Practical Psychiatry for the

PHYSICIAN

A continuing medical education series

Post Traumatic Stress Disorder (PTSD)

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Presenter Disclosure

- I have no conflict of interest to disclose
- I have no financial or scientific disclosures
- I will discuss the off-label use of Prazosin and Topamax for nightmares

Objectives

- Outline evidence-based care for patients with psychiatric illness
- Practice evidence-based care for patients with psychiatry illness
- Translate information learnt at this course to improve the assessment and treatment of common psychiatric disorders by physicians

Preaching to the choir…

- March 2010 paper estimated that PCPs treat 30% of their patients for MH problems
  - Primarily depression & anxiety
- Some research has suggested as much as 70% of psychiatric patients are treated in primary care
  - ~66-75% of all depression cases

Faghri, Ment Health Fam Med 2010; 7 (1) ; 17-25

Psychiatric History

- Psychiatric evaluation focuses on two main sections:
  - Series of histories (psychiatric, medical, family)
  - Mental Status Examination
- Psychiatric history does not have external validating criteria so dx is only as good as the knowledge and skill of physician making it
- DSM5

Historical Background

- Shakespeare's Henry IV
- Stephen Crane's Red Badge of Courage (Civil War)
- "Shellshock" and "Soldier's Heart" in WWI became "traumatic war neurosis" and "combat fatigue" in WWII
- 1980: APA changed name from "post-traumatic neurosis" to PTSD
- Revisions have been made in every version since of DSM

DSM-IV to DSM5

A(2) criterion removed

- "Person's response involved intense fear, helplessness, or horror."

- No longer categorized as an "Anxiety Disorder"
  - "Trauma- and Stress-Related Disorders"

DSM-5 Diagnostic Criteria

- Criterion A:
  - Exposure to actual/threatened death, serious injury or sexual violence via:
    - Directly experiencing
    - Witnessing *in person* the event as occurred to others
    - Learning that violent/accidental event occurred to close family member/friend
    - Experiencing repeated or extreme exposure to aversive details of traumatic events (first responders w/human remains; police officers to abuse of children, etc.) **

DSM-5 Diagnostic Criteria

Criterion A + 4 Symptom Clusters

Re-experiencing Cluster

- 1 or more
  - Intrusive memories
  - Recurrent distressing dreams
  - Flashbacks
  - Psychological distress to cues
  - Physiological distress to cues

Avoidance Cluster

- 1 or both
  - Avoidance of distressing memories, thoughts, feelings associated with event
  - Avoidance of people, places, conversations, activities, objects, situations that arouse distressing memories/thoughts/feelings of event

DSM-5 Diagnostic Criteria

Negative Alterations Cluster

- 2 or more:
  - Inability to remember important aspect of event
  - Persistent/Exaggerated negative belief ("No one can be trusted.")
  - Distorted cognitions about cause/consequence of event that leads patient to blame himself
  - Persistent fear, horror, anger, guilt shame
  - Decreased interest
  - Detachment from others
  - Restricted range of emotions

