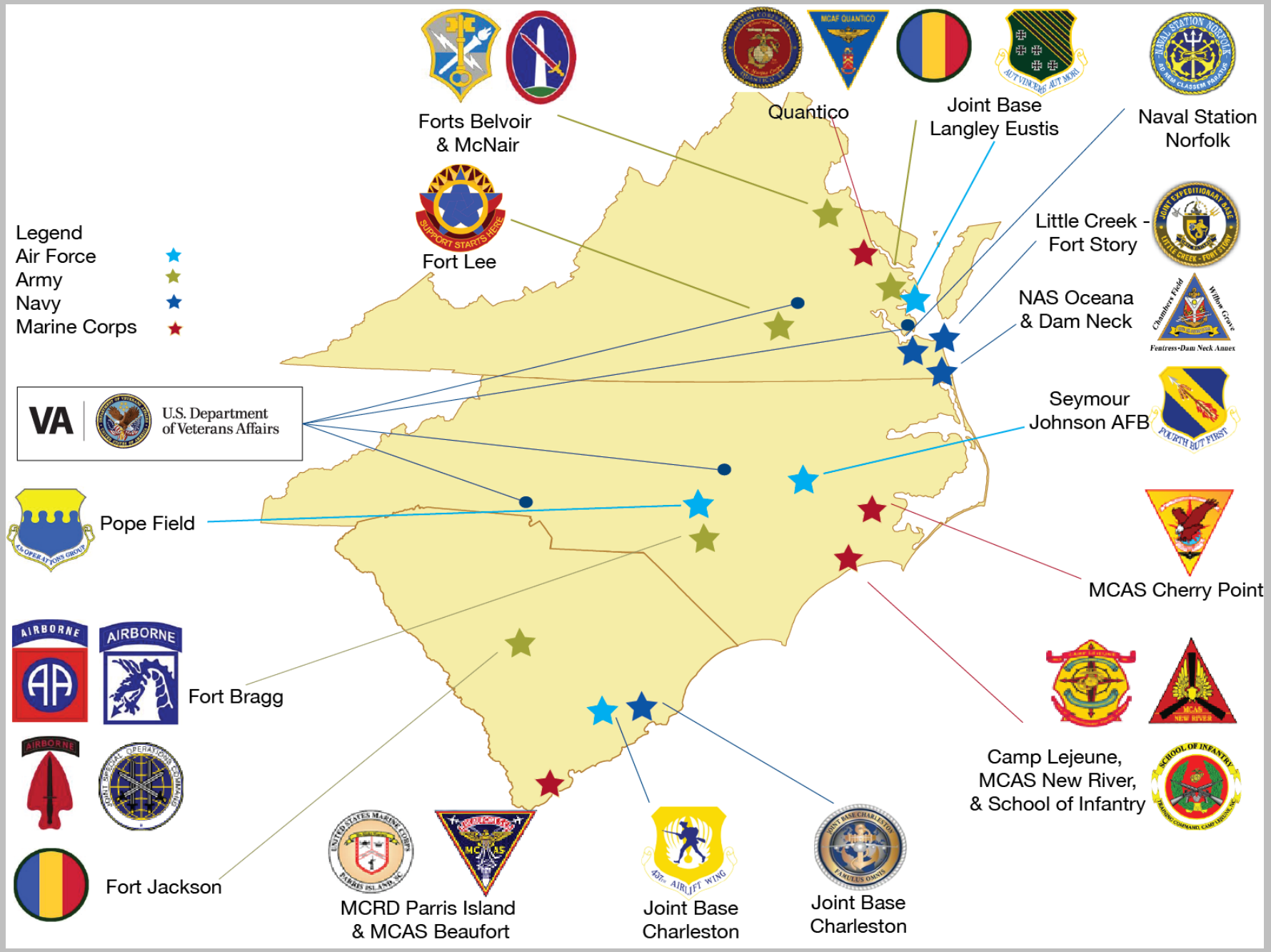
- Vietnam: 9-19%
- 1990-1991 Gulf War: 2-24%
- OEF/OIF: 5-20%

- Deployment to a combat zone creates a 1.5 – 3.5x greater risk for developing PTSD

The woods are lovely, dark and deep. But I have promises to keep, and miles to go before I sleep. - Robert Frost

An infantry soldier serves as a sentinel at The Tomb of the Unknown Soldier, Arlington National Cemetery. May 2014.

20% of US Military Within 5 Hours of Durham



Epidemiology for Civilians

- PTSD risk after…
  - Motor Vehicle Accident: meta-analysis reported point prevalence of 16.5% (8-30%) at 3 months, 14% (7-26%) at 12 months
  - Child admitted to ICU: review reported 10-21% of parents diagnosed with PTSD
  - Breast cancer: prospective study found point prevalence 6 months post-operatively of 11-16% depending upon rating scale
  - NYC residents after 9/11: 16% diagnosed with PTSD after 9 years

NC-Specific Civilian Epidemiology

- Disasters overall show PTSD prevalence around 11%, but mostly disasters linked with fires
- Hurricanes: a multivariable model of Florida hurricane survivors showed 3.6% prevalence of PTSD with significant risk factors as:
  - Displaced from home >7 days
  - Low social support
  - Significant fear of injury or death
- Floods: cross-sectional mail survey after floods in the UK showed 28% screening positive for PTSD (not necessarily having the full diagnosis)

PTSD Treatment

PTSD: Non-Emergent Initial Management

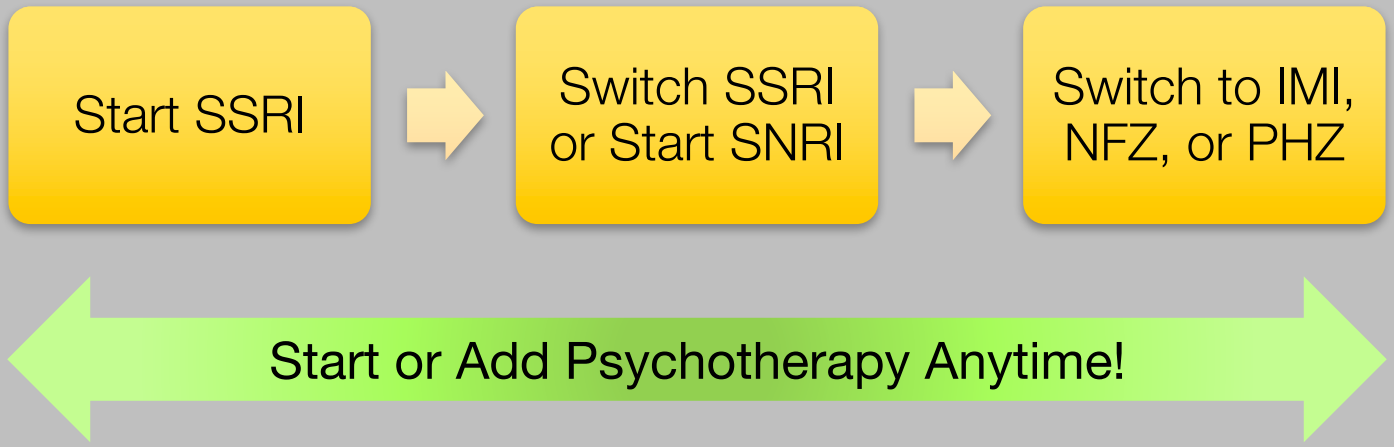
- Offer trauma-focused psychotherapy
  - If not available or not accepted by the patient, then
- Offer either medication or other psychotherapy
- Treat comorbid conditions and problems

Dr. Rothbaum will address psychotherapy later this morning

Pharmacotherapy vs. Psychotherapy

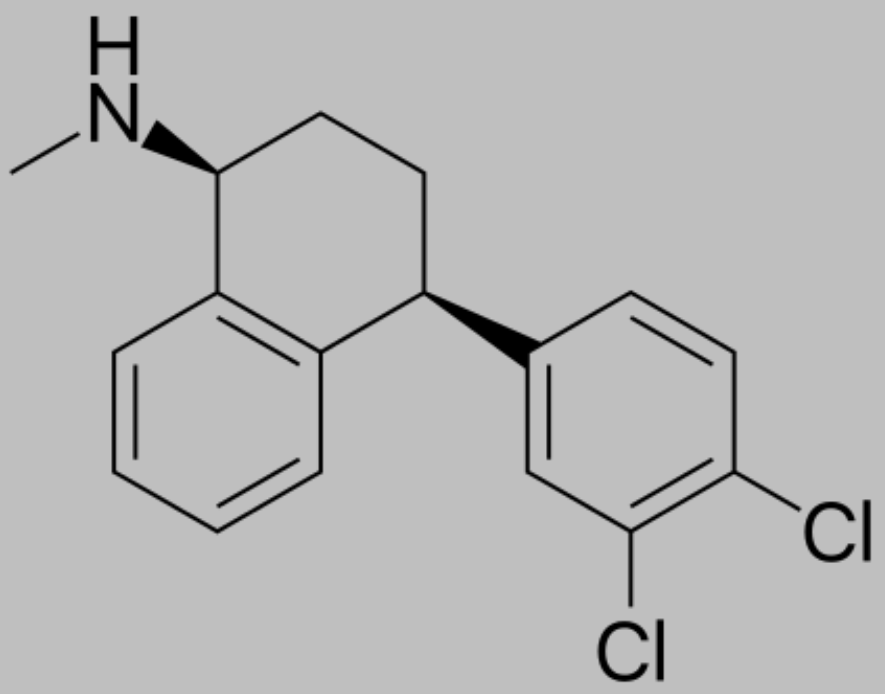
- One excellent meta-analysis by Watts, et al, from the VA National Center for PTSD
- Their analysis found large effect sizes (Hedges' g) of psychotherapy (1.0 – 1.6) compared to more modest effect sizes for medications (0.4 – 0.7)
- Recommended therapies and Hedges' g:
  - CPT: 1.69 (1.27 – 2.11)
  - PE: 1.38 (0.9 – 1.86)

Stepped care approach

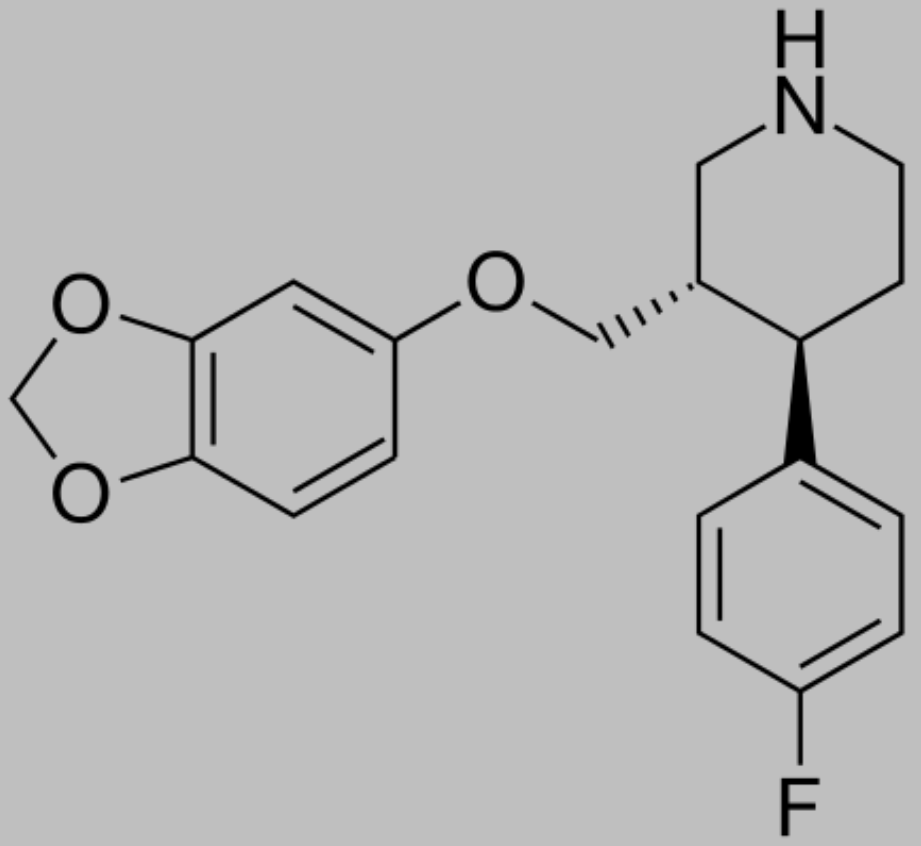


Abbreviations:
SSRI – serotonin-specific reuptake inhibitors (paroxetine, sertraline, fluoxetine)
SNRI – serotonin-norepinephrine reuptake inhibitors (venlafaxine)
IMI – imipramine
NFZ – nefazodone
PHZ – phenelzine (re-read the psychopharm book chapter first!)

Pharmacotherapy for PTSD



Sertraline



Paroxetine

PTSD and Medication: the 2017 Update

Monotherapy Options	Evidence Strength
Sertraline or Paroxetine – FDA indicated for PTSD; all others are off-label usage Venlafaxine or Fluoxetine	Strong Yes
Nefazodone, Phenelzine, Imipramine	Weak Yes
Atypicals (except risperidone), Citalopram, Amitriptyline, Lamotrigine, Topiramate	Weak No
Divalproex, Tiagabine, Guanfacine, Risperidone, benzodiazepines, Ketamine, Hydrocortisone, D-cycloserine, or cannabis	Strong No

First-Line Choices

- **Sertraline, Paroxetine, Fluoxetine, Venlafaxine**
  - All are excellent options
  - Other SSRIs and Duloxetine are **not** first-line recommendations
- Aim for higher rather than lower daily doses
  - Sertraline 150-200mg
  - Paroxetine 30-40mg
  - Fluoxetine 40-60mg
  - Venlafaxine 150-300mg

Strong Yes

Key points in using first line agents

- These medications treat the core symptom clusters of PTSD and not just co-morbid conditions
- Be sure to provide an adequate trial at an adequate dosage
  - Reduction of anger within two weeks is a positive prognostic sign of good response at 12 weeks
  - Anxiety disorders and PTSD may require up to 12 weeks and dosing closer to the maximum recommended dose for an adequate medication response

Second Line Options: Serious Risks to Consider

- **Nefazodone** — Weak Yes
  - 1/300,000 serious hepatotoxicity
  - No sexual side-effects
- **Imipramine** — Weak Yes
  - 100mg per day x 30 days = 3 grams = LETHAL OD RISK!
  - Anticholinergic side effects worse with increasing doses
  - TCAs generally helpful for neuropathic pain
- **Phenelzine** — Weak Yes
  - If you need to ask, you should re-read the chapter. Orthostasis and drug-drug interactions can be problematic
  - Useful medication but no beer, pepperoni pizza, or OTC cold medications

Try to Avoid

- Unless no other options exist, avoid monotherapy with these medications
  - Some antidepressants (amitriptyline, citalopram)
  - Atypical antipsychotics (except risperidone)
  - Lamotrigine
  - Topiramate

Weak
No

What to Avoid for PTSD Monotherapy

- Either lack of efficacy or problematic side-effects recommend against routine use of:
  - Divalproex
  - Tiagabine
  - Guanfacine
  - Risperidone
  - Benzodiazepines
  - Ketamine
  - Hydrocortisone
  - D-cycloserine
  - cannabis

Strong No

The Known Unknowns

- There is **insufficient evidence to recommend for or against monotherapy or augmentation therapy** for the treatment of PTSD with:
  - Antidepressants: escitalopram, bupropion, desipramine, doxepin, duloxetine, desvenlafaxine, fluvoxamine, levomilnacipran, mirtazapine, nortriptyline, trazodone, vilazodone, and vortioxetine
  - Hypnotics: eszopiclone, zaleplon, and zolpidem
  - Others: buspirone, cyproheptadine, D-serine, and hydroxyzine

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PTSD and Medication: the 2017 Update

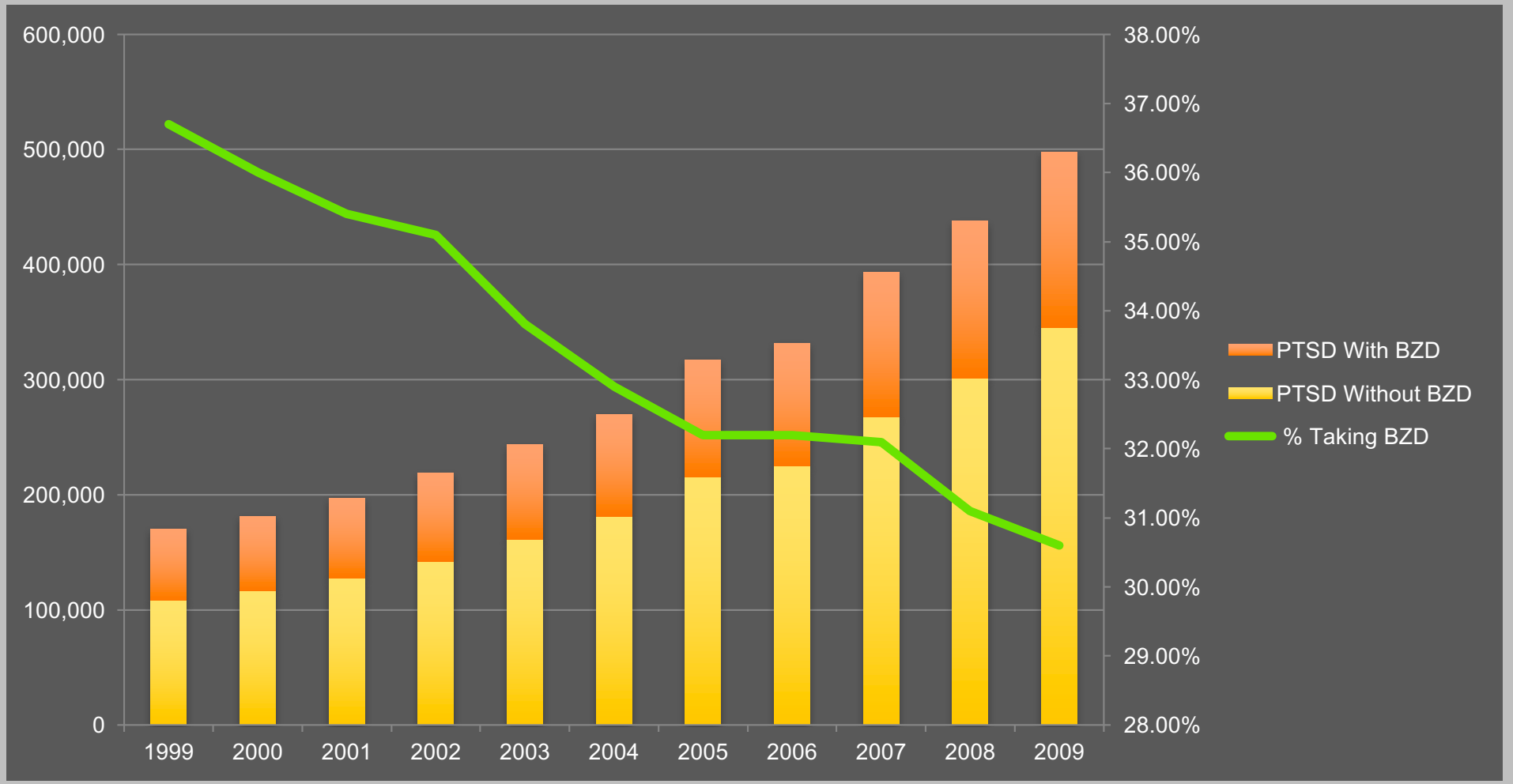
Augmentation Options	Evidence Strength
Topiramate, Baclofen, or Pregabalin D-cycloserine outside of research protocols	Weak No
Atypical antipsychotics, benzodiazepines, and divalproex	Strong No

Benzodiazepines in PTSD

Benzodiazepines are to be avoided in veterans with PTSD because these medications:

1. Do not treat the underlying PTSD
2. Are potentially habit-forming
3. Interfere with fear extinction, thus making Prolonged Exposure and EMDR sessions pointless
4. Increase the risk of household and motor vehicle accidents

PTSD & Benzodiazepines in the VA



Although the percentage (right-axis) of veterans taking benzodiazepines is declining, the absolute numbers continue to increase. Source: Lund et al, 2011.

What about Prazosin?

- For global symptoms of PTSD
  - not recommended
- For nightmares
  - No recommendation for or against
- Reason: in a high quality VA multi-site trial (N=304), prazosin failed to separate from placebo in the treatment of both global symptoms of PTSD and nightmares
  - Still unpublished three years after completion

"the decision to stop or continue prazosin should be individualized"
- 2017 VA-DoD CPG

From My Experience

- For PTSD with either Migraines or Neuropathic Pain, try Nortriptyline + Sertraline
  - Decrease sertraline dose
- A complete lack of response to venlafaxine could be due to poor metabolism
  - Try desvenlafaxine in this instance
- Anything for sleep should not be taken more than 5 times per week
  - Trazodone, hydroxyzine, z-drugs, diphenhydramine

My Experiences, continued

- Prazosin has been very useful
  - Placebo? Pharmacologic? Lessons from zolpidem meta-analysis?
- Most combat veterans with a TBI also have PTSD
  - The reverse isn't true as often
  - Blast injuries can't be ignored but are poorly understood, causing them to be over-rated as an injury mechanism
- Psychotherapy does far more good than medication
- TBI-related cognitive issues are not a barrier to psychotherapy

Other Treatments: More Known Unknowns

- There is **insufficient evidence to recommend for or against**:
  - Augmenting meds with therapy or therapy with meds in partial or non-responders
  - repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), hyperbaric oxygen therapy (HBOT), stellate ganglion block (SGB), or vagal nerve stimulation (VNS)
  - acupuncture as a primary treatment for PTSD
  - any complementary and integrative health (CIH) practice, such as meditation (including mindfulness), yoga, and meditation as a primary treatment for PTSD

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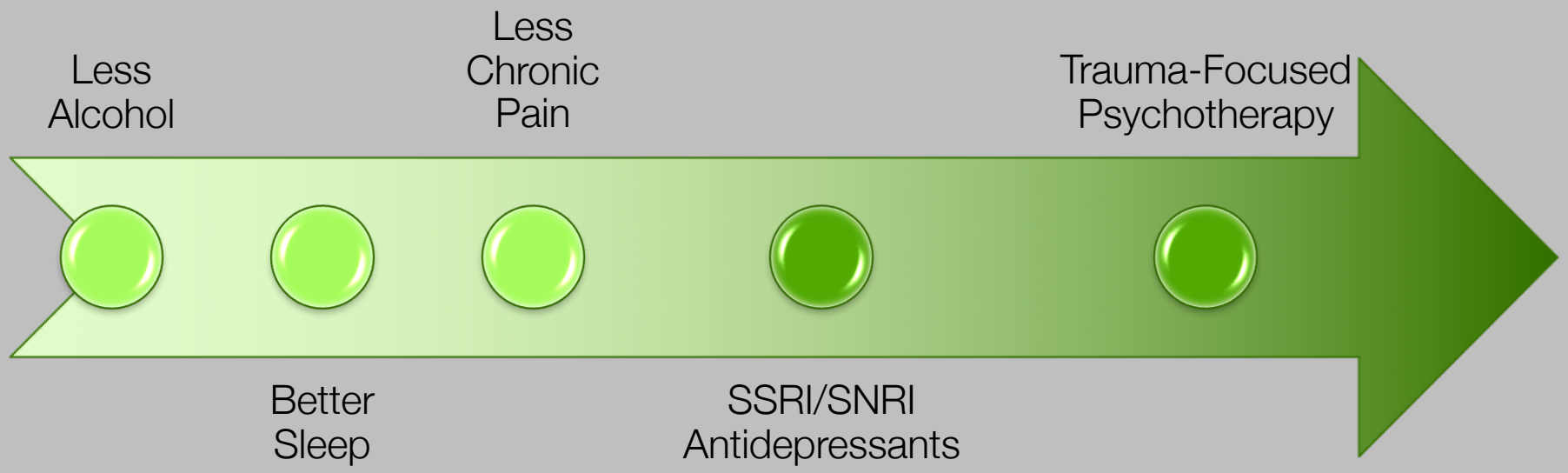
PTSD and Comorbidity: What Helps Recovery?



PTSD & Comorbid Conditions

- Particularly common conditions include:
  - Major Depression
  - Substance Use Disorders
  - Chronic Pain
  - Mild TBI (especially after combat, crime, and MVA)
- Consider suicide risk
- PTSD is a new risk factor for Coronary Artery Disease
  - Not just smoking (which is more common in PTSD)
  - Insomnia's effect upon HPA system?

PTSD May Worsen Medical Disorders

- The Heart and Soul Study showed PTSD associated with worse cardiovascular health (Cohen 2009)
- VanCauter (2009) reported insomnia is associated with:
  - Reduced slow wave sleep (Stage 3-4 NREM sleep)
  - Endocrine changes that stimulate daytime appetite
  - Weight gain and insulin resistance
- Edmondson (2013) suggested PTSD may be a modifiable risk factor for new-onset coronary heart disease

Likely implication: treating insomnia in PTSD may reduce the long-term risk of developing cardiovascular disease. This relationship is very important given the high rates of smoking among combat veterans with PTSD.

Treating Co-Morbid Issues

- Substance Use Disorders
  - Consider collaborative care with a substance use specialist
  - Consider opiate use agreement with the primary care physician
  - Does the SUD represent avoidance?
- Medical co-morbidities such as chronic pain
  - Consider risks of inadvertent iatrogenic SUD
  - Recommend non-narcotic medication when feasible
  - Reducing PTSD symptoms will reduce chronic pain
  - Consider CBT - Pain

PTSD and Insomnia

- How many of you have heard this complaint from a veteran: “I can’t sleep, I can’t remember anything, and I’m angry all the time”
- Up to 87% of patients with PTSD report insomnia, and up to 52% of combat veterans with PTSD report nightmares *
- Insomnia represents a substantial problem among veterans with PTSD

* See the excellent review by Schoenfeld, DeViva, and Manber in JRRD 2012;49:729-52

PTSD: Treating Insomnia

- It seems obvious, but treating insomnia associated with PTSD begins with optimal treatment for PTSD

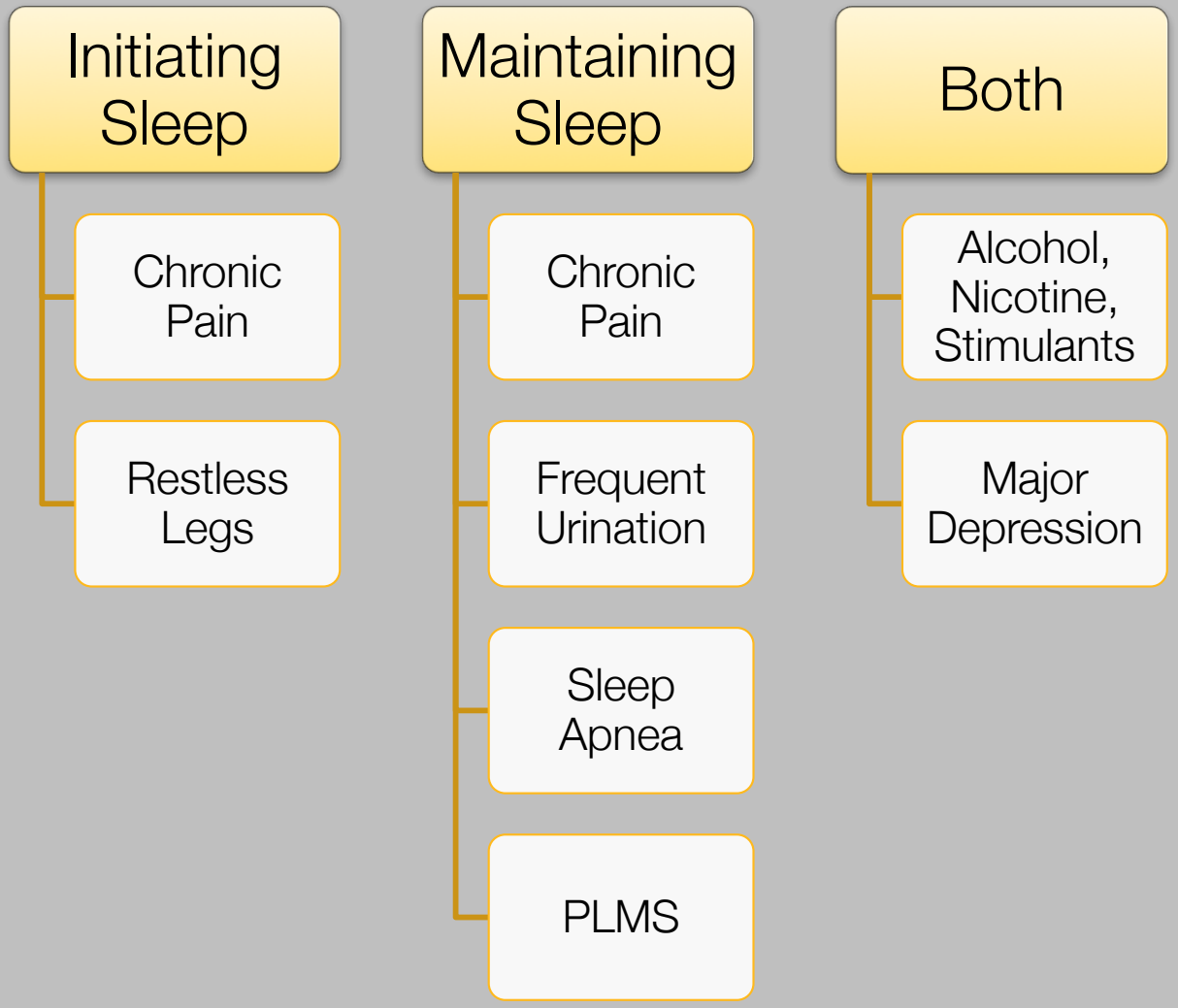
- Although it sounds like I am making this up, this is a true account. At a Durham VA treatment team meeting, we discussed a patient who had been prescribed four psychiatric medications (including two benzos!), none of which were recommended by VA-DoD guidelines

Non-Medical Effects Upon Sleep

At my house, we have about 70 pounds of hyperactive dog and temperamental cat.

Consider also children, the sleep environment (noise, light, temperature), and occupational demands (shift work; on-call schedules).

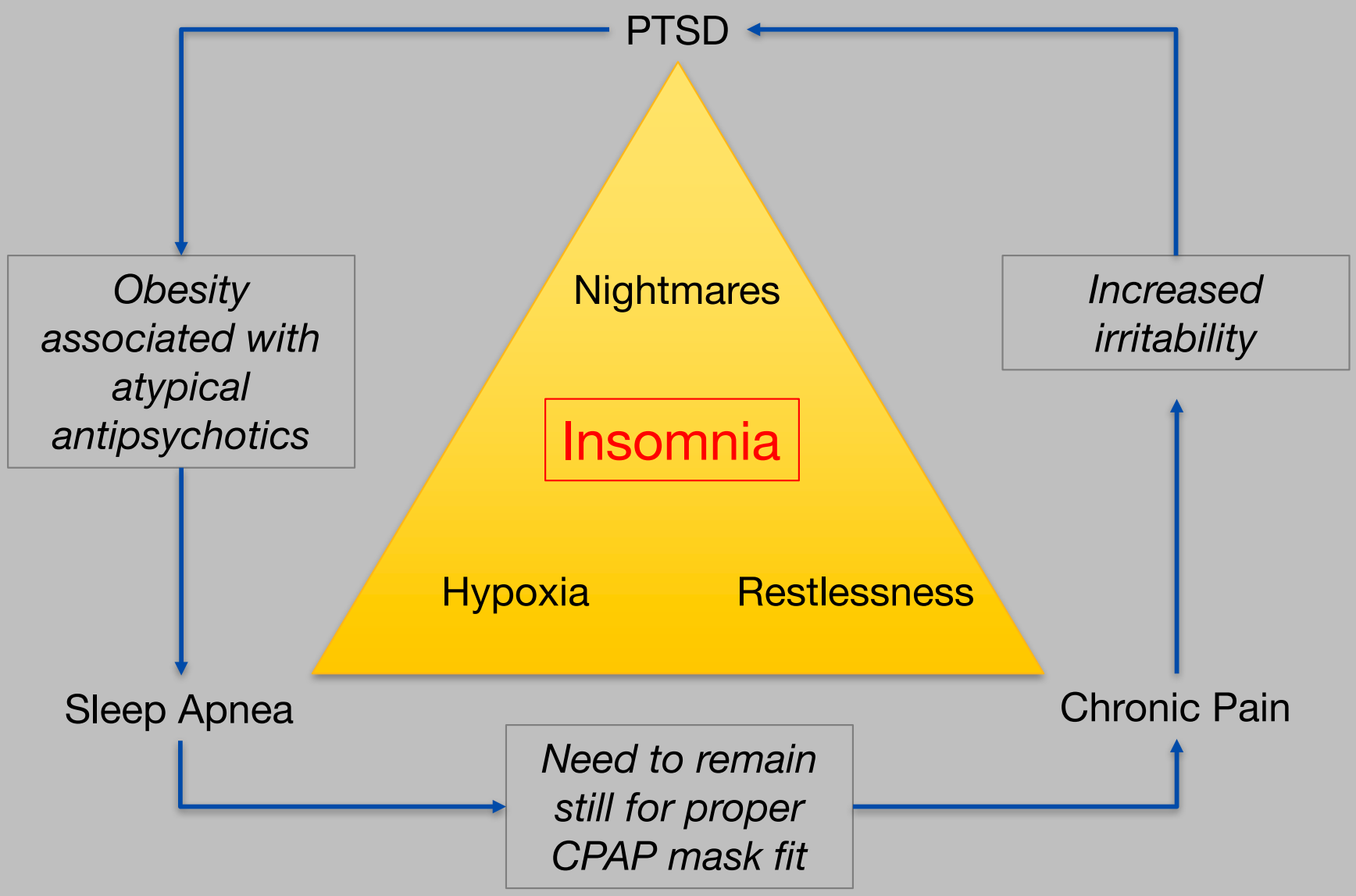
Comorbid Conditions Affecting Sleep



PTSD: Treating Insomnia

- Improved sleep is one of the most important PTSD interventions
  - Better sleep won't fix PTSD, but your patients will report an improved quality of life, better cognition, and less irritability
  - Improve sleep and patients are more likely to accept additional treatment recommendations
- Initial insomnia: trazodone, mirtazapine, diphenhydramine, hydroxyzine
- Middle insomnia: prazosin; tizanidine might help individuals without hypertension

Insomnia and Comorbidity Example



Co-Morbid Depression

- Major depressive disorder
  - Start with SSRI/SNRI antidepressants
  - Use the STAR*D algorithm
  - Check for adherence, medical causes, and SUD
- Bipolar disorder
  - Very complicated problem because antidepressants increase risk for cycling into mania
  - Decrease the SSRI/SNRI to lowest effective dose
  - Add a mood stabilizer (e.g. divalproex)
  - Refer for evidence-based therapy to minimize antidepressant use

Traumatic Brain Injury

- Diagnosis can be difficult
  - Helpful: neuropsychology testing for complaints that persist after other PTSD symptoms have improved
- TBI can mimic other disorders
  - Depression: frontal or subcortical injury → apathy
  - Psychosis and/or Mania: ?mechanism but reported in literature
  - Cognitive: wide variety of potential complaints in different cognitive domains

TBI Treatment

- Treat symptoms as the related Axis I condition
  - Example: treat depression with antidepressant
  - Use caution with stimulants!!
- Evidence-Based Psychotherapy
  - Consider neuropsychology testing prior to therapy
  - Customize the therapy approach to address any cognitive deficits
  - PE may be preferred for patients who cannot complete CPT homework assignments

QUESTIONS?

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Optional Material: Atypical Antipsychotic Medications

Why is Quetiapine Widely Used for PTSD?

- In 2007, VA clinicians prescribed quetiapine off-label for 72,312 Veterans, more than twice the number of the next most common antipsychotic medication
- 10.6% of all Veterans with PTSD were given quetiapine in 2007
- These data are problematic because quetiapine:
  - Doesn't work well for insomnia (see next slide)
  - Can cause the metabolic syndrome
  - Can cause tardive dyskinesia

Quetiapine, despite its popularity, should be used only after other treatments fail. This point is especially true for veterans who should not gain weight (e.g. diabetes; obstructive sleep apnea; osteoarthritis)

Problems with Quetiapine

- A historical cohort study of 237 veterans with PTSD was followed for 3-6 years. Initial medications for insomnia included either prazosin or quetiapine
- In the prazosin group, 8% were switched to quetiapine and none continued to the study end date
- In the quetiapine group, 20% were given prazosin in addition to quetiapine and nearly half continued the prazosin
- Quetiapine was less likely to improve sleep and more likely to cause side-effects (sedation 21%, metabolic effects 9%)

Atypical Antipsychotic Use and Sleep Apnea

- One recent study examined PSG records for a relationship between atypical antipsychotic use and obstructive sleep apnea (OSA)
- Results: diagnosis of depression with concomitant atypical antipsychotic use showed odds ratio of 4.5 compared to other groups
- Separately, benzodiazepines were associated with more frequent apneic episodes on polysomnogram testing
- A second study found AA use associated with a 1.9-fold increase in sleep apnea risk, even after controlling for body mass index