

# Psychopharmacologic Treatment of Posttraumatic Stress Disorder in Children and Adolescents: A Review

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**Objective:** Despite the high prevalence and significant morbidity associated with posttraumatic stress disorder (PTSD) in children and adolescents, there are limited and conflicting data to guide psychopharmacologic interventions. With these considerations in mind, we sought to summarize the current evidence for psychopharmacologic interventions in youth with PTSD.

**Data Sources/Study Selection:** We conducted a literature review of the National Library of Medicine to identify publications of pharmacologic treatments for youth with PTSD or posttraumatic stress symptoms. The search was limited to articles written in English and published between 1966 and 2009. In addition, we manually searched each citation for additional references and the following journals: *Journal of the American Academy of Child and Adolescent Psychiatry* and the *Journal of Child and Adolescent Psychopharmacology*.

**Data Extraction:** All articles were manually reviewed and evaluated. Thereafter, each agent or class of medication was categorized by level of evidence.

**Data Synthesis:** Three double-blind, randomized controlled trials of selective serotonin reuptake inhibitors (SSRIs) and 1 double-blind randomized controlled trial of imipramine in children and adolescents with PTSD or acute stress disorder were identified. Additionally, several open-label studies and case series involving other classes of medications (eg, antiadrenergics, other antidepressants, and second-generation antipsychotics) were reviewed.

**Conclusions:** The extant data do not support the use of SSRIs as first-line treatments for PTSD in children and adolescents. There is limited evidence that the brief use of antiadrenergic agents, second-generation antipsychotics, and several mood stabilizers may attenuate some PTSD symptoms in youth. However, controlled trials of these agents in children and adolescents with PTSD are needed.

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Exposure to traumatic events, including neglect, domestic violence, as well as physical and sexual abuse, is not uncommon for many children and adolescents. In fact, a recent study of 1,420 children aged 9, 11, and 13 years at intake who were followed annually until the age of 16 years found that nearly two-thirds of these individuals experienced at least 1 traumatic event.<sup>1</sup> A significant number of traumatized children and adolescents will develop posttraumatic stress disorder (PTSD), a condition intrinsically linked to the experience of extraordinary stress and characterized by intrusive hyperarousal and avoidant symptoms. Though the prevalence varies by report, 10% of physically abused adolescents may meet criteria for PTSD.<sup>2</sup> Other samples of youth exposed to urban violence suggest that PTSD rates may be as high as 24%–34%.<sup>3,4</sup> While following a single motor vehicle accident, the prevalence of PTSD in children at 6 months after the accident is approximately 12%.<sup>5</sup> Finally, pediatric patients with PTSD or clinically significant posttraumatic stress symptoms often have comorbid depression, bipolar disorder, substance use disorders, social deficits, internalizing, and externalizing behavioral problems, and, in preschool age children, these individuals may experience dysfunctional attachment, aggressiveness, and impulsivity.<sup>6</sup>

Child and adolescent psychiatrists have utilized a myriad of pharmacologic treatments in youth with PTSD or trauma-related psychological sequelae.<sup>6–11</sup> These interventions are often directed at attenuating symptoms in the core symptom domains of PTSD (intrusive, avoidance, hyperarousal), often with differential effects by symptom cluster.<sup>12</sup> However, despite the prevalence and significant morbidity associated with pediatric PTSD, there are limited and conflicting data available to guide psychopharmacologic treatments for this condition in youth. With these considerations in mind, the aim of this article was to summarize the current evidence for psychopharmacologic interventions in youth with PTSD.

## DATA SOURCES AND STUDY SELECTION

We conducted a literature review of the National Library of Medicine using the following key words: *trauma, post-traumatic stress disorder, posttraumatic stress symptoms, stress, acute stress disorder; child abuse, sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, clonidine, guanfacine, prazosin, doxazosin, propranolol, antiepileptics, lithium, valproate, divalproex, carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, atypical antipsychotics, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, benzodiazepines, alprazolam, clonazepam, lorazepam, diazepam, cyproheptadine* to identify pharmacologic treatment reports of these agents in children and adolescents with PTSD or posttraumatic stress symptoms. The search was limited to studies written in English and published between 1966 and 2009. In addition, we manually searched each citation for additional references and searched the following journals: *Journal of the American Academy of Child and Adolescent Psychiatry* and the *Journal of Child and Adolescent Psychopharmacology*. All articles were manually reviewed and evaluated. Thereafter, each agent or class of medication was categorized by level of evidence.

