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UPDATE ON PTSD PHARMACOTHERAPY: IS THERE ANYTHING THAT WORKS BETTER THAN SSRIS FOR PTSD?

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

-No conflicts of interest

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OBJECTIVES

1. To review definition and epidemiology of PTSD
2. To review pharmacologic treatments of PTSD and their evidence base
3. To review novel treatments for PTSD

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INTRODUCTION TO PTSD

- What is PTSD?

  A disorder characterized by disabling symptoms that occur **4 weeks after a trauma** that threatened death, serious injury, or sexual violence. Symptoms are characterized into 4 clusters:

  – Intrusion symptoms

  – Avoidance

  – Negative alterations in cognition and mood

  – Marked alterations in arousal

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CASE AND QUESTION

- 36 year old woman with PTSD secondary to sexual assault presents to your office to request help with insomnia and anxiety. No h/o hospitalizations, she is taking sertraline 200mg/day. She is drinking 4 glasses of wine every night to "help with sleep".
- When compared to the general population, how prevalent are anxiety disorders, depressive disorders and substance use disorders in patients with PTSD?
  - A- These psychiatric illnesses occur in the same rate as in the general population
  - B- Anxiety, depressive, and substance use disorders are 2-4 times more prevalent in patients with PTSD than the general population
  - C- Anxiety, depressive, and substance use disorders are 10-12 times more prevalent in patients with PTSD than the general population
  - D- Patients with PTSD experience anxiety, depressive and substance use disorders at a lower rate than the general population

EPIDEMIOLOGY OF PTSD AND COMORBID DISORDERS

- Lifetime prevalence 6.8 to 12.3 % (adult N America)
- One-year prevalence 3.5 to 6 %
  - Women are 2x's as likely to develop PTSD v men

- Anxiety, depression, and substance use disorders are **2-4 times** more prevalent in patients with PTSD
  - 20% will use substances to reduce symptoms

Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, Pickering RP, Ruan WJ, Huang B, Grant BF. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016;51(8):1137. Epub 2016 Apr 22.

A BRIEF WORD ON SSRI'S & PTSD

- Sertraline and paroxetine are FDA approved
  - But, any of the SSRIs can be used to treat PTSD
- A meta-analysis of 7 RCTs
  - SSRIs vs placebo ↓ PTSD symptoms NNT of 4.85
- Dosing
  - should be at the highest end of the dosing range (or as high as tolerated by the patient)

Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2006 Jan 25;(1):CD002795.

OTHER ANTIDEPRESSANTS IN PTSD

- SNRIs: venlafaxine ER vs placebo
  - 2 RCTs in 2006
  - – Remission rates
    - 50.9% for venlafaxine ER vs 37.5% for placebo

Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, Pedersen R, Musgnung J. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry. 2006;63(10):1158.

Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. J Clin Psychopharmacol. 2006;26(3):259

CASE AND QUESTION

You've educated your patient on the disruptive effect alcohol has on sleep and she's been able to stop drinking at night but her sleep has worsened due to nightmares of her trauma.

- What medication has the strongest evidence base for treating nightmares/sleep disturbance in PTSD?
  - A- Trazodone
  - B- Mirtazapine
  - C- Prazosin
  - D- Ambien

OTHER ANTIDEPRESSANTS IN PTSD CONTINUED

- Little evidence of effectiveness for PTSD
  - Trazodone
  - Mirtazapine
  - MAOIs
  - TCAs

PRAZOSIN

- Several RCTs (conducted by Dr. Raskind at the Seattle VA) as well as a meta-analysis from 2016
  - Demonstrated prazosin is effective in treating PTSD nightmares

- Typical dosing range is 3-5mg QHS, usual maximum dose is 10mg QHS

- Singh B, Hughes AJ, Mehta G, et al. Efficacy of Prazosin in Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. Prim Care Companion CNS Disord. 2016

CASE AND QUESTION

Your patient's sleep has improved with prazosin 5mg QHS but she is still having difficulty with daytime hyperarousal- feeling very anxious and reporting she's easily startled. She's tried some of her friend's Xanax and has noted a significant improvement in symptoms. She would like a prescription of this to help with her symptoms.

