An Open-Label Study of Guanfacine Extended Release for Traumatic Stress Related Symptoms in Children and Adolescents

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Abstract

Objective: The purpose of this open-label pilot study was to investigate the effectiveness and tolerability of guanfacine extended release (GXR) 1–4 mg given in the evening, on the symptoms of traumatic stress (reexperiencing, avoidance, overarousal), generalized anxiety, and functional impairment in children and adolescents with a history of traumatic stress with or without posttraumatic stress disorder (PTSD). As many of our sample had associated attention-deficit/hyperactivity disorder (ADHD) symptoms, we also assessed whether the presence of traumatic stress symptoms impaired the effectiveness of GXR in the treatment of comorbid ADHD symptoms.

Methods: Participants were 19 children and adolescents 6–18 years of age, with current traumatic stress symptoms. In an 8 week open-label design, each patient's scores on parent-, child-, and clinician-reported symptom rating scales assessing traumatic stress symptoms, generalized anxiety, ADHD symptoms, functional impairment, and global symptom severity and improvement ($n = 17$) were evaluated off and on GXR using χ^2 goodness-of-fit tests, paired t tests, and repeated measures analyses of variance (ANOVAs). To examine patterns of change in outcome measures across treatment, MPlus software was used to conduct linear growth curves modeled with individual-varying times of observation (i.e., random slopes).

Results: Using an average GXR daily dose of $1.19 \text{ mg} \pm 0.35 \text{ mg}$ and an average weight-adjusted daily dose of $0.03 \text{ mg/kg} \pm 0.01 \text{ mg/kg}$, significant differences were found on all symptom severity measures. Parent reported UCLA Reaction Index scores assessing cluster B (reexperiencing), C (avoidant), and D (overarousal) symptoms significantly improved. In the presence of PTSD symptoms, children with ADHD experienced significantly improved ADHD symptom scores, suggesting that comorbidity does not attenuate an ADHD symptom response to GXR therapy. Medication was generally well tolerated.

Conclusions: Within the limits of an open-label, hypothesis-generating pilot study, our results suggest that the α_{2A} -adrenoceptor agonist GXR may have therapeutic effects in the treatment of PTSD symptoms in traumatically stressed children and adolescents. The effective dose may be lower than that found for ADHD. Our pilot study supports the need for further controlled research on the effects of GXR and other α_{2A} -adrenoceptor agonists in pediatric disorders of traumatic stress.

Introduction

EXPOSURE TO TRAUMATIC STRESS IS COMMON among children. Traumatic events can include physical abuse, sexual abuse, witnessing violence, natural disasters, illness, accidents, and/or injury. Approximately 60% of children are exposed to some form of abuse or violence and 10% are the victims of child maltreatment annually in the United States (Finkelhor et al. 2009). One longitudinal general population study of youth found that 25% of children had experienced at least one American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) extreme stressor by age 16 (Costello et al. 2002). In clinically referred samples, rates of exposure to violence

may be much higher and complicated by combined physical and sexual abuse, neglect, multiple perpetrators, out-of-home placements, and disrupted caregiving attachments (Ford et al. 2009).

Trauma-exposed children may develop posttraumatic stress disorder (PTSD) a psychiatric condition characterized by intrusive and impairing reexperiencing, avoidant, and hyperarousal symptoms. Rates of PTSD vary between 10% and 34% in youth exposed to physical abuse (Pelcovitz et al. 1994), single motor vehicle accident (Meiser-Stedman et al. 2008), or exposure to urban violence (Breslau et al. 1991). Children with PTSD or exposure to traumatic stress resulting in PTSD symptoms often have associated comorbid symptoms of depression, anxiety, impulsivity, aggression, behavior problems, sleep difficulties, and

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attentional deficits that further impair daily functioning (Ford et al. 2010; Strawn et al. 2010).