## RESULTS

### Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Serotonin-Norepinephrine Reuptake Inhibitors

Although SSRIs are considered to be among the first line pharmacologic interventions for adults with PTSD<sup>13</sup> and their use is supported by many<sup>14–22</sup> but not all<sup>23,24</sup> studies in adult patients with PTSD, results of clinical trials in children and adolescents have often failed to demonstrate significant advantages compared to placebo.

The first double-blind placebo-controlled trial of SSRIs in pediatric PTSD compared the use of flexibly dosed sertraline (mean dose, 150 mg/d; range, 50–200 mg/d) and placebo as adjunctive treatment to trauma-focused cognitive-behavioral therapy (TF-CBT). Both treatment groups experienced significant improvement in posttraumatic stress symptoms and other clinical outcomes, suggesting minimal benefit to adjunctive sertraline use in TF-CBT.<sup>25</sup> In a subsequent multisite placebo-controlled trial of flexibly dosed sertraline (50–200 mg/d), Robb and colleagues<sup>26</sup> examined 131 children and adolescents with PTSD over 10 weeks and noted no differences in primary outcome (change in University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index 17-item total score) between sertraline-treated patients and those receiving placebo though sertraline was noted to be generally well tolerated.<sup>26</sup> Finally, one very recent study found no difference among fluoxetine (5 mg/d for children < 40 kg, 10 mg/d for those weighing 40–60 kg, and 20 mg/d for children weighing > 60

kg), imipramine (1 mg/kg), and placebo for the treatment of acute stress disorder symptoms in children with thermal burns; however, the duration of treatment was only 1 week<sup>27</sup> and thus would have been unlikely to have shown clinical benefit.

In addition to these double-blind placebo-controlled trials, a number of case reports and open-label studies have examined the utility of SSRIs in pediatric patients with PTSD. For example, Seedat et al<sup>28</sup> treated 24 youth with PTSD with citalopram (20–40 mg/d) for 8 weeks and noted improvements in Clinician-Administered PTSD Scale (CAPS) total and symptom cluster scores as well as the Clinical Global Impressions-Improvement scale (CGI-I) score. In a prior open-label study of citalopram in adolescents with PTSD, Seedat et al<sup>29</sup> treated 8 patients with moderate to severe PTSD with a fixed dose of citalopram (20 mg/d) and found reductions in total CAPS Child and Adolescent Version (CAPS-CA) score (38% decrease from baseline to endpoint) and scores on CAPS-CA subscales for reexperiencing, avoidance, and hyperarousal symptoms.<sup>29</sup> We are unable to locate pediatric treatment trials of escitalopram, fluvoxamine, or paroxetine or the selective serotonin-norepinephrine reuptake inhibitors duloxetine, venlafaxine, or desvenlafaxine.

### Other Antidepressant Medications

In a brief (7-day) comparison trial of imipramine and chloral hydrate, Robert and colleagues<sup>30</sup> found that low-dose imipramine provided superior reduction in acute stress disorder symptoms for pediatric burn victims.<sup>30</sup>

Despite several open-label trials of trazodone<sup>31</sup> and nefazodone<sup>32</sup> in adults with PTSD, there are limited data supporting the use of these agents in youth with PTSD. Doman and Anderson<sup>33</sup> noted tolerability of nefazodone in adolescents with PTSD at doses up to 600 mg/d as well as clinical improvement in all 3 symptom clusters as well as anger and aggression.<sup>33</sup> The norepinephrine-dopamine reuptake inhibiting agent bupropion has yielded disappointing results in both open-label<sup>34</sup> and double-blind trials of adults with PTSD.<sup>35</sup> At present, we are unable to locate any published reports of using bupropion in youth with PTSD. Finally, many randomized controlled trials of monoamine oxidase inhibitors have supported the use of these compounds in the management of PTSD in adults,<sup>36</sup> although results of these randomized controlled trials have not been universally positive.<sup>37</sup> We are unable to locate any reports of monoamine oxidase inhibitors in the treatment of pediatric PTSD.