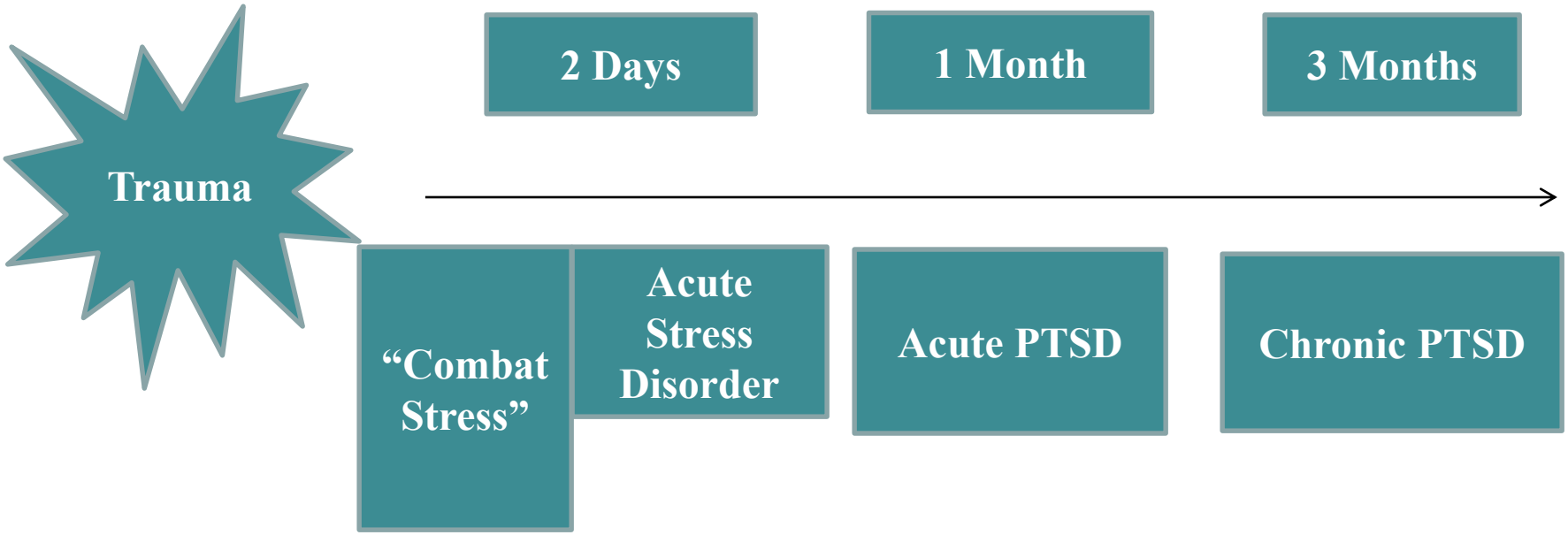
Hyperarousal Cluster

- 2 or more:
  - Irritability or angry outbursts
  - Reckless or self-destructive behavior
  - Hypervigilance
  - Exaggerated startle
  - Decreased concentration
  - Sleep disturbances

DSM-5 Diagnostic Criteria

- Symptoms exist > 1 month
- "Clinically significant distress/impairment in social/occupational functioning"
- Not due to substance
- Specify whether:
  - Dissociative symptoms of either depersonalization or derealization
- Delayed expression → symptoms begin after 6 months

Stress Reaction Timeline



VA/DoD CPG, Management of Post-Traumatic Stress, 2010

Epidemiology

- National Comorbidity Study found that 60% of males and 50% of females are exposed to qualifying traumatic event at some point in life
- Lifetime prevalence ranges from 6.8-12.3% in the general US adult population
  - Increased in veterans
    - Some studies cite up to 30% in men; 22% with sub-threshold symptoms
    - 13% of vets from OIF/OEF
- One-year prevalence rates 3.5-6%

UpToDate, Kaplan & Sadock's Synopsis of Psychiatry, 2015

Vulnerability Factors

- Female > Male
- Age at trauma
- Race
- Education
- Lower SES
- Previous trauma (esp. childhood)
- General childhood adversity
- Personal and family past psych history
- Poor social support
- Initial severity of reaction to trauma
- Certain populations

Kaplan & Sadock's Synopsis of Psychiatry, 2015

Common Traumatic Events

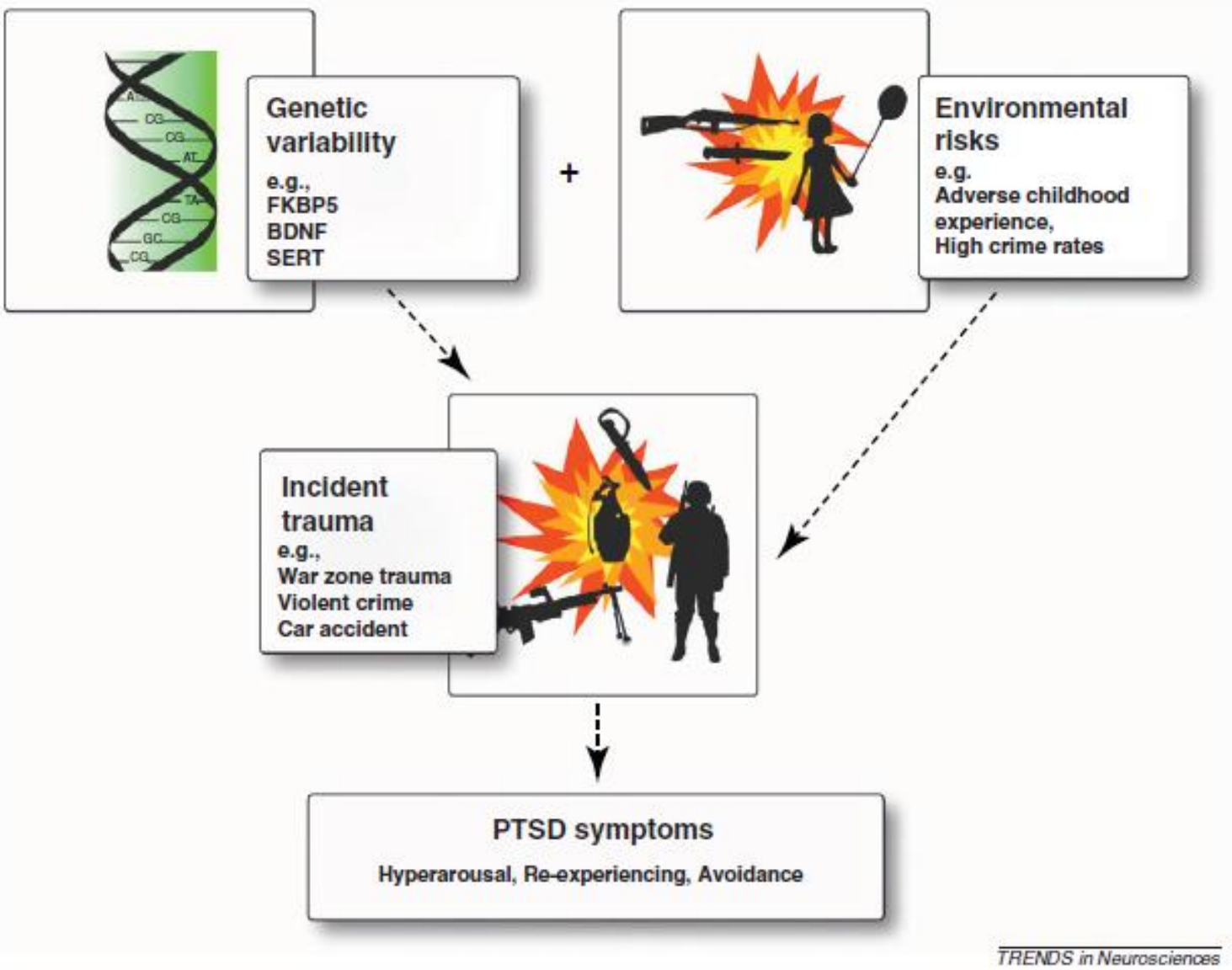
- Sexual Assault
- Mass Conflict & Displacement
- Combat
- ICU hospitalization
- Myocardial Infarction
- Natural disasters
- MVAs
- Abuse