Evidence-based practice emphasizes trauma-focused cognitive behavior therapy (TF-CBT), for disorders of traumatic stress (Cohen et al. 2007). Despite the success of TF-CBT, up to 21% may not respond to this type of treatment (Cohen et al. 2007) and in community samples up to 40% drop out before treatment is complete (Cohen et al. 2011). Furthermore, given the paucity of trained TF-CBT psychotherapists in the community and the frequency of comorbid symptoms associated with PTSD, medications are often used in the clinical setting. In adults, the serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are United States Food and Drug Administration (FDA) approved for PTSD, and algorithmic approaches to PTSD treatment are recommended (Bajor et al. 2011). Pediatric psychopharmacological research is quite limited, and extant rates of medication effectiveness for childhood PTSD appear less than that for adults (Strawn et al. 2010). Despite evidence for the efficacy of SSRIs in adult PTSD, controlled trials in pediatric PTSD have shown little support for sertraline (Cohen et al. 2007; Robb et al. 2010; Stoddard et al. 2011) or fluoxetine (Robert et al. 2008), and only open label support for citalopram (Seedat et al. 2001). There currently exists limited evidence to support the use of second-generation antipsychotics, mood stabilizers, α_1 antagonists such as prazosin, and centrally acting β blockers such as propranolol for symptoms associated with pediatric PTSD (Strawn et al. 2010). Given the prevalence and impairment associated with PTSD and traumatic stress symptoms, further research is needed to find effective medications.

Guanfacine extended release (GXR) is a new long-acting formulation of guanfacine designed to reduce peak-to-trough plasma fluctuations, potentially improving the drug's safety and tolerability profile. GXR is a selective α_{2A} -adrenoceptor agonist shown in controlled studies to improve symptoms of attention-deficit/hyperactivity disorder (ADHD) in 6–17-year-old children and adolescents in doses of 1–4 mg/day, and in weight-adjusted doses between 0.05 mg/kg/day and 0.17 mg/kg/day (Biederman et al. 2007, 2008; Sallee et al. 2009). The actions of GXR are thought to be mediated by noradrenergic neurotransmission in the prefrontal cortex (PFC), with GXR strengthening PFC regulation of attention and behavior through direct stimulation of postsynaptic α_{2A} -adrenoceptors, thus improving attention regulation, behavioral inhibition, working memory, and impulse control in children and adolescents with ADHD (Arnsten et al. 2007).

Preclinical research in animals has reported that exposure to stress can produce a “functional dysfunction” of the PFC wherein high levels of circulating catecholamines such as norepinephrine take the PFC “offline” and allow the expression of more instinctual mechanisms regulated by subcortical areas to quickly regulate “fight/flight” behaviors during times of acute danger and stress (Arnsten 1999). Studies have consistently implicated increased noradrenergic activity in traumatized humans with disorders of posttraumatic stress, and suggest that altered reactivity of noradrenergic neurotransmission is associated with a variety of hyperarousal symptoms and anxiety in PTSD (Southwick et al. 1999; Arnsten and Rubia 2012). In traumatized, neglected, and/or abused children this may manifest itself in disorders of overarousal accompanied by maladaptive symptoms of sleep disturbance, hyperstartle reactions, constant vigilance for cues of danger/threat, irritability/aggression, hyperactivity, and exaggerated anxiety about/fear of minimal or misinterpreted cues from the environment. Furthermore, preclinical rodent and primate studies suggest that high circulating levels of norepinephrine impair working memory

in the PFC during times of stress, and impair top-down central nervous system (CNS) regulation of more reflexive behaviors (Arnsten 2011). Because guanfacine mimics the enhancing effects of norepinephrine at postsynaptic PFC α_{2A} -receptors, it may strengthen prefrontal cortical norepinephrine connectivity (Arnsten and Rubia 2012) and enhance prefrontal cortical inhibition over midbrain structures such as the amygdala, when dysregulated by exposure to traumatic stress (Jovanovi and Ressler 2010). Studies suggest that guanfacine is effective in preventing stress-induced working memory deficits and enhancing prefrontal cortical functioning in both preclinical (Wang et al. 2007) and clinical studies (Southwick et al. 1997). A similar centrally acting α agonist, clonidine, appears to be effective in attenuating hyperarousal, hypervigilance, sleep disruption, and hyperstartle responses in adults with war-related PTSD (Kinzie et al. 1989). Case reports suggest that clonidine and guanfacine may decrease core symptoms of traumatic stress, including reenactment symptoms and nightmares in traumatized children (Harmon and Riggs 1996; Horrigan and Barnhill 1996).