### Antiadrenergic Medications

Supported by adult<sup>38–45</sup> and pediatric data<sup>46–48</sup> that have demonstrated noradrenergic hyperactivity in PTSD, clinicians have often utilized antiadrenergic agents to treat children and adolescents with PTSD or posttraumatic stress symptoms (Table 1). The dysregulated noradrenergic system observed in patients with PTSD can be pharmacologically modified in a variety of ways by a number of agonists or

Table 1. Pediatric Pharmacology of the Central Noradrenergic System in Posttraumatic Stress Disorder (PTSD)

Receptor/ Target	Drug	Initial Pediatric Dose (mg)	Target Pediatric Dose (mg) <sup>a</sup>	Adult, t <sub>1/2</sub> (h)	Pediatric, t <sub>1/2</sub> (h)	Common Adverse Effects and Notes
α <sub>1</sub> Antagonist	Prazosin	1 qhs	2–4 reported in the literature <sup>b</sup>	2–4	unknown	Reflex tachycardia, orthostatic hypotension (may have first dose hypotension); lack of energy; nausea Use with caution in children < 12 years of age
α <sub>2</sub> Agonist	Clonidine	0.05 qhs (children aged 5–10 years) 0.1 qhs (children aged > 10 years)	0.2–0.5	6–20	8–12	Dry mouth, dizziness, sedation, bradycardia, rebound hypertension
β <sub>1</sub> /β <sub>2</sub>	Guanfacine	0.5 bid	1–3	12–24	13–14	Dry mouth, sedation, dizziness
	Propranolol	10 tid	40–80	4–6	4–6.4	Bradycardia, sedation, thrombocytopenic purpura and bronchospasm

<sup>a</sup>Slow titration of these medications is recommended in children and adolescents.

<sup>b</sup>The target dose of 2–4 mg/d is based on the current available pediatric PTSD literature; however, the maximum approved dose of this medication for the management of pediatric hypertension is 15 mg/d. It is likely that such a dose in a normotensive pediatric patient would be poorly tolerated.

Abbreviations: bid = twice a day, qhs = every night, t<sub>1/2</sub> = half-life, tid = three times a day.

antagonists (see Strawn and Geraciotti<sup>49</sup> for a review of the relationship between noradrenergic neurobiology and potential therapeutic targets). Specifically, the α<sub>2</sub> agonists (eg, clonidine and guanfacine) decrease norepinephrine release, centrally-acting β-antagonists (eg, propranolol) and α<sub>1</sub> antagonists (eg, prazosin) attenuate the effects of norepinephrine postsynaptically and dampen sympathetic tone, which presumably ameliorates associated symptoms such as hyperarousal, intrusive symptoms, and impulsivity.<sup>49</sup>

**α<sub>1</sub> Antagonists.** In case series of adults with PTSD<sup>50–53</sup> and at least 2 randomized controlled studies of adult combat-related PTSD, the α<sub>1</sub> antagonist prazosin appears to be efficacious, particularly with regard to intrusive symptoms.<sup>54,55</sup> At present, there are limited data on the use of these agents in children and adolescents with PTSD, although Brkanac and colleagues<sup>56</sup> reported the successful use of adjunctive prazosin (4 mg every night [qhs]) in an adolescent female with severe PTSD. This patient had been hospitalized in a long-term residential facility and noted improvement in sleep and cessation of nightmares.<sup>56</sup> Similarly, we have recently reported an adolescent female armed robbery victim who was successfully treated with prazosin monotherapy (2 mg qhs) and experienced rapid reduction in intrusive symptoms.<sup>12</sup>

There are limited data regarding the dosing of prazosin in youth though our experience and dosing strategies, which have been extrapolated from adults, suggest that prazosin should be initiated at 1 mg at bedtime and may be increased by 1 mg/wk as tolerated to a maximum dosage of 4 mg/d. However, significantly higher doses are reported in the adult PTSD literature, and this medication is used for the treatment of hypertension in children at doses up to 15 mg/d (400 μg/kg/d).