- What are two medication options you could try to help with her daytime anxiety and hypervigilance?
  - A- Alprazolam
  - B- Quetiapine
  - C- Valproic acid
  - D- Prazosin

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PRAZOSIN FOR DAYTIME HYPERVIGILANCE SYMPTOMS?

- The evidence base for this is sparse
  - Raskind et al demonstrated that QAM dosing of prazosin can improve daytime symptoms of PTSD.
  - **Dosing**: a 1/3 to a 1/2 of the night time dose

Taylor FB, Lowe K, Thompson C, McFall MM, Peskind ER, Kanter ED, Allison N, Williams J, Martin P, Raskind MA. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. Biol Psychiatry. 2006 Apr 1;59(7):577-81. Epub 2006 Feb 7.

PROPRANOLOL & PTSD PREVENTION?

- Propranolol was given shortly after the time of a trauma to try to decrease the rate of conversion to PTSD

Conclusion: Not Effective

BENZODIAZEPINES IN PTSD

- 2014 Virtual Reality PTSD trial found Alprazolam impaired recovery
  - Benzodiazepines work in direct opposition to help patients overcome avoidance
- PTSD is a risk factor for SUDs
  - Reducing use of benzos will reduce this risk
- Exceptions are few

MOOD STABILIZERS

- Limited evidence for mood stabilizers
- Topiramate—mixed evidence base.
  - 2007 RCT: **no separation** vs placebo
  - 2007 RCT: significant ↓ **in re-experiencing symptoms** and **Treatment Outcome PTSD Scale** vs placebo.
    - Mean dose was 150mg dosed BID (max dose 400mg)
  - 2011 RCT:↓ **in Clinician Adminstered PTSD Scale (CAPS)** vs placebo.
    - Mean dose was 100mg (max was 200mg)

2007- Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study.

2007- A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder.

2011- A double-blind randomized controlled trial to study the efficacy of topiramate in a civilian sample of PTSD.

MOOD STABILIZERS CONTINUED

Valproic Acid—mixed evidence

- 2007 systemic review and meta-analysis reviewed
    - (1 single-blinded study, 4 open-label studies and 3 case reports)
  - Conclusion:
  - **COULD** help **hyperarousal:** ↓ irritability and anger outbursts
    - ↑ mood (evidence was limited)
- RCTs in 2008 and 2009
  - 85 and 29 participants
  - No difference vs placebo in hyperarousal symptoms or CAPS score

Hamner MB, Faldowski RA, Robert S, Ulmer HG, Horner MD, Lorberbaum JP. A preliminary controlled trial of divalproex in posttraumatic stress disorder. Ann Clin Psychiatry. 2009;21(2):89.

Davis LL, Davidson JR, Ward LC, Bartolucci A, Bowden CL, Petty F. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. J Clin Psychopharmacol. 2008;28(1):84.

ANTIPSYCHOTICS IN PTSD

- RCTs have shown improvement in PTSD symptoms with:
  - Quetiapine
  - Risperidone
  - Olanzapine (13-22lb weight gain)

Villarreal G, Hamner MB, Cañive JM, Robert S, Calais LA, Durklaski V, Zhai Y, Qualls C. Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial. Am J Psychiatry. 2016;173(12):1205. Epub 2016 Jul 15.

Carey P, Suliman S, Ganesan K, Seedat S, Stein DJ. Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. Hum Psychopharmacol. 2012 Jul;27(4):386-91. Epub 2012 Jun 22.

Padala PR, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S, Din AU, Wilson DR, Petty F. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol. 2006;21(5):275.

