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Pharmacologic Considerations for Youth with Posttraumatic Stress Disorder

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Children exposed to potentially traumatic events are at risk of developing posttraumatic stress disorder (PTSD). However, the subsequent developmental course of posttraumatic stress symptoms appears to vary considerably. In this regard, some PTSD symptoms resolve without significant interventions, while for many children and adolescents, they persist until the patient receives appropriate treatment specifically designed to address PTSD and other trauma related symptoms. Evidence-based psychotherapies represent the standard of care for children with PTSD and, while psychopharmacologic interventions are utilized for many youth with posttraumatic stress symptoms and PTSD, there is little data available to guide the use of these medications in this population. However, given the structural challenges involved in disseminating and delivering evidence-based psychotherapies in all settings, prescribing clinicians should be aware of the medications whose use in children with pediatric PTSD has been studied. Herein, we review the PTSD assessment modalities, as well as the use of pharmacologic interventions in PTSD, including antiadrenergic agents, selective serotonin reuptake inhibitors and other medications.

Key Words: Posttraumatic stress disorder; Treatment; Medication.

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INTRODUCTION

The Diagnostic and Statistics Manual of Mental Disorders fifth edition (DSM-5)1) revised the diagnostic criterion for PTSD to be more developmentally sensitive than previous versions,²⁾ while at the same time, identifying a unique qualifier for diagnosing children under 7 with posttraumatic stress disorder (PTSD). Some of the core components of PTSD are similar with only minor changes.³⁾ Studies in both adults as well as children have identified that the shift in criteria from DSM-IV to DSM-5, andthere is still great overlap and prevalence rates are consistent between versions.4 In the United States, phone survey data suggest that up to 80% of children and adolescents will experience at least one traumatic event in childhood.⁵⁾ Risk factors for the development of childhood PTSD have been identified, including: female gender, number of traumas experienced, greater exposure to the index trauma, presence of a pre-existing psychiatric disorder, parental psychopathology, and availability of social support (particularly family support). 6) Although risk factors can help identify those most at risk, when 15-30% of those who

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experience trauma develop PTSD, 7,8) it is clear that broad based and effective interventions are necessary to address trauma specific symptoms.

Although evidence-based interventions and treatments are urgently needed, the literature does not provide strong support to many of the pharmacotherapies provided to children with known trauma histories and symptoms of PTSD. 9) This is in contrast to the large body of literature that supports the effectiveness of evidence-based psychotherapies for children and adolescent with PTSD. 10) Several components common to evidence based psychotherapies include: providing psychoeducation regarding the common effects of traumatic experiences; developing effective and healthy relaxation skills and coping responses when confronted by intrusive trauma memories or reminders; and accessing family and social supports to enhance safety and routine. 11) Over the following sections, we will review effective methods of assessing and treating pediatric PTSD, with a special focus on the limited potential role of pharmacotherapy.

SCREENING FOR TRAUMATIC **EXPERIENCES AND TRAUMA SYMPTOMS**

Standardized approaches to the detection of childhood trau-

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ma is critical to identifying children at risk for PTSD. Unfortunately, many children who present to primary care providers or to specialized psychiatric services do not identify traumatic experiences at the time of their initial evaluations, and often times refer to concerns or potentially, to traumarelated symptoms, in commonly used lay terms such as anxiety, depression, or hyperactivity. Moreover, children with a history of trauma exposure are more at risk to develop symptoms of anxiety or depression. 12) However, it is also possible for children to meet DSM-5 diagnostic criteria for a number of disorders simply as a result of syndromic overlap, yet for some of those children, their symptoms might be better explained by a unifying diagnosis of PTSD if their trauma is known and trauma specific symptoms are identified. As will be described in detail later, an accurate diagnosis is critical to the appropriate choice of medication as part of a comprehensive treatment plan. Medications that are considered first line treatment for common disorders such as generalized anxiety disorder, panic disorder, major depressive disorder and attention-deficit hyperactivity disorder (ADHD) are not indicated for the treatment of PTSD in trauma exposed children. The use of such medications where there is true co-morbidity may be helpful. However, when syndromic overlap leads a practitioner to misinterpret the hypervigilance and reckless behavior of PTSD for hyperactivity concerning for ADHD, the child is exposed to medication that is not indicated, and initiation of effective treatment is delayed.

Standardized screening measures for trauma symptoms are an effective way to measure trauma symptoms once it has been determined that the child has experienced or witnessed potentially traumatic events. Several of these measures are available in Korean (ref), and others that have been newly developed in the past several years to reflect changes in the diagnosis of PTSD from DSM-IV to DSM-5 can be requested to be translated and validated. A currently available measure is the Children's Revised Impact of Event Scale, a 13-item measure that detects trauma specific symptoms (http://www.childrenandwar.org/measures/children's-revised-impact-of-event-scale-8---cries-8/ies13/). The Child PTSD Symptom Scale¹³⁾ is a 17 item measure with both self-report and parent report formats that identify PTSD symptoms as well as assess for possible functional impairment. The DSM-IV version has been translated into Korean, and the recently developed version for DSM-5 (20 items instead of 17) would likely be able to be translated and validated in the future. For symptom detection that is inclusive, but not limited to PTSD specific symptoms, one might consider the Trauma Symptom Checklist for Children (TSCC).¹⁴⁾ The TSCC is a 54 item self report measure with strong psychometric properties and validity measures that identifies clinically significant symptoms of anger, anxiety, de-

pression, PTSD and dissociative symptoms. The TSCC was recently validated in Korean¹⁵⁾ and was effective in identifying trauma specific symptoms.