**Centrally acting α<sub>2</sub> agonists.** The α<sub>2</sub> agonist clonidine appears to be effective in attenuating hyperarousal,

hypervigilance, sleep disruption, exaggerated startle responses, and nightmares in open-label trials of adults with war-related PTSD<sup>57,58</sup> as well as in a double-blind, placebo-controlled trial<sup>59</sup> conducted in adult patients with borderline personality disorder and comorbid PTSD. By contrast, 2 recent double-blind placebo-controlled trials of adults with chronic, combat-related PTSD have failed to detect differences between those treated with the less potent α<sub>2</sub> agonist guanfacine and those treated with placebo.<sup>60,61</sup>

Despite the frequency with which the α<sub>2</sub> agonists are used by child and adolescent psychiatrists,<sup>62</sup> there are limited data for their use in youth with PTSD. In abused youth, clonidine decreases reenactment symptoms.<sup>63,64</sup> Similarly, the α<sub>2</sub> agonist guanfacine may reduce nightmares in children with PTSD.<sup>65,66</sup> At present, there are no double-blind trials of clonidine or guanfacine in pediatric patients with PTSD.

Clonidine is highly bioavailable (75%–95% bioavailability) and has a rapid onset of action (generally within 30–60 minutes). This agent is often initiated at doses of 0.05 or 0.1 mg given initially at bedtime, and doses are increased by 0.05 mg every 3 days<sup>67</sup>; however, multiple doses are often required, given the short half-life of this agent, and dosages should not exceed 0.5 mg/d. Also, as with many of the antiadrenergic medications, heart rate and blood pressure should be monitored, and the medication should not be discontinued abruptly. Common adverse effects of α<sub>2</sub> agonists include dry mouth and sedation, both of which lessen with time. Compared to adults in whom the half-life is approximately 6–20 hours, the half-life in children is significantly shorter (8–12 hours). The α<sub>2</sub> agonist guanfacine also rapidly penetrates the central nervous system and is actually more rapidly absorbed than clonidine and reaches peak levels in 1–4 hours. In addition, this agent is substantially more selective for the α<sub>2</sub> receptor than clonidine.<sup>67</sup>

**Centrally acting β-blockers.** Adult studies of the long-chain β-blocker propranolol suggest that it may both

prevent<sup>68</sup> and treat<sup>57,69</sup> PTSD. In a case series (on-off-on design), 11 children with abuse-related PTSD had significantly fewer symptoms when receiving propranolol.<sup>70</sup>

Of particular interest, there are 2 published double-blind controlled trials of propranolol in the secondary prevention of PTSD in adults,<sup>68,71</sup> although in 1 of these trials the low dose of propranolol may have been inadequate (as evidenced by heart rates between the 2 groups) and thus the 40 mg dose utilized may have been “insufficient to fully attenuate patients’ acute posttraumatic hyperadrenergic states,” which may have accounted for the lack of a significant longer term preventive effect on PTSD development.<sup>68</sup> One recent pediatric pilot study evaluated propranolol (2.5 mg/kg/d; maximum dose, 40 mg bid; duration of treatment, 10 days) as a secondary prevention of PTSD in children and adolescents aged 10–18 years.<sup>72</sup> In this study, 29 children were randomized to receive propranolol (or placebo) within 12 hours of accidental traumatization and there were no differences in CAPS-CA scores or in the number of patients meeting criteria for PTSD or subthreshold criteria for PTSD at 6 weeks follow-up.<sup>72</sup>

Propranolol is approximately 30%–40% orally bioavailable (though this may be increased in some conditions, such as Down syndrome) and its onset of action typically occurs within 2 hours. Its half-life in children and adults is similar (4–6 hours) and typical doses are 10–40 mg every 6 hours. Blood pressure and heart rate should be monitored carefully over the course of dose titration, and common adverse events include hypotension, bradycardia, lightheadedness, fatigue, dizziness, nausea, and bronchospasm.

### Second-Generation Antipsychotics

Second-generation antipsychotics have been used extensively for the treatment of children and adolescents with a constellation of severe neuropsychiatric conditions and have generally been well tolerated.<sup>73</sup> In addition, both aripiprazole and risperidone have recently received US Food and Drug Administration (FDA) indications for the treatment of several psychiatric disorders in children and adolescents (eg, bipolar disorder, schizophrenia, aggression associated with autism).

