INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Post Traumatic Stress Disorder*
-August 2021-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed the medical management of Post-Traumatic Stress Disorder (PTSD) at the August 2021 Summer meeting. There is a growing recognition of the impact of adverse childhood events for adult morbidity and mortality.[1] Some of the long term impacts of developmental trauma are now being captured by the diagnosis of complex PTSD, which is newly recognized in the International Classification of Diseases 11th Revision (ICD-11), as of 2018. The review sought to determine whether medications listed on the IHS National Core Formulary remained current in the management of complex as well as simple PTSD. The Committee found that although treatment recommendations may differ in terms of emphasis in the setting of complex PTSD, all recommended psychotropic medications needed to treat both simple and complex PTSD were currently included on the National Core Formulary. In particular, the role of prazosin was highlighted as one of the few medications which is effective in both forms of PTSD. As a result of the evaluation, the NPTC **made no modifications** to the National Core Formulary.

Discussion:

PTSD is a highly prevalent disorder in health care settings as 14 to 48% of clinical samples have a lifetime history of PTSD.[2] Underdiagnosis is common and clinically significant because the presence of PTSD predicts the later development of suicidality, substance abuse, and depressive and anxiety disorders. When PTSD remits, these psychiatric comorbidities tend to lessen.[3] PTSD is associated with increased medical morbidities as well.[4] In addition, first-line pharmacotherapies for PTSD can be routinely prescribed in primary care settings and are an important alternative when community-based psychotherapy is not readily available. Interestingly, a 2016 meta-analysis of 55 studies (N = 6,313) compared psychopharmacology to general psychotherapy and revealed both were similarly effective in PTSD treatment [effect size of first-line drugs: -0.43 (-0.49 to -0.36)], [effect size of general psychotherapies -0.45 (-0.89 to -0.01)].[5]

There are several key treatment considerations that can be implemented in primary care settings which can have a significant impact on the treatment of PTSD. Prazosin, an alpha-1-noradrenergic receptor inhibitor, is a highly efficacious medication for traumatic nightmares, boasting an effect size three times greater than the effect sizes observed for antidepressants [prazosin effect size for reducing nightmares: -1.13 (-1.91 to -0.36)].[6] Therefore, it is important to specifically query for the presence of traumatic nightmares to determine if the patient could benefit from the initiation of prazosin. This is in distinction to the usual treatment of mental health disorders in primary care. Depression, anxiety and PTSD all have the same first-line psychopharmacology recommendation, namely an antidepressant.[7] Therefore, a patient can often benefit from an antidepressant even when there is not a high level of diagnostic precision. But unless traumatic nightmares are specifically identified, a patient is unlikely to receive prazosin which highlights the importance of this line of focused patient inquiry.

It is also important that IHS clinicians are familiar with the concept of complex PTSD because it has therapeutic implications. Complex PTSD was newly introduced to the ICD-11 in 2018[8]. The classic cause of complex PTSD in adults is a history of childhood abuse.[9] Due to a history of settler colonialism and historical trauma[10], Native Americans have the highest rates of childhood abuse of any ethnic group.[11] The more adverse childhood events a patient has experienced, the more that complex PTSD is likely to be present.[9] Complex PTSD is thought to be biologically distinct from simple PTSD and appears to require a different psychopharmacological approach.[12]

In simple PTSD, the first line of treatment is the selective serotonin reuptake inhibitor (SSRI) class of medications which consist of fluoxetine, sertraline, paroxetine, escitalopram, citalopram (although citalopram above 40mg has a black box warning of sudden death).[13] Network meta-analysis reveals that fluoxetine is better tolerated but equally efficacious to the other SSRIs [fluoxetine effect size: -0.30 (0.51 to -0.09)].[14] Although venlafaxine is a serotonin-norepinephrine reuptake inhibitor, it can be added to this list because it has the neurotransmitter profile of an SSRI when dosed up to 150 mg and is similarly efficacious in PTSD [venlafaxine effect size: -0.32 (0.53 to -0.11)] versus other SSRIs when dosed in the SSRI range.