PSYCHOPHARMACOLOGIC APPROACHES FOR YOUTH WITH PTSD

Antiadrenergic agents

Propranolol

Given that research has consistently demonstrated increased noradrenergic tone in both adults (for review see)¹⁶⁾ and youth with PTSD, 17) several investigators have explored the efficacy of anti-adrenergic agents for the prevention and treatment of PTSD. Propranolol is a centrally-acting, long-chain β-blocker that is used primarily for hypertension, and has been used off-label for the treatment of situational anxiety, such a stage fright or performance anxiety. Famularo et al. 18) demonstrated reductions in PTSD symptoms, and observed that propranolol was well tolerated. However, there are significant reasons for cautions when viewing Famularo et al.'s findings. Specifically, there was no documentation to the presence or absence of a co-morbid anxiety disorder, which given the accepted use of propranolol, could impact reported improvement by children, and there was no control group, a common issue in open label trials. Additionally, more rigorous studies examining the use of propranolol among trauma exposed youth have had negative results. Specifically, in a PTSD prevention study, children and adolescents aged 10-18 years were randomized to receive propranolol or placebo shortly after a potentially traumatic event. At follow up, there were no significant differences in PTSD severity or PTSD diagnosis at 6-week follow-up.¹⁹⁾ Given the underlying noradrenergic dysregulation hypothesis that explains many of the symptoms of PTSD, these negative prevention studies likely reflect a lack of overall efficacy in either the prevention or treatment of PTSD in youth.

Prazosin

Prazosin is a centrally acting alpha 1 blocking agent that blocks the effect of norepinephrnine centrally, and adult studies demonstrate effectiveness in randomized controlled trials and other large comparative studies. 20-22) Several case reports suggest benefit for prazosin²³⁻²⁶⁾ in youth diagnosed with PTSD. The use of prazosin is limited to evening dose, focusing on the treatment of PTSD related sleep disturbances and nightmares. Increased sympathetic nervous system activity is associated with pediatric PTSD, especially intrusive and hyperarousal sympotms. 17,27,28) However, caution is warranted as there are no large, double-blind, placebo-controlled

trials that demonstrate safety or efficacy of prazosin in children.

α₂ agonists

 α_2 agonists such as clonidine and guanfacine are regularly used as second line agents in the treatment of ADHD, 29) as well as aggression in children. Based on the theoretical construct that many of the symptoms of PTSD are likely related to sympathetic nervous system dysregulation, 17) and the known tolerability, it is reasonable to consider the use of these agents in trauma exposed children with severe trauma related behavioral manifestations who are not responding to first line psychotherapies. However, similar to prazosin, caution is advised as there is little evidence to support the use of these agents. Clonidine appears to attenuate hyperarousal, hypervigilance, sleep disruption, exaggerated startle responses and nightmares in open label trials. In abused youth, clonidine decreases reenactment symptoms. ^{30,31)} Similarly, the α_2 agonist guanfacine may reduce nightmares in children with PTSD. 32) However, when extended-release guanfacine was examined with regard to the treatment of PTSD symptoms, although improvements were noted for the UCLA Reaction Index scores for reexperiencing, avoidant, and hyperarousal symptoms, 33) most children with nightmares did not experience resolution of their nightmares while taking extended-release guanfacine. Of note, guanfacine was well tolerated and adverse events were consistent with the known side effect profile of this medication.³⁴⁾

Antidepressant medications

Several selective serotonin reuptake inhibitors (SSRIs), including sertraline and paroxetine, are FDA approved for the treatment of adults with PTSD. Unfortunately, this is a clear area of pharmacotherapy that highlights the benefit of researching the effects of treatment on pediatric conditions rather than extrapolating adult findings to the care of children and adolescents.35) Two open-label studies suggest improvement in PTSD symptoms in youth treated with citalopram, $^{36,37)}$ however, two randomized controlled trials failed to demonstrate benefit with sertraline in youth with PTSD compared to placebo. Adjunctive sertraline (mean dose 150 mg/day, range 50-200 mg/day) vs. placebo combined with traumafocused cognitive behavioral therapy (TF-CBT) yielded only limited improvement in the sertraline-treated youth, 38) although this study was underpowered to detect differences in efficacy. A subsequent 10 week trial of sertraline monotherapy did not result in significant differences (compared to placebo) in PTSD or depression symptoms.³⁹⁾