Over the last decade, there have been 7 double-blind placebo controlled trials of second-generation antipsychotic agents (either as monotherapy or as adjunctive therapy) in the treatment of adults with PTSD.<sup>74</sup> A recent meta-analysis of these studies suggests that second-generation antipsychotics may be beneficial in the treatment of PTSD and notes that these agents may be particularly effective in reducing intrusive symptoms of the disorder.<sup>74</sup>

**Risperidone.** Multiple placebo-controlled<sup>75,76</sup> and open-label<sup>77–81</sup> trials of risperidone support its use in adults with PTSD. Although some of these trials have examined the usefulness of risperidone monotherapy, most have focused on adjunctive treatment. In addition, Meighen and colleagues<sup>82</sup> recently treated 3 preschool-aged children with

serious thermal burns and acute stress disorder and noted that risperidone reduced all symptom clusters of acute stress disorder.<sup>82</sup> We recently reported significant improvement associated with adjunctive risperidone in a 13-year-old boy with severe sexual abuse- and neglect-related PTSD, although his treatment was complicated by transient hyperprolactinemia.<sup>83</sup>

**Quetiapine.** A number of open-label trials<sup>84–88</sup> and retrospective reviews<sup>89</sup> have noted quetiapine to be effective in reducing symptoms of PTSD in adults, although generally at lower doses than typically employed in the treatment of acute manic or mixed episodes associated with bipolar disorder or in the treatment of schizophrenia. In addition, a 12-week, double-blind, placebo-controlled, randomized, fixed-flexible dose trial of quetiapine monotherapy for the treatment of adults with PTSD is currently underway (clinicaltrials.gov identifier: NCT00237393) as is a randomized placebo-controlled trial of adjunctive quetiapine for adult PTSD (clinicaltrials.gov identifier: NCT00306540). At present, there is 1 study<sup>90</sup> that has examined the efficacy of this agent in youth with PTSD. In this study, adolescents with PTSD (n=6, aged 15–17 years) were treated with flexibly dosed quetiapine (50–200 mg/d). Improvement in Traumatic Symptom Checklist for Children posttraumatic stress *t* scores (mean ± SD, 75 ± 5.2 to 54 ± 7.4) and in symptoms of anxiety, depression, and anger were noted over a 6-week treatment period.

**Ziprasidone.** There is 1 small case series<sup>91</sup> that describes beneficial effects of ziprasidone in adult patients with PTSD, and a trial of ziprasidone for the treatment of adults with PTSD has been registered (clinicaltrials.gov identifier: NCT00208208); however, the results have not been published and there are no reports of ziprasidone in children or adolescents with PTSD.

**Olanzapine.** At least 1 double-blind placebo controlled trial<sup>92</sup> of adjunctive olanzapine in SSRI-refractory PTSD has demonstrated reasonable improvement in adults with PTSD. However, not all double-blind placebo-controlled trials of olanzapine in adults with PTSD have observed differences between placebo and olanzapine though this may have been attributable to a high placebo response rate.<sup>93</sup> Finally, a number of open-label trials<sup>94,95</sup> and case reports/series<sup>96,97</sup> support the efficacy of olanzapine in the treatment of adults with PTSD. To our knowledge, there are no reports of olanzapine for the treatment of children or adolescents with PTSD.

**Aripiprazole.** Although several studies of adults with PTSD have noted aripiprazole monotherapy<sup>98,99</sup> and adjunctive aripiprazole<sup>100–102</sup> to be effective in reducing target symptoms, there are no studies of aripiprazole in children or adolescents with PTSD.

The second-generation antipsychotics, though potentially effective and efficacious, may also cause significant side effects in the pediatric population that must be recognized and managed effectively. These side effects include

extrapyramidal effects, tardive dyskinesia, obesity, hyperlipidemia, increased prolactin levels, and increased QTc interval. Importantly, the long-term sequelae of these adverse effects (eg, hyperprolactinemia, extrapyramidal symptoms/tardive dyskinesia) remain largely unknown. Moreover, the relative liabilities of these agents to precipitate these adverse effects may be different in children as compared to adults.<sup>103</sup>