Although SSRIs are the first line of treatment for simple PTSD, a recent meta-analysis published in 2020 revealed that if there is a history of childhood abuse, neither SSRIs, monoamine oxidase inhibitors or tricyclic antidepressants may be effective.[15] Again, prazosin stands out as uniquely efficacious. Not only is prazosin helpful for traumatic nightmares as

previously discussed, but it appears to be helpful in overall PTSD symptom reduction [prazosin overall PTSD symptom reduction effect size, complex trauma: -0.52 (-1.03 to -0.02)], presumably because it calms the noradrenergic-mediated symptoms of PTSD such as hypervigilance and exaggerated startle.[6] Should an antidepressant be trialed in a patient with a history of childhood abuse, the more highly serotonin-selective antidepressants, such as escitalopram, may be more effective.[12]

In PTSD, benzodiazepines should be avoided because they can cause an overall worsening of PTSD severity, mediated by deepening the avoidance which is characteristic of the disorder.[16]

Findings:

In 2018, the ICD-11 introduced a new diagnostic category, complex PTSD, which is highly relevant for the IHS patient population. While the SSRI class of medications are considered the first-line treatment for PTSD, the SSRIs may not be as efficacious for complex PTSD. The more highly serotonin-selective SSRIs such as escitalopram presently show the most promise for effectiveness. While many of the agents that are effective in simple PTSD have questionable efficacy in complex PTSD, prazosin stands out as a medication that is effective in both PTSD subtypes for the treatment of nightmares. Prazosin has also been shown to be effective for general symptom reduction for complex PTSD. Prazosin is currently included on the National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med.* 1998; 14(4):245-58.
2. Spottswood M, Davydow DS, Huang H. The Prevalence of Posttraumatic Stress Disorder in Primary Care: A Systematic Review. *Harv Rev Psychiatry*. 2017: 25(4):159-69.
3. Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. *J Clin Psychiatry*. 2000; 61(5):4-12; discussion 13-4.
4. Seng JS, Graham-Bermann SA, Clark MK, et al. Posttraumatic stress disorder and physical comorbidity among female children and adolescents: results from service-use data. *Pediatrics.* 2005; 116(6):e767-76.
5. Lee DJ, Schnitzlein CW, Wolf JP, et al. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety*. 2016; 33(9):792-806.
6. Zhang Y, Ren R, Sanford LD, et al. The effects of prazosin on sleep disturbances in post-traumatic stress disorder: a systematic review and meta-analysis. *Sleep Med*. 2020; 67:225-31.
7. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder: Clinician Summary. Focus *Am Psychiatr Publ*. 2018; 16(4):430-48.
8. World Health Organization. ICD-11 for mortality and morbidity statistics. Version: 2019 April.
9. Guo T, Huang L, Hall DL. The relationship between childhood adversities and complex posttraumatic stress symptoms: a multiple mediation model. *Eur J Psychotraumatol*. 2021: 28;12(1):1936921.
10. Brave Heart MY, DeBruyn LM. The American Indian Holocaust: healing historical unresolved grief. *Am Indian Alsk Native Ment Health Res.* 1998;8(2):56-78.
11. Richards TN, Schwartz JA, Wright E. Examining adverse childhood experiences among Native American persons in a nationally representative sample: Differences among racial/ethnic groups and race/ethnicity-sex dyads. *Child Abuse Negl.* 2021; 111:104812.
12. Perna G, Daccò S, Alciati A, et al. Childhood maltreatment history for guiding personalized antidepressant choice in major depressive disorder: Preliminary results from a systematic review. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021; 20(107):110208.
13. National Guideline Alliance (UK). Evidence reviews for pharmacological interventions for the prevention and treatment of PTSD in adults: Post-traumatic stress disorder: Evidence review. London: National Institute for Health and Care Excellence (UK); 2018 Dec.
14. Cipriani A, Williams T, Nikolakopoulou A, et al. Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. *Psychol Med*. 2018; 48(12):1975-84.
15. Coventry PA, Meader N, Melton H, et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. *PLoS Med.* 2020; 19;17(8):e1003262.
16. Rothbaum BO, Price M, Jovanovic T, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. *Am J Psychiatry*. 2014; 171(6):640-8.