Other medications

Second generation antipsychotics (SGA) such as quetiap-

ine and risperidone have been examined in youth with PTSD and these open label studies and case series have demonstrated improvement in trauma specific symptoms. 40-42) However, even these small, uncontrolled studies have consistently found the development of significant side effects including weight gain among treated youth. Given the risk of obesity among trauma exposed youth in both childhood and adulthood, the availability of other medications without the significant risk of weight gain, and the lack of evidence supporting the use of SGAs, there is little role in the use of SGAs among most children with PTSD. The same can be said for mood stabilizers such as carbamazepine, divalproex and oxcarbazepine, all of which have open label trial or retrospective case series evidence demonstrating that use of medication was associated with some improvement in PTSD symptoms. 43-45)

PSYCHOTHERAPEUTIC INTERVENTIONS

Evidence based and trauma focused psychotherapies are the gold standard in the treatment of pediatric PTSD. Numerous professional organizations, guidelines and meta-analyses support the use of psychotherapies in the treatment of traumatized children. 46) Although not universally available, it is critical that the practicing child psychiatrist understand and advocate for the dissemination and implementation of these modalities in both specialized and community settings. Numerous therapies have been developed and tested in a number of different countries with different trauma exposed populations. A comprehensive review of all evidence-based modalities is beyond the scope of this review. However, two examples of effective interventions, Trauma Focused Cognitive Behavior Therapy⁴⁷⁾ and Child and Family Traumatic Stress Intervention⁴⁸⁾ will highlight components and strengths common to many interventions. Additional information, including information on interventions can be found on the National Child Traumatic Stress Network website (http://nctsn. org/).

Trauma focused cognitive behavioral therapy

TF-CBT is a manualized and stepwise approach to the treatment of children and adolescents 3–17 years of age who have trauma related symptoms. ⁴⁷⁾ Children and adolescents who benefit from TF-CBT include those with PTSD, anxiety, depressive or externalizing behaviors. Randomized controlled trials comparing TF-CBT efficacy against other psychotherapies have been performed by multiple investigators who have replicated findings of the original treatment developers. ^{9,10)} Furthermore, TF-CBT offers the opportunity to address commonly experienced psychological sequallae of traumatic experiences such as childhood sexual abuse such as

traumatic sexualization, betrayal, feeling powerless and stigmatization. 49) TF-CBT is generally provided over 12-24 weeks for symptoms that result from a single episode of trauma, but might last longer for children and adolescents who suffer from polyvictimization. 50)

TF-CBT consists of psychoeducational, stress reduction and cognitive coping components as well as the development of a trauma narrative. The goal of the trauma narrative is to provide the child or adolescent with gradual exposure to the troubling memories in a safe environment where the therapist can help the child utilize skills learned during therapy to decrease distress and correct ongoing cognitive distortions that often perpetuate symptoms. Once the child has completed the trauma narrative, the focus of therapy moves towards re-establishing the normal parent-child dynamic, supporting the child in sharing the narrative with the parent and encouraging the establishment of improved communication within the family as well as safety guidance to prevent subsequent

Although the trauma narrative is considered a core component of TF-CBT, some evidence suggests that not all children need the narrative to have significant reduction in symptoms, especially when provided the psychoeducation, relaxation skills and cognitive coping strategies. One randomized controlled trial demonstrated that children who received TF-CBT with versus without a trauma narrative demonstrated similar symptom improvement, especially when the trauma narrative was replaced with additional coping skills and parental guidance.⁵¹⁾ Child Family Traumatic Stress Intervention (CFTSI) is a similarly effective, family based, PTSD prevention program that also focuses on skills without a discrete exposure component such as a trauma narrative. 48) CFTSI is best suited for recently traumatized children with new onset of symptoms or worsening symptoms shortly after the trauma and can be provided over four to six sessions. CFTSI focuses on the identification of trauma symptoms as observed by the parent and experienced by the child. After identifying current trauma symptoms, the remainder of the psychotherapy focuses on enhancing communication within the family about the child's symptoms and utilizing specific coping strategies to decrease symptom specific distress. In a randomized controlled trial of recently traumatized youth comparing CFTSI to supportive therapy (n=106, ages 7-17 years), CFTSI-treated patients were 65% less likely to meet DSM-IV criteria for PTSD at 3-month follow-up than youth in the comparison group. CFTSI was also associated with lower levels of behavior avoidance and re-experiencing of the event. When necessary, CFTSI can transition to more definitive treatments for PTSD such as TF-CBT in children who need more comprehensive trauma treatment after the initial 4-6 sessions.

CONCLUSION

Children and adolescents exposed to potentially traumatic events are at risk for the development of PTSD. Evidence based interventions exists and are effective in the treatment of pediatric PTSD, yet the overwhelming evidence supports the use of psychotherapeutic modalities over psychopharmacologic interventions. In cases where medication may be warranted to augment the effect of psychotherapy, the biological underpinnings of PTSD (dysregulation of the stress response systems) as well as side effect profiles suggest the cautious and limited use of antiadrenergic agents be considered. There is no evidence that strongly supports the use of SSRIs without clear anxiety or depression co-morbidity. Finally, SGAs and mood stabilizers are not recommended for the treatment of pediatric PTSD given the lack of supporting evidence and side effect profile.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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