### Mood Stabilizers

The extant literature supporting the use of antiepileptic drugs (ie, mood stabilizers) in adults with PTSD consists of several double-blind placebo-controlled trials (lamotrigine, divalproex, topiramate, and tiagabine) as well as a number of open-label trials of divalproex,<sup>104,105</sup> carbamazepine,<sup>106</sup> topiramate,<sup>107</sup> phenytoin,<sup>108</sup> levetiracetam,<sup>109</sup> and gabapentin.<sup>110</sup> In addition, the new antiepileptic agent pregabalin has been found to be effective in case reports of adults with PTSD,<sup>111</sup> although no case series or open-label series exist for the use of this agent in adults with PTSD. In many of these studies as is commonly observed in clinical practice, mood stabilizers were used adjunctively in combination with SSRIs<sup>107</sup>; however, some studies have examined mood stabilizers as monotherapy for PTSD. Overall, most studies have demonstrated modest improvement in at least 2, if not all 3 of the primary PTSD clusters, and a variety of traumatized populations have been studied (eg, combat, abuse).

Topiramate monotherapy was more effective than placebo in reducing reexperiencing symptoms in adults with PTSD<sup>112</sup> and has been examined in a controlled, double-blind comparison study as an adjunctive agent for the treatment of PTSD.<sup>113</sup> Mixed effects have been observed for tiagabine-treated patients in placebo-controlled discontinuation trials<sup>114</sup> and other placebo-controlled trials of tiagabine have failed to show benefit.<sup>115</sup> Hertzberg and colleagues<sup>116</sup> noted the efficacy of flexibly dosed lamotrigine monotherapy (25–500 mg/d) in adults with chronic PTSD.<sup>116</sup> Finally, 2 double-blind, placebo-controlled trials of divalproex monotherapy have failed to demonstrate efficacy in reducing CAPS scores in veterans with chronic PTSD.<sup>117,118</sup>

With regard to trials of mood stabilizers in children and adolescents with PTSD, we were able to locate only 1 open-label trial of carbamazepine in children (aged 8 and 17 years) with sexual abuse-related PTSD<sup>119</sup> and 1 trial of divalproex in youth with PTSD.<sup>120</sup> In the carbamazepine study,<sup>119</sup> after attaining target carbamazepine serum levels of 10–11.5 µg/mL, 22 of the 28 patients were asymptomatic, while the remaining 6 showed improvement as well. In general, carbamazepine was well tolerated, with no adverse events being reported in the study, and all patients were discharged to community outpatient providers on their remission doses of carbamazepine.<sup>119</sup> In the trial<sup>120</sup> of divalproex, 12 male subjects (mean ± SD age, 16 ± 1 years) with comorbid conduct disorder and PTSD were randomly assigned to receive high- or low-dose divalproex, and those receiving high dose

exhibited improvements in CGI score over the course of treatment. In addition, a chart review of 14 patients (aged 6–14 years) who were prescribed oxcarbazepine for mood symptoms and behavior problems associated with anger and irritability showed moderate clinical global improvement 50% of the time; however, the 1 patient in the study who carried the diagnosis of PTSD did not improve but instead was hospitalized due to worsening symptoms.<sup>121</sup>

### Other Agents

**Benzodiazepines.** There are limited data to support the use of benzodiazepines in adults with PTSD,<sup>122</sup> although these medications are often utilized to attenuate anxiety. Benzodiazepines used acutely following traumatization in adults do not produce differences in PTSD diagnosis at 3 or 6 months and do not appear to improve symptoms of dyssomnia or intrusive symptoms in adults with PTSD.<sup>123,124</sup> Given the limited role of benzodiazepines in child and adolescent psychiatry and the unique consequences that they may have in youth (eg, disinhibition), it is not surprising that we are unable to locate any reports on the use of benzodiazepines in the management of PTSD in children and adolescents. In general, there are few controlled trials of benzodiazepines in children and adolescents, and many of those that exist are limited by brief duration, dose and high placebo response rates, as well as small sample sizes.<sup>125</sup> At present, extrapolation from the available adult studies would suggest that these agents have limited value, although clinicians choosing to use these agents in children and adolescents with PTSD should be aware that benzodiazepines are more rapidly absorbed and metabolized in children as compared to adults.<sup>126</sup>

**Cyproheptadine.** Several case reports have examined the efficacy of the antihistamine and 5-HT<sub>2</sub> antagonist cyproheptadine in the treatment of adults with PTSD and, in particular, its effect on intrusive symptoms.<sup>127–130</sup> In the only pediatric report of which we are aware, Gupta and colleagues<sup>131</sup> retrospectively evaluated the efficacy of adjunctive cyproheptadine in youth with PTSD and noted effects ranging from “complete remission to a decrease in the intensity and frequency of nightmares.”<sup>131</sup>

## DISCUSSION

Despite accumulating data that suggest that PTSD in children and adolescents is associated with significant morbidity,<sup>132,133</sup> often persists,<sup>134</sup> and may worsen the course of other psychiatric comorbidities, there is scant evidence to guide psychopharmacologic treatment of PTSD in children and adolescents.