ANTIPSYCHOTICS IN PTSD CONTINUED

- What antipsychotic to choose? As with any medication choice it's a matter of weighing risks vs benefits:
  - Risks of weight gain
  - Street value

- Quetiapine as monotherapy or augmentation- 100-300mg QHS, can also dose 25-50mg TID PRN for anxiety/hypervigilence during the day
- Risperidone as monotherapy or augmentation: 0.5-4mg QHS

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HOW TO MANAGE ANTIPSYCHOTICS

- Check:
  - Weight: Baseline, every 4-12 weeks
  - Waist circumference: baseline, at 3 months, annually
  - Fasting glucose: baseline, at 3 months, annually
  - Blood pressure: baseline, at 3 months, annually
  - AIMS (Abnormal involuntary movements scale): baseline, every 6-12 months
  - EKG

  - Video on how to conduct AIMS: http://www.psychiatrictimes.com/clinical-scales-movement-disorders/clinical-scales-movement-disorders/aims-abnormal-involuntary-movement-scale
  - AIMS rating scale with instructions on how to conduct the test: http://www.cqaimh.org/pdf/tool_aims.pdf

CASE AND QUESTION

Your patient has had improvement in her symptoms of insomnia and anxiety with sertraline 200mg, prazosin 2mg QAM and 5mg QHS. She's still struggling with her views of herself and is blaming herself for her sexual assault. She's thinking about starting therapy and is wondering if there is anything you can prescribe that will help her with the therapeutic process.

- Which of the following drugs is has been granted a Breakthrough Therapy Designation by the FDA for treatment of PTSD and will be starting a Phase 3 trial in Spring of 2018?
  - A- MDMA
  - B- Marijuana
  - C- Ketamine
  - D- Lorazepam

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EMERGING EVIDENCE- MDMA FOR PTSD

- "Breakthrough Therapy Designation" by the FDA.
- Phase 3 trial to begin Spring 2018
- Phase 2 trial:
  - 107 participants suffered from PTSD for an average of 17.8 years
  - 61% no longer met criteria for PTSD after three sessions of MDMA assisted psychotherapy

http://www.maps.org/news/media/6786-press-release-fda-grants-breakthrough-therapy-designation-for-mdma-assisted-psychotherapy-for-ptsd,-agrees-on-special-protocol-assessment-for-phase-3-trials

EMERGING EVIDENCE- KETAMINE FOR PTSD

- A 2014 proof of concept, double blind RCT with 41 patients
- Single dose of ketamine
- 24 hours later patients showed decrease in PTSD symptoms
  - At 7 days any difference between ketamine and placebo had disappeared

Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D, Charney DS. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry. 2014;71(6):681.

MARIJUANA FOR PTSD

- Systematic review (3 observational studies and 2 other systematic reviews)
  - Insufficient evidence to draw conclusions about benefits and harms
  - Two RTCs and 6 other studies examining cannabis use and PTSD should be completed within 3 years.

Benefits and Harms of Plant-Based Cannabis for Posttraumatic Stress Disorder: A Systematic Review. Ann Intern Med. 2017 Sep 5;167(5):332-340. doi: 10.7326/M17-0477. Epub 2017 Aug 15.

TO RECAP: IS THERE A MEDICATION THAT WORKS BETTER THAN SSRIS FOR PTSD?

- Difficult question to answer as most trials compare treatment to placebo
- Overall SSRIs/SNRI or trauma-focused CBT or a combination is still recommended as first line treatment for PTSD
    - This is a lecture on the pharmacotherapy for PTSD, but I want to emphasize the importance of utilizing CBT or exposure based therapies in treating PTSD.

TO RECAP: IS THERE A MEDICATION THAT WORKS BETTER THAN SSRIS FOR PTSD?

- Prazosin- shown in clinical trials to be effective for nightmares. Can be used with daytime dosing as well
- Quetiapine and risperidone- can be tried as monotherapy or augmenting agents in patients who do not respond to SSRIs and SNRI (at least 2 trials of antidepressants).
- MDMA assisted psychotherapy for PTSD will begin a Phase 3 trial in Spring 2018, other novel treatments such as marijuana or ketamine have limited evidence at this time.