In a pilot study using an open-label design, we investigated the effectiveness of GXR 1–4 mg/day on symptoms of traumatic stress (reexperiencing, avoidance, overarousal), generalized anxiety, and functional impairment in 6–18-year-old children and adolescents with a history of traumatic stress with or without PTSD. As many of our sample had associated ADHD symptoms, we also investigated whether the presence of traumatic stress symptoms impaired the effectiveness of GXR in the treatment of comorbid ADHD symptoms.

Methods

This was a single-site, 8 week, open-label outpatient pilot study investigating the tolerability and effectiveness of GXR 1–4 mg on symptoms of traumatic stress in 6–18-year-old children and adolescents with current trauma symptoms. Patients were recruited by advertisement or word of mouth, and from newly evaluated patients to child and adolescent ambulatory psychiatry clinics in the local area. Enrolled patients were paid a stipend of \$20 per visit to compensate them for study time and effort. Children and parent/guardians interested in study participation were first screened by a telephone interview for eligibility. Children and parents providing informed assent/consent were screened at the next visit including physical examination, medical review of systems, psychiatric evaluation, medication and treatment history, and child or parent report rating scales including the UCLA PTSD Reaction Index, the generalized anxiety disorder (GAD) scale of the Screen for Childhood Anxiety and Related Disorders (SCARED), the Columbia Impairment Scale (CIS), the ADHD Rating Scale IV (ADHD-RS-IV), and the clinician-completed Clinical Global Impressions (CGI)-Severity Scale.

Inclusion criteria included 1) age 6–18 years, with a history of traumatic stress as documented by parent-report on the UCLA Reaction Index; 2) clinical impairment from traumatic stress overarousal symptoms as measured by a baseline UCLA Reaction D Index overarousal score (questions 1, 4, 12, 13, and 16) ≥ 13 (e.g., symptoms of hypervigilance, startle reaction, concentration, sleep disturbance, aggression/irritability, and/or anxiety/fear) as completed by parent or guardian or child; 3) a baseline CGI-Severity (CGI-S) score ≥ 4 ; and 4) freedom from any concomitant psychiatric medication at baseline and for the duration of the study. Consenting subjects eligible for study participation and receiving psychotropic medication had their psychiatric medications tapered

prior to study enrollment. Only one subject (5%) discontinued a stimulant medication to enter the study. At baseline screening, all consenting subjects were psychiatric medication free. Ongoing psychotherapy was allowed, as long as therapy did not start or stop during the 8 study weeks.

Exclusion criteria included 1) any history of cardiovascular disease, previous history of electrocardiogram (ECG) abnormalities, syncope, or any other currently unstable medical illness/allergy; 2) any use of psychiatric medication during the study; 3) a diagnosis of pervasive developmental disorder, mental retardation, active substance abuse disorder (within the past 30 days), bipolar disorder, schizophrenia or other psychotic disorder, or major depressive disorder with symptoms severe enough (e.g., suicidality) to exclude study participation as assessed by the Principal Investigator; 4) females of childbearing age who are sexually active and not receiving a medically acceptable form of birth control; and 5) pregnant females (as determined by a positive urine pregnancy test prior to starting medication or at any on-medication study visit). In the opinion of parents or the child's treating clinician, subjects receiving effective psychiatric medication treatment prior to study screen were not eligible to enroll in the study, as it was believed to be unethical to stop effective medication in order to become study eligible.

The institutional review board for research in human subjects at the University of Connecticut Medical School approved this study. All parents consented and children assented to participation in this study.

Assessment

All children and parents were clinically interviewed by board-certified child and adolescent psychiatrists. Psychiatric diagnoses were assigned based on American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) criteria after interview of parent and child (American Psychiatric Association 2000). As ours was a symptom-based study and not a diagnosis-based study, a gold standard diagnostic interview such as the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) was not used.

UCLA PTSD Reaction Index (UCLA-RI) for DSM-IV. The UCLA-RI for DSM-IV (Steinberg et al. 2004) is a trauma history questionnaire and a 21 item parent-reported instrument for the assessment of posttraumatic stress symptoms among children and adolescents, including DSM-IV PTSD criterion B (intrusive symptoms), PTSD criterion C (symptoms of avoidance), and PTSD criterion D (symptoms of overarousal). Questions evaluating sleep problems, irritability/anger, and anxiety/fear are included. The UCLA-RI has good psychometric properties, is treatment sensitive, and has been used in previous research in children and adolescents. The complete UCLA-RI including traumatic stress history was completed at baseline by a parent or guardian to establish a traumatic events history for the child. The UCLA-RI PTSD symptom severity scale (21 items) was completed at each study week by the parent/guardian to assess the response of PTSD symptoms to GXR treatment. A score >37 may indicate the presence of PTSD (Steinberg et al. 2004).

SCARED generalized anxiety symptom subscale. The SCARED (Birmaher et al. 1997) is a 41 item screen for childhood anxiety-related disorders that contains a 9 item generalized anxiety

subscale. The GAD subscale parent and child report was used in this study to assess symptoms of generalized anxiety and worry associated with traumatic stress and symptom overarousal. In order to reduce the burden on caregivers and children of answering numerous questions each week, the total 41-item SCARED was not administered. The SCARED GAD subscale was completed each week separately by the parent and the child. A score ≥ 9 may indicate the presence of a GAD (Birmaher et al. 1997).

CIS. The CIS (Bird et al. 1993) is a 13 item scale that was completed by the parent or guardian at each visit. The items tap four major areas of functioning: Interpersonal relations, psychopathology, functioning in job/school work, and use of leisure time. Items are scored on a spectrum ranging from 0 to 4. Validated on a sample of 182 children and adolescents, 9–17 years of age, the CIS is a measure of global impairment. Total score is reported. Scores ≥ 15 may indicate the presence of clinically significant functional impairment (Bird et al. 1993).

ADHD-RS-IV. ADHD-RS-IV (DuPaul et al. 1998) is a standard 18 item ADHD rating scale assessing symptom severity in ADHD clinical trials. The ADHD-RS-IV was reported by the parent or guardian during weeks 1, 5, and 8/final study visit. A total score was used. A symptom score ≥ 18 may indicate the presence of clinically significant ADHD symptoms (Ramos-Quiroga and Casas 2011).

CGI Severity and Improvement Scales. The CGI (Guy 1976) is a clinician-completed scale extensively used in pediatric clinical trials research. The CGI-S scale assesses the overall severity of a patient's psychiatric condition on a seven point scale with scores ranging from 1 ("not ill") to 7 ("extremely severe"). The CGI-S is completed at each weekly study visit by board-certified child and adolescent psychiatrists. The CGI-Improvement scale assesses patient overall improvement of symptoms compared with symptoms at study baseline. It is rated on a seven point scale with scores ranging between 1 ("very much improved"), 2 ("improved"), 4 ("no change from baseline"), and 7 ("very much worse"). The CGI-Improvement scale was assessed at each on-drug visit after consideration of all available clinical information for that week relative to baseline by board-certified child and adolescent psychiatrists.

Responder. Responder status was defined *a priori* as a $\geq 30\%$ reduction relative to baseline in the UCLA RI total score and a CGI-Improvement score of 1 or 2.

Safety assessments. At baseline and at each visit, parent- and child-reported treatment-emergent adverse events (AEs) were assessed by direct questioning. Parents also completed the Guanfacine Side Effects Profile rating scale that assesses 18 common side effects from α -adrenergic medications on a 0 (absent) to 9 (very frequent/serious) Likert-type scale (Connor and Meltzer 2006). Side effects assessed include sedation, headache, dizziness, faintness, stomachache, nausea, vomiting, depression, dry mouth, dry eyes, constipation, diarrhea, nightmares, sleep difficulties, tingling in fingers and toes upon cold exposure, anxiety, and exercise-related fainting. Total number of side effects endorsed and a mean AE severity score were ascertained at each visit. Because of risk of inflating type I error in a study with a small sample size, pairwise comparisons between each individual side effect on- and off-drug were not done. Weight and vital signs were assessed at each visit.

Compliance. GXR was dispensed in weekly allotments (seven pills) to the parent/guardian. At each visit clinicians performed a pill count to assess compliance. Weekly compliance of at least 80% was necessary to remain in the study. No patient was discontinued from the study because of medication noncompliance.

Concomitant medications. No concomitant psychiatric medications were allowed during the study. No p.r.n. psychiatric medications were allowed during the study.

Ongoing psychotherapy. Seven patients continued in active psychotherapy while participating in the study. No patient started/stopped therapy during study participation.

Medication procedures. Medication was initiated at the completion of the baseline measures on week 1. GXR was started at 1 mg/day at week 1 and tapered up by 1 mg per week to a maximum dose of 4 mg/day by week 5 (4 weeks on drug). Maximum GXR dose was achieved by and maintained on weeks 5 and 6. For those not wishing to continue GXR treatment at study end, dose discontinuation occurred by tapering GXR down 1 mg every 3–5 days over weeks 7 and 8. GXR dosing for the study occurred in the evening.

Analysis

Chi-square goodness-of-fit tests, paired *t* tests, and repeated measures analyses of variance (ANOVAs) were conducted using IBM SPSS Version 19. To examine patterns of change in outcome measures across treatment, MPlus software (Muthen and Muthen 2007) was used to conduct linear growth curves modeled with individual varying times of observation (i.e., random slopes). For this hypothesis-generating study, $p \leq 0.05$, and no correction for multiple comparisons was made.

Results

The baseline sample included 19 eligible and consenting participants (47.4% female) between the ages of 6.9 and 18.4 years (mean = 11.9 ± 1.5 years). Self-identified ethnicity included 36.8% Caucasian, 15.8% African American, 26.3% Hispanic, and 21.1% multiethnic. Traumatic stress incidents identified by parents on the UCLA PTSD-RI as “bothers your child the most now” included being hit or beaten (26%), hearing of or seeing someone gravely hurt (27%), death of a relative (5%), or “other” (bullying, motor vehicle accident, illness) (42%). Time of trauma reportedly occurred ≤ 12 months from the referral date in 42%, and 42% reported the time of trauma as occurring > 12 months before the referral date (the remaining 16% either did not give or were unable to identify time of onset).

Psychiatric diagnoses included ADHD (89.5%), PTSD (68.4%), GAD (47.4%), depression (21.1%), separation anxiety disorder (10.6%), and reactive attachment disorder (5.3%). Number of diagnoses ranged from 1 to 4 (mean = 2.6 ± 0.9). Of the sample, 52.6% reported a history of psychiatric treatment, with 36.8% reporting a history of psychotherapy, 10.5% antidepressants, 26.3% stimulant medication, and 10.5% α antagonist medication. More than one treatment modality was reported by 47.4% of the sample.

According to clinician-rated baseline CGI-S scores (mean = 4.53 ± 0.61) the majority of the sample was rated as moderately ill (CGI-S = 4, 52.6%), followed by markedly ill (CGI-S = 5, 42.1%), and severely ill (CGI-S = 6, 5.3%).

UCLA PTSD-RI

The majority of the sample (94.7%) endorsed exposure to one or more potentially traumatic events. Total potential traumas ranged from 1 to 7, with 57.9% endorsing three or more exposures. Total symptom severity scores on the UCLA PTSD-RI ranged from 13 to 72 (mean = 42.2 ± 19.1) with 63.2% exceeding the clinical threshold score of 37.

SCARED GAD child report

Total scores on the SCARED GAD child report ranged from 1 to 17 (mean = 9 ± 5.07), with 57.9% scoring at or above the clinical threshold score of 9.

SCARED GAD parent report

Total scores on the SCARED GAD parent report ranged from 4 to 18 (mean = 11.16 ± 4.1), with 73.7% scoring at or above the clinical threshold score of 9.

CIS

Total scores ranged from 6 to 45 (mean = 27.9 ± 11.02) with 78.9% scoring at or above the clinical threshold score of 15.

ADHD-RS.

Scores on the Inattention subscale of the ADHD Rating Scale ranged from 6 to 27 (mean = 18.1 ± 6.31) and scores on the Hyperactivity subscale ranged from 6 to 23 (mean = 13.6 ± 4.4). Of the sample, 68.4% fell at or above the 95th percentile on the Inattention subscale and 42.1% fell at or above the 95th percentile on the Hyperactivity subscale. All children with ADHD also experienced traumatic stress symptoms as part of the inclusion criteria for study entry.

Treatment adherence

Out of 19 eligible participants, 2 withdrew from the study prior to receiving study medication. One withdrew consent and the other violated study protocol. Therefore, the analyzable sample included 17 patients. Of the 17 participants, the range of sessions completed was 3–8 (mean = 7.1 ± 1.76). Thirteen participants (76.5%) completed all 8 sessions. Among the four patients who did not complete treatment one dropped out because of side effects including sedation and fatigue, one because of transportation issues, one to pursue treatment of comorbid and worsening depression, and one for lack of GXR effectiveness.

GXR dose

Among treatment completers, the average daily GXR dose across 8 weeks was $1.19 \text{ mg} \pm 0.35 \text{ mg}$ and the average weight-adjusted daily dose was $0.03 \text{ mg/kg} \pm 0.01 \text{ mg/kg}$. Mean dosages (mg) across the 8 weeks were 0, 0, 1.0 ± 0 , 1.47 ± 0.51 , 1.76 ± 0.66 , 1.88 ± 0.86 , 1.71 ± 0.85 , and 1.71 ± 0.77 . Weight-adjusted mean dosages (mg/kg) across the eight weeks were 0, 0, 0.02 ± 0.01 , 0.03 ± 0.02 , 0.04 ± 0.02 , 0.04 ± 0.02 , 0.03 ± 0.01 , and 0.03 ± 0.01 .

Treatment outcome and response

Clinician-rated improvement on the CGI-Improvement scale showed a significant linear trend across treatment, $F = 21.2$, $p < 0.001$. Of treatment completers ($n = 13$), 70.6% were rated as either very much improved or much improved at posttreatment,

TABLE 1. GROWTH CURVES AND PAIRED *t* TESTS (*N* = 17)

	<i>Intercept (SE)</i>	<i>Slope (SE)</i>	<i>Baseline mean (SD)</i>	<i>Post mean (SD)</i>	<i>t</i>
UCLA PTSD-RI					
Reexperiencing	8.38 (1.81)	−0.11 (0.03)*	11.41 (6.88)	3.35 (3.77)	5.67**
Avoidance	12.39 (1.57)	−0.15 (0.04)**	13.82 (7.91)	5.41 (4.54)	4.23**
Hyperarousal	13.26 (0.08)	−0.13 (0.03)**	14.06 (3.23)	7.18 (4.46)	5.53**
Total Score	39.26 (5.31)	−0.45 (0.13)**	43.59 (4.64)	16.71 (2.67)	5.58**
SCARED GAD					
Child-report	7.89 (1.32)	−0.06 (0.03)**	9.24 (5.27)	5.12 (5.85)	3.13*
Parent-report	11.45 (0.89)	−0.14 (0.03)*	11.76 (3.88)	6.18 (4.68)	4.36**
CIS	16.93 (1.93)	−0.31 (0.05)**	29.0 (10.16)	13.87 (8.12)	5.66**
ADHD Rating Scale					
Inattention	16.93 (1.93)	−0.17 (0.04)**	18.65 (6.26)	9.24 (4.84)	6.94**
Hyperactivity	12.56 (1.57)	−0.17 (0.04)**	13.76 (4.28)	5.0 (5.06)	7.59**
CGI Severity	4.59 (0.12)	−0.03 (0.01)**	4.53 (0.62)	3.06 (0.97)	6.02**

n = 17 for all except CIS (*n* = 15).

**p* < 0.01.

***p* < 0.001.

UCLA PTSD-RI, UCLA Posttraumatic Stress Disorder Reaction Index; SCARED GAD, Screen for Childhood Anxiety and Related Disorders, Generalized Anxiety Disorder Scale; CIS, Columbia Impairment Scale; ADHD, attention-deficit/hyperactivity disorder; CGI, Clinical Global Impressions.

followed by minimally improved (15.8%), having no change (5.3%), and presenting as minimally worse (5.3%). In addition, 82.4% of treatment completers showed a $\geq 30\%$ reduction in baseline traumatic stress as measured by the UCLA PTSD-RI. Further, of treatment completers, 70.6% showed both a CGI-Improvement of 1 or 2 and a $\geq 30\%$ reduction of UCLA PTSD-RI scores from baseline to posttreatment (responder status).

Table 1 presents the intercepts, slopes, and statistical significance of linear growth curves modeled with individual-varying times of observation (i.e., random slopes). Results from nine pairwise *t* tests comparing baseline and posttreatment scores are also presented. For each measure, participants' mean posttreatment score was significantly improved relative to baseline. Significant improvements were noted in the UCLA Index total score, cluster B (reexperiencing), cluster C (avoidance), cluster D (overarousal), as well as parent and child reported generalized anxiety symptoms on the SCARED GAD subscale. On the ADHD-RS-IV scale, significant improvement on GXR was noted for the ADHD domains of inattention and hyperactivity. Significant parent-reported improvement in daily impairment was also found (see Table 1).

Upon study end, 11 of 13 (85%) of study completers and 12 of 17 overall study participants (71%) elected to continue GXR in outpatient treatment.

AEs

Table 2 presents the number of participants reporting side effect by type off- versus on-GXR. Mean number of reported side effects off medication ranged from 2 to 13.5 (mean = 6.7 ± 3.1) and mean number of side effects on medication ranged from 0.67 to 13.3 (mean = 5.9 ± 3.5) (*p* > 0.10). As noted previously, to limit type I error inflation, pairwise comparisons across each side effect were not done. Many side effects reported as present off-drug at baseline were reported as improved on-drug. No patient reported on-drug syncope. Dry mouth was a commonly reported on-drug side effect. One patient dropped out of the study citing worsening depression on GXR. Given the fact that guanfacine may cause or worsen depression (Connor and Meltzer, 2006), this may be a drug side effect.

Paired *t* tests were conducted to test for significant differences in weight, blood pressure, and pulse between these values at baseline and at week 6 (peak dose). Results indicated a significant increase in weight (kg) from baseline (mean = 48.7 ± 14.5) to week 6 (mean = 49.6 ± 14.6), *t*(16) = −3.9, *p* = 0.001, and a significant decrease in diastolic blood pressure from baseline (mean = 66.8 ± 6.3) to week 6 (mean = 61.8 ± 6.3), *t*(16) = 3.15, *p* = 0.006. There were

TABLE 2. MEAN NUMBER OF PARTICIPANTS REPORTING SIDE EFFECTS BY TYPE ON AND OFF GUANFACINE EXTENDED RELEASE (GXR)^a

	<i>Off guanfacine</i>	<i>On guanfacine</i>
Sedation	10.00 ± 1.41	12.17 ± 2.14
Headache	11.00 ± 1.41	12.67 ± 1.75
Dizziness	6.50 ± 2.12	7.83 ± 1.60
Feeling faint	1.50 ± 2.12	2.00 ± 0.00
Stomachache	11.00 ± 1.41	10.33 ± 1.21
Nausea	8.50 ± 0.71	6.67 ± 1.21
Vomiting	3.00 ± 2.83	3.33 ± 1.03
Depression	15.50 ± 0.71	13.67 ± 1.86
Dry mouth	4.50 ± 0.71	9.00 ± 2.00
Dry eye	4.50 ± 2.12	3.67 ± 0.82
Constipation	5.50 ± 0.71	6.18 ± 1.17
Diarrhea	3.00 ± 1.41	5.00 ± 0.89
Nightmares	13.50 ± 0.71	9.33 ± 1.97
Sleep difficulties	15.50 ± 2.12	10.83 ± 1.17
Tingling	4.00 ± 0.00	4.00 ± 0.89
Anxiety	14.50 ± 0.71	10.33 ± 0.82
Feeling faint during exercise	3.50 ± 2.12	5.50 ± 1.05
Other ^b	3.00 ± 2.83	3.83 ± 0.75

^aSee text for statistical analysis.

^bOther includes two patients reporting congestion and fever, which resolved within 1 week, one patient reporting hyperarousal symptoms both on- and off-drug which decreased as the trial progressed, one patient reporting joint pain that resolved within 1 week, and one patient reporting chest pain off-drug before introduction of GXR and then again on-drug that resolved upon dose reduction from GXR 2 mg h.s. to GXR 1 mg h.s.

no significant differences in systolic blood pressure or pulse between baseline and week 6 ($p > 0.10$).

Discussion

Using an open-label design, we investigated the effectiveness of GXR 1–4 mg given in the evening (0.02–0.04 mg/kg/day) on symptoms of traumatic stress, anxiety, and ADHD, and on clinical impairment ratings in a sample of 6–18-year-old children and adolescents with current trauma symptoms. Within the limitations of an open-label pilot study, our results suggest that GXR may be effective in decreasing PTSD symptoms including cluster B (re-experiencing), cluster C (avoidant), and cluster D (overarousal) symptoms. Indeed, 71% of completers were classified as responders to GXR based on *a priori* defined criteria. Previous studies of GXR for ADHD report optimum weight-based dosing between 0.05 and 0.12 mg/kg/day (Biederman et al. 2008). We found effectiveness for PTSD symptoms between 0.02 and 0.04 mg/kg/day. Although further confirmatory research is needed from controlled trials, this suggests the possibility that a lower GXR dose range may be helpful in disorders of pediatric traumatic stress as compared with ADHD.

Parent- and child-reported symptoms of generalized anxiety also improved comparing baseline with on-drug SCARED GAD scores. Previous studies report that guanfacine may be effective for anxiety related to cocaine withdrawal (Buffalari et al. 2012) and possibly contribute to tic reduction when associated with anxiety (Qasaymeh and Mink 2006). However, we are unaware of any previous reports suggesting that GXR may be effective for symptoms of generalized anxiety in the pediatric population. This is important, as symptoms of generalized anxiety often accompany anxiety associated with traumatic stress (Strawn and Geraciotti 2008).

Using all available information at each visit, clinicians rated overall symptom severity as improved on drug compared with baseline, as assessed by the CGI-S score (Guy 1976). Not surprisingly, given the improvement in rating scale scores, parents rated their child's overall functional impairment as significantly improved over the course of the study.

Although further and more methodologically controlled research is necessary, our data are consistent with research supporting the actions of GXR on PFC enhancing top-down inhibitory control of more reflexive fear-driven behaviors (Wang et al. 2007; Strawn and Geraciotti 2008; Jovanovic and Ressler 2010; Arnsten 2011; Arnsten and Rubia 2012). Possible outcomes may include diminished fear conditioning leading to reduced nightmares, flashbacks, avoidance, and/or sympathetic nervous system driven symptoms of overarousal (Jovanovic and Ressler 2010), or diminished impulsivity leading to a reduction of aggressive behaviors (Coccaro et al. 2011). A further possibility of GXR's mechanism of action on