From the literature reviewed (Table 2), 2 placebo-controlled trials do not support the use of SSRIs in the treatment of children and adolescents with PTSD. However, depressive-spectrum disorders and other anxiety disorders are often comorbid in youth with PTSD, and SSRIs may have

**Table 2. Current Psychopharmacologic Treatments for Posttraumatic Stress Disorder in Children and Adolescents**

Medication	Level of Evidence <sup>a</sup>	Notes
<b>Antiadrenergics</b>		
Prazosin	IV	↓ Intrusive/hyperarousal symptoms
Clonidine	IV	↓ Reenactment symptoms
Guanfacine	IV	↓ Intrusive symptoms
Propranolol	IV, 1 Negative RCT for secondary prevention	↓ Hyperarousal symptoms
<b>Second-generation antipsychotics</b>		
Quetiapine	IV	↓ TSSC scores and anxiety, depression and anger
Risperidone	IV	↓ Intrusive/hyperarousal
<b>Antiepileptic drugs</b>		
Carbamazepine	IV	
Divalproex	IV	
<b>SSRIs</b>		
Sertraline	2 Negative RCTs	
Citalopram	IV	
<b>Other agents/classes</b>		
Cyproheptadine	IV	↓ Intrusive symptoms
Benzodiazepines	No evidence to support use	

<sup>a</sup>Levels of evidence: level I, systematic review or multiple randomized controlled trials; level II, randomized trial; level III, individual case-control studies; level IV, case-series; level V, expert opinion or based on physiology.

Symbol: ↓ = decrease.

Abbreviations: RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor, TSSC = Trauma Symptom Checklist for Children.

a treatment role in patients with both conditions. Extrapolation from adult studies and open-label trials in children preliminarily support the use of antiadrenergic agents, particularly with regard to the management of intrusive and hyperarousal symptoms. Available evidence supports the need for a trial of an adjunctive second-generation antipsychotic (eg, quetiapine or risperidone) or the mood stabilizer carbamazepine in youth with PTSD. However, importantly, the extant pediatric data inform child and adolescent psychiatrists that caution must be used when extrapolating findings from adult studies to the treatment of youth with PTSD, as some agents that have been shown to be effective in adult populations have failed to yield such results in children and adolescents. It remains to be determined if the differential efficacy of these agents in pediatric populations relates to pharmacokinetic or pharmacodynamic differences between children and adults or possibly to differences in the PTSD-related pathophysiology (see below).

Accumulating data suggest that the noradrenergic system is hyperactivated in PTSD and specifically that these neurochemical and neuroanatomic changes might be symptom linked, particularly with regard to intrusive and hyperarousal symptoms. Of note, many of the structures, such as the hippocampus and amygdala, that have been pathophysiologically implicated in PTSD in adults and

children are coated in  $\alpha$  receptors.<sup>135,136</sup> It is of pharmacologic interest that several of the antipsychotics utilized to treat pediatric (and adult) PTSD (eg, risperidone and quetiapine) are potent antagonists at  $\alpha_1$  receptors. However, at present pediatric data for the use of these agents is limited to case report-level evidence. Thus, double-blind placebo-controlled trials with centrally acting  $\alpha_1$  and  $\beta$  receptor antagonists and  $\alpha_2$  agonists in pediatric PTSD populations are needed.

In addition to the noradrenergic system, a number of other neurochemical systems also have been implicated in the pathophysiology of PTSD in adults, including substance P,<sup>137</sup> hypothalamic-pituitary-axis products (eg, corticotropin-releasing hormone, adrenocorticotropin-releasing hormone, and cortisol),<sup>138</sup> neuropeptide Y,<sup>139</sup>  $\beta$ -endorphin,<sup>140</sup> and orexin-A<sup>141</sup> among others. Although studies are necessary to evaluate the degree to which these systems are similarly dysregulated in children and adolescents with PTSD, early work in this field has implicated adrenocortical dysregulation and noradrenergic hyperactivity.<sup>48,142</sup> Also dysregulation of cytokine physiology may prove to be both pathophysiologically and therapeutically important in traumatized children.<sup>143</sup> More immediately, substance P antagonists, orexin agonists, and neuropeptide Y antagonists are in various stages of development.<sup>144</sup>

Beyond the increasing understanding of the neurochemical changes in PTSD, advances have been made in identifying neurofunctional and neuroanatomic changes that may similarly serve as therapeutic substrates and targets. For example, functional imaging studies and magnetic spectroscopy have identified metabolic differences in anterior cingulate activity in children with maltreatment-related PTSD<sup>145</sup> and have suggested differences in amygdalar activation, potentially supporting the process termed *limbic kindling*. Specifically, this putative kindling process has been suggested to occur between the amygdala and hippocampus in a manner similar to the seizure model.<sup>106,146</sup> Hypothetically, this process could result in primary symptom clusters of PTSD. As functional neuroimaging techniques and probes advance, it is likely that kindling will be better understood and the respective effects of specific antiepileptic agents will be more precisely targeted.

Given that many pediatric patients with PTSD have experienced symptomatic improvement over the course of psychotherapy, studies that address the role of complementary pharmacotherapy in ameliorating residual symptoms are necessary. It is also of interest that many of the trials of pharmacotherapies, such as of the antiadrenergic agents and some second-generation antipsychotics, suggest that these medications may be preferentially effective in reducing intrusive and hyperarousal symptoms, whereas some modalities of therapy (eg, TF-CBT) may confer particular benefit in reducing avoidant symptoms. Thus, some clinical experience suggests psychotherapy with adjunctive pharmacotherapy while other evidence suggests pharmacotherapy

with adjunctive psychotherapy. The combination of the modalities appears to be of importance as a future area of study and an option for clinicians treating patients.

With regard to secondary prevention of PTSD (eg, administration of a medication following traumatization), 1 small, negative pilot trial has examined the role of propranolol in this capacity in children and adolescents.<sup>72</sup> Beyond adrenergic targets, it is hoped that additional agents might be explored, such as substance P antagonists, glucocorticoid antagonists, or even high-dose glucocorticoids and corticotropin receptor antagonists. We are unaware of any proposals in children and adolescents.

From a public policy standpoint, the state of evidence for the psychopharmacologic treatment of PTSD in children and adolescents highlights the ubiquitous gap in child psychiatry between how medications are used and the evidence that supports their use.<sup>147</sup> A number of multilevel, but controversial solutions have been proposed to address this gap.<sup>147</sup> Specifically, the pharmaceutical industry might be encouraged to examine available agents in children and adolescents with PTSD and the National Institutes of Health might facilitate “short term trials of medications... where knowledge gaps are greatest, levels of prescribing are highest and potential for toxicities with long-term exposure is most prominent.”<sup>147(p564)</sup> Finally, it has been suggested that the FDA implement proposed regulations that mandate studies of new medications in children and adolescents.<sup>147</sup> Given the large numbers of youth exposed to traumatizing experiences through child maltreatment, domestic violence, and community violence, it is imperative to improve the scientific basis for the psychopharmacologic treatment of PTSD and trauma-related symptoms.

Importantly, clinicians must bear in mind that traumatized children often suffer from a variety of psychiatric sequelae that can be comorbid with PTSD symptoms, including depression, ADHD, affective instability, disruptive behaviors, and dysregulated attachment. Clinicians would do well to use psychopharmacologic strategies (as clinically appropriate) to address these symptoms when present in patients with PTSD. While we have focused on psychopharmacologic approaches to the management of PTSD, individual or group psychotherapy should be considered part of comprehensive treatment.

**Drug names:** alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clonidine (Duraclon, Catapres, and others), desvenlafaxine (Pristiq), diazepam (Diastat, Valium, and others), divalproex (Depakote and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), guanfacine (Intuniv, Tenex, and others), lamotrigine (Lamictal and others), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), prazosin (Minipress and others), pregabalin (Lyrica), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel), risperidone

(Risperdal and others), sertraline (Zoloft and others), tiagabine (Gabitril), topiramate (Topamax and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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