Estimated Risk for Developing PTSD Based on Event

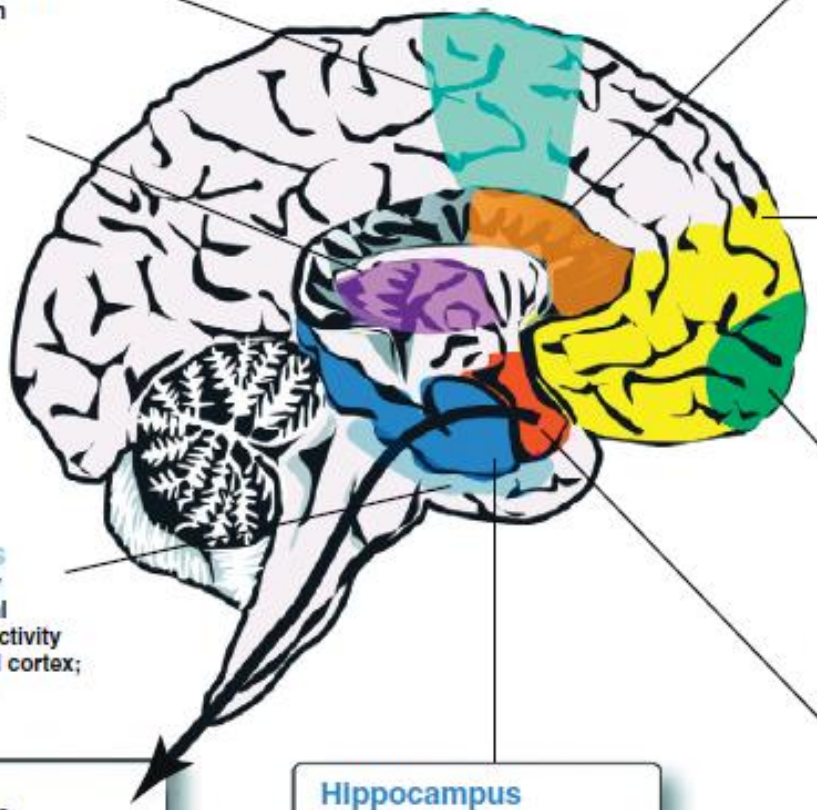
Rape (49%)
Severe beating or physical assault (31.9%)
Other sexual assault (23.7%)
Serious accident or injury (i.e. MVA) (16.8%)
Shooting or stabbing (15.4%)
Unexpected death of family member or friend(14.3%)
Child's life-threatening illness (10.4%)
Witness to killing of serious injury (7.3%)
Natural Disaster (3.8%)

www.ptsdalliance.org
www.nimh.nih.gov/pulicat/reliving.cfm

Multifactorial Mechanism



Fear Conditioning



Sensorimotor cortex
Function: Coordination of sensory and motor functions
In PTSD: Symptom provocation results in increased activation

Thalamus
Function: Sensory relay station
In PTSD: Decreased cerebral blood flow

Parahippocampal gyrus
Function: Important for memory encoding and retrieval
In PTSD: Show stronger connectivity with medial prefrontal cortex; decreases in volume

Anterior cingulate cortex
Function: Autonomic functions, cognition
In PTSD: Reduced volume, higher resting metabolic activity

Prefrontal cortex
Function:
- Emotional
- Regulation

In PTSD:
- Decreased gray and white matter density
- Decreased responsiveness to trauma and emotional stimulia

Orbitofrontal cortex:
Function: Executive function
In PTSD: Decreases in volume

Amygdala
Function:
- Conditioned fear
- Associative learning

In PTSD:
- Increased responsiveness to traumatic and emotional

Fear response
Function:
- Evolutionary survival

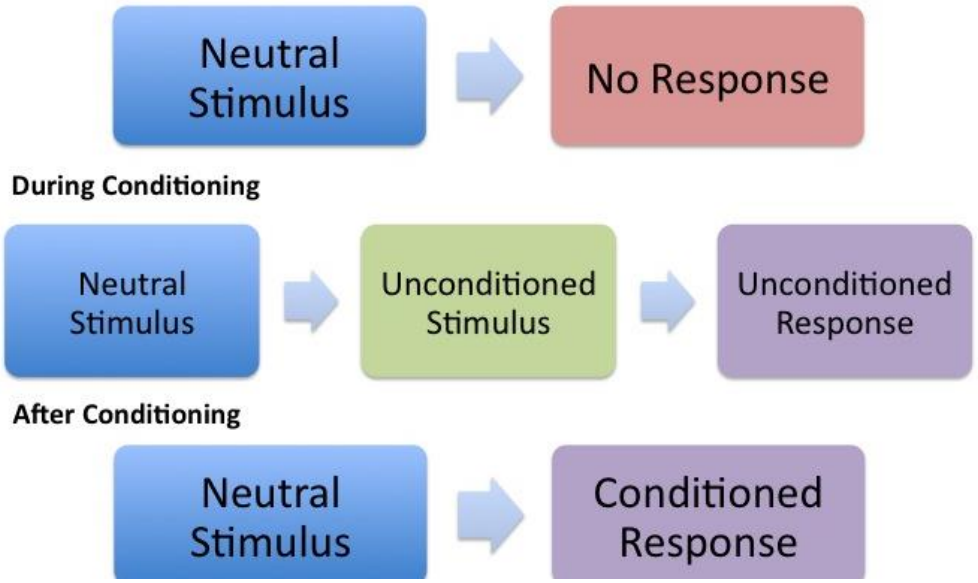
In PTSD:
- Stress sensitivity
- Generalization of fear response
- Impaired extinction

Hippocampus
Function:
- Conditioned fear
- Associative learning

In PTSD:
- Increased responsiveness to traumatic and emotional stimuli

Trends in Neuroscience

Fear Conditioning



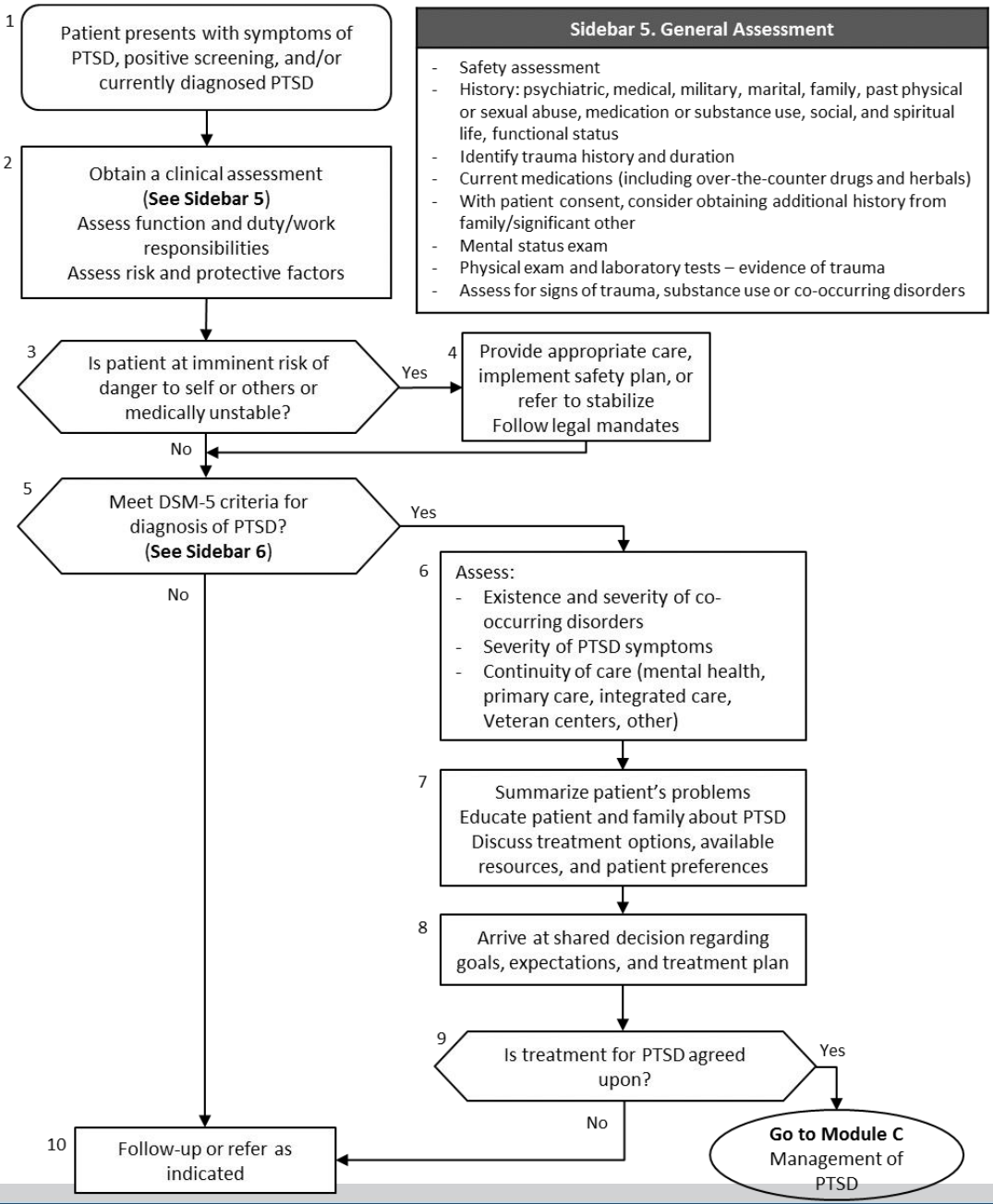
CS (e.g. tone, light, odor) is paired with an aversive US (eg. Foot-shock, air-blast) → evokes a CR (e.g. freezing, acoustic startle response, autonomic arousal).

Patients with PTSD show significantly different responses to fear conditioning paradigms relative to trauma survivors without PTSD.

They demonstrate behavioral sensitization to stress and over-generalization of the conditioned stimulus (CS)-unconditioned stimulus (US) response.

Such patients show impaired extinction of CS-CR pairings once the aversive US is removed.

Flowchart for Assessment & Diagnosis of PTSD



Abbreviations: DSM: Diagnostic and Statistical Manual of Mental Disorders; PTSD: posttraumatic stress disorder

Primary Care PTSD Screen for DSM-5

- Sometimes things happen to people that are unusually or especially frightening, horrible, or traumatic. For example:
  - A serious accident or fire
  - A physical assault or abuse
  - An earthquake or flood
  - A war
  - Seeing someone be killed or seriously injured
  - Having a loved one die through homicide or suicide
- Have you ever experienced this kind of event?
  - If no, screen total = 0. If yes, continue on with screening.

In the past month have you:

1. had nightmares about the event(s) or thought about the event(s) when you did not want to? YES/NO
2. tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)? YES/NO
3. been consistently on guard, watchful, or easily started? YES/NO
4. felt numb or detached from people, activities, or your surroundings? YES/NO
5. Felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused? YES/NO

Screen: PCL-5

Patient's name: _____

Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem in the last month.

No.	Response:	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing memories, thoughts, or images of a stressful experience from the past?					
2.	Repeated, disturbing dreams of a stressful experience from the past?					
3.	Suddenly acting or feeling as if a stressful experience were happening again (as if you were reliving it)?					
4.	Feeling very upset when something reminded you of a stressful experience from the past?					
5.	Having physical reactions (eg, heart pounding, trouble breathing, or sweating) when something reminded you of a stressful experience from the past?					
6.	Avoid thinking about or talking about a stressful experience from the past or avoid having feelings related to it?					
7.	Avoid activities or situations because they remind you of a stressful experience from the past?					
8.	Trouble remembering important parts of a stressful experience from the past?					
9.	Loss of interest in things that you used to enjoy?					
10.	Feeling distant or cut off from other people?					
11.	Feeling emotionally numb or being unable to have loving feelings for those close to you?					
12.	Feeling as if your future will somehow be cut short?					
13.	Trouble falling or staying asleep?					
14.	Feeling irritable or having angry outbursts?					
15.	Having difficulty concentrating?					
16.	Being "super alert" or watchful on guard?					
17.	Feeling jumpy or easily startled?					

Total score: ☐

Treatment of PTSD

- The Work Group's recommendation to use individual trauma-focused psychotherapy over pharmacotherapy reflects the current body of research.
  - Two recent meta-analyses compared the two
    - Trauma-focused therapy imparts greater change with regard to core PTSD sx than pharmacotherapies & results persist for longer periods of time

Psychotherapies for PTSD

- "Trauma-focused"
- Strongest evidence lies with:
  - Prolonged Exposure (PE)
  - Cognitive Processing Therapy (CPT)
  - Eye Movement Desensitization and Reprocessing (EMDR)
- If TF therapy is not available, use of Stress-Inoculation Therapy, Present-Centered Therapy, or Interpersonal Therapy are all non-trauma-focused therapies with the most evidence based support
- Limited data to support that individual > group therapy

Table 2. Medication Monotherapy for the Treatment of PTSD by Recommendation and Strength of Evidence

Quality of Evidence*	Recommend For	Suggest For	Suggest Against	Recommend Against	No Recommendation For or Against
Moderate	Sertraline^ Paroxetine^ Fluoxetine Venlafaxine		Prazosin (excluding the treatment of PTSD associated nightmares)		Prazosin for the treatment of PTSD associated nightmares
Low		Nefazodone ±	Quetiapine Olanzapine Citalopram Amitriptyline	Divalproex Tiagabine Guanfacine	Eszopiclone
Very Low		Imipramine Phenelzine±	Lamotrigine Topiramate	Risperidone Benzodiazepines D-cycloserine Hydrocortisone Ketamine	Bupropion Desipramine D-serine Escitalopram Mirtazapine
No Data†					<u>Antidepressants</u> Doxepin Duloxetine‡ Desvenlafaxine Fluvoxamine‡ Levomilnacipran Nortriptyline Trazodone Vilazodone Vortioxetine <u>Anxiolytic/Hypnotics</u> Buspirone‡ Cyproheptadine Hydroxyzine Zaleplon Zolpidem

*The Work Group determined there was no high quality evidence regarding medication monotherapy
^FDA approved for PTSD
±Serious potential toxicity, should be managed carefully
†No data were captured in the evidence review for the CPG and were not considered in development of this table

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Therapeutic Category	Initial Dose	Dose Range	Clinical Considerations: Comorbidities and Safety
Antidepressants ***Monotherapy***			▪ Avoid abrupt discontinuation; withdrawal symptoms with sudden discontinuation of SSRIs and SNRIs, paroxetine and venlafaxine in particular ▪ Paroxetine and sertraline have FDA label indications for treating PTSD ▪ Common adverse effects of the SSRIs and SNRIs include nausea, headache, diarrhea, anxiety, nervousness, sexual dysfunction, agitation, dizziness, hyponatremia or SIADH, and serotonin syndrome ▪ Venlafaxine can elevate blood pressure; caution advised with patients with hypertension
▪ Fluoxetine*	10-20 mg daily	20-80 mg daily	
▪ Paroxetine*	10-20 mg daily	20-50 mg daily	
▪ Sertraline*	25-60 mg daily	50-200 mg daily	
▪ Venlafaxine*	IR: 25 mg 2 or 3 times a day XR: 37.5 mg once daily	75-375 mg in 2-3 divided doses 75-225 mg once daily	
▪ Nefazodone±	25–100 mg 2 times daily	150-600 mg in 2 divided doses	▪ Nefazodone is associated with life-threatening hepatic failure; monitor for signs and symptoms including LFTs; avoid if active liver disease; do not re-challenge ▪ Nefazodone is subject to many drug interactions, particularly those involving CYP3A4 and glycoprotein
▪ Imipramine±	25-75 mg daily	100-300 mg in 1 or 2 divided doses	▪ Avoid TCAs within three months of an acute MI ▪ TCAs are relatively contraindicated in patients with coronary artery disease or prostatic enlargement ▪ TCAs side effects include dry mouth, dry eyes, constipation, orthostatic hypotension, tachycardia, ventricular arrhythmias, weight gain, and drowsiness Photosensitivity may occur
▪ Phenelzine±	15 mg 3 times daily	15 mg daily; 90 mg in divided doses	▪ Phenelzine considerations include drug-drug and drug-food interactions, risk of hypertensive crisis, hypotension, and anticholinergic effects

Abbreviations: FDA: Food and Drug Administration; IR: immediate release; LFT: liver function tests; mg: milligram; MI: myocardial infarction; PTSD: posttraumatic stress disorder; SIADH: syndrome of inappropriate anti-diuretic hormone; SIT: Stress Inoculation Training; SNRI: Serotonin–norepinephrine reuptake inhibitors; SSRI: serotonin reuptake inhibitors; TCA: tricyclic antidepressant; XR: extended release

*Strong For recommendation

±Weak For recommendation

Augmentation Strategies

- Conflicting evidence about Prazosin currently
  - Clinically have found significant benefit in AM dosing for daytime hyperarousal
- Growing evidence for use of Topamax for nightmares
  - 25-75mg qHS based on tolerance and response
- Insufficient evidence to recommend the majority of somatic therapies including: rTMS, ECT, hyperbaric oxygen therapy, stellate ganglion block, or vagal nerve stimulation
- Complementary and Integrative treatments
  - Widespread use
  - Not recommended against, but not demonstrated in EBM yet
  - Acupuncture, meditation/mindfulness, & yoga all show promise but require high quality trials with adequate power, controls, and longer follow-up periods
    - Mindfulness is showing the most promise
  - No quality evidence to support use of animal-assisted therapy

Atypical Antipsychotics

- 80% of vets receive Rx treatment; 79% are antidepressants
- Civilian population of privately insured Americans shows 60% receive Rx
- Rx of atypical antipsychotics for PTSD remains controversial
  - Large multisite study showed no significant benefit for risperidone
  - More recent clinical trial showed quetiapine monotherapy to be effective in alleviating re-experiencing and hyperarousal sx > placebo
    - Military population: 1:5 receives SGA even in absence of SMI

Benzos & PTSD

- Strongly recommended *against* the use of benzos
  - Mounting evidence that they are harmful
  - 2 placebo-controlled, randomized studies that showed negative results for both alprazolam & clonazepam
  - Meta-analysis of 18 studies (5,200 patients) showed they were ineffective for sx control and risks > short-term benefits

So What About Marijuana?

- Preliminary evidence that natural and synthetic cannabinoids could improve PTSD sx, particularly nightmares, is offset by significant SE including tolerance, dependence, withdrawal sx, psychosis, cognitive deficits, and respiratory sx if smoked

Mechanism	Drugs
1) Inhibition of platelet aggregation: THC/CBD may increase risk of bleeding when used with anticoagulant and antiplatelet drugs (Levy et al. 1976)	- NSAIDs: Diclofenac, ibuprofen, naproxen - Anticoagulants: Clopidogrel, dalteparin, enoxaparin, heparin, warfarin* *Decreased warfarin metabolism or decreased amount bound to plasma proteins results in increased warfarin effects and elevated INR (Yamreudeewong et al. 2009)
1) Competition with barbiturate metabolism → increased drug levels (Solvay Pharmaceuticals 2008)	- Pentobarbital, phenobarbital, secobarbital
1) Antiestrogenic effects (Lee et al. 2005)	- Contraceptive drugs - Estrogens/hormone therapy
1) Cytochrome P450 2E1 (CYP2E1) induction --> Increased levels of drugs metabolized by CYP2E1 (Sheweita 2003)	- Acetaminophen, chlorzoxazone, ethanol, theophylline, anesthetics (enflurane, halothane, isoflurane, methyoxyflurane)
1) Cytochrome P450 3A4 (CYP3A4) inhibition --> Increased levels (Pellinen et al. 1994)	- Lovastatin, clarithromycin, cyclosporine, diltiazem, estrogens, indinavir, triazolam
1) Inhibition of P glycoproteins (CBD/THC) --> Increased levels of substrates (Zhu et al. 2006)	- Chemotherapy agents: Etoposide, paclitaxel, vinblastine, vincristine, vindesine - Antifungals: Ketoconazole, itraconazole - Protease inhibitors: Amprenavir, indinavir, nelfinavir, sagninavir - H2 antagonists: Cimetidine, ranitidine - Calcium channel blockers: Diltiazem, verapamil - Corticosteroids, erythromycin, cisapride, fexofenadine, cyclosporine, quinidine, loperamide
1) Increased metabolism of theophylline (Solvay Pharmaceuticals 2008)	
1) Additive/Synergistic effects (Hebel 1998)	- ETOH - CNS depressants
1) Induction of hypomania (Solvay Pharnaceuticals 2008)	- Fluoxetine - Disulfram

Common Comorbidities

- Vast majority of patients with PTSD will have 1 or more co-occurring conditions
  - Sleep disturbance
  - Substance Use Disorder
  - Depression
- Screening for other conditions & other common high-risk behaviors is warranted
- Presence of co-occurring disorder should not prevent concurrent treatment

Common Presentations

- Headaches!
- Chronic Pain
  - LBP, Joint pain
- Chronic Fatigue Syndrome
- Fibromyalgia
- IBS
- Alopecia
- Lower Back Pain
- Co-occurring disorders such as ADHD / Depression / Anxiety / Drug & Alcohol

Role of Primary Care Physician

- PCPs regularly provide services for patients with trauma-related disorders, especially those patients who may be reluctant to see psychiatry
- PCP goals:
  - Education about disorder and importance of not letting stigma interfere with care
  - Provision of EBM within primary care environment to extent comfortable
  - Regular follow-up care / monitoring of comorbid health concerns

VA/DoD CPG for PTSD, 2010

Example Patient #1

- 52 y/o WM presents to your office for c/o headache and fatigue. Further hx reveals that 9 mos prior, he was involved in MVA in which the other driver was killed. Currently is experiencing sx of intrusive thoughts about the accident, nightmares of the event and visions of his car hitting the other driver. He has found it difficult to get back into a car and has switched to taking the metro to work. Finds it difficult to talk about the accident and now is avoiding watching Nascar races. His wife has noticed that the patient is ”always angry” and “jumps at the slightest noise.” Averages about 4 hours of broken sleep per night now. Has been increasing his alcohol consumption to > 3 beers per night in order to fall asleep but denies black outs or social/occupational impairment from use.

What is the likely diagnosis?

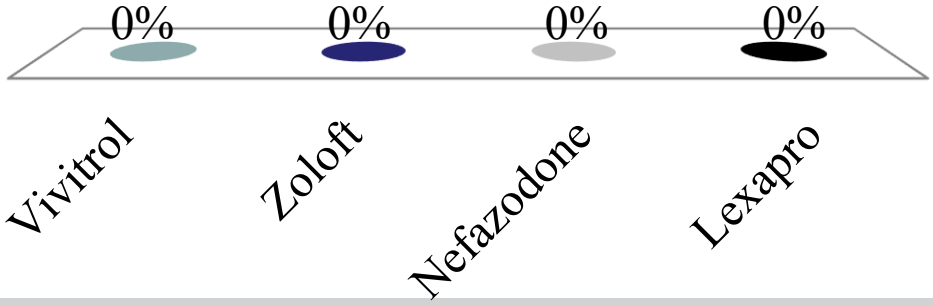
He accepts your referral to psychotherapy but also desires to start a medication. Which one do you choose & how would you dose?

A. Vivitrol

B. Zoloft

C. Nefazodone

D. Lexapro



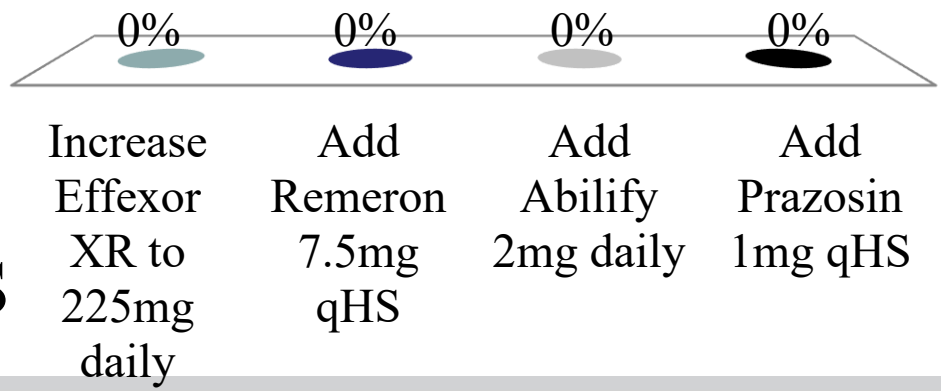
Patient #2

- 25 y/o AAF presents to your office after 4 months' participation in trauma-focused psychotherapy for PTSD and MDD after being raped at a college party. She has previously failed treatment with adequate trials of Prozac, Lexapro, and Wellbutrin XL. Is still struggling with nightmares, anhedonia, and depression. Has been on Effexor XR 150mg daily for 3 months. What action(s) would you take?

What action(s) would you take? **Think Like a Shrink** ☺

Possibilities include:

A. Increase Effexor XR to 225mg daily
B. Add Remeron 7.5mg qHS
C. Add Abilify 2mg daily
D. Add Prazosin 1mg qHS



Patient #3

You diagnosed a 29 y/o WM with PTSD from previous combat duty. He is underweight, can't sleep, often struggles with premature ejaculation and will take medication reliably.

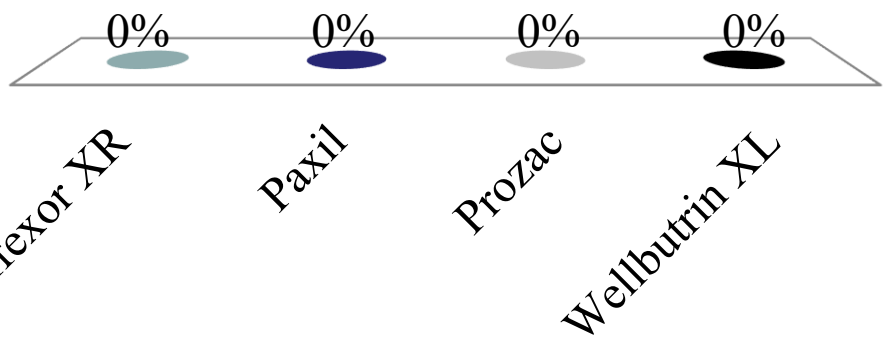
You're super savvy & choose which med:

A. Effexor XR

B. Paxil

C. Prozac

D. Wellbutrin XL



Future presentations…

- How can I make this series the most beneficial for you?
- What things would you change?
- You can bring in brief case summaries to discuss where you're stuck and we discuss as a group?

References

- Bennet, Glin. "Shakespeare and post-traumatic stress disorder" The British Jouranl of Psychiatry (2011) 198, 255. doi: 10.1191/bjp.198.4.255
- Ciechanowski, P. and Katon, W. "Posttraumatic Stress Disorder: Epidemiology, pathophysiology, clinical manifestations, course, and diagnosis." 30 Dec 2014. www.uptodate.com
- Crocq, Marc-Antoine & Louis. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology Dialogues Clin Neurosci. Mar 2000; 2(1): 47–55.
- Gupta S, Phalen T, Gupta S. Medical marijuana: Do the benefits outweigh the risks? *Current Psychiatry*. 2018 January;17(1):34-41
- Heim & Nemeroff. Neurobiology of PTSD. CNS Spectrum. July 2009. Vol 14:1.
- Hoge et al. "Effect of Acute Posttrauma Propranolol on PTSD Outcome and Physiological Responses During Script-Driven Imagery" CNS Neuroscience and Therapeutics vol 18, 2012
- Institute of Medicine Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations, June 2014. www.iom.edu/PTSD
- Mahan & Ressler, "Fear Conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder." Trends in Neurosciences, January 2012, Vol 35, No.1
- http://www.ptsd.va.gov
- Kaplan and Sadock Synopsis of Psychiatry. 11th ed. 2015.
- Spoont MR, Williams JW, Jr., Kehle-Forbes S, Nieuwsma JA, Mann-Wrobel MC, Gross R. Does this patient have posttraumatic stress disorder?: Rational clinical examination systematic review. *JAMA.* Aug 04 2015;314(5):501-510
- VA/DoD Clinical Practice Guidelines Management of Post Traumatic Stress, 2017
- VA (Department of Veterans Affairs). Post-traumatic stress disorder: Implications for primary care. Washington, DC: VA Employee Education System: The National Center for PTSD.; 2002. [Reference list]
- Zoet HA, Wagenmans A, van Minnen A, de Jongh A. Presence of the dissociative subtype of PTSD does not moderate the outcome of intensive trauma-focused treatment for PTSD. *Eur J Psychotraumatol*. 2018;9(1):1468707. Published 2018 May 18. doi:10.1080/20008198.2018.1468707
- Websites:
  - *www.ptsdalliance.org*
  - *www.nimh.nih.gov/pulicat/reliving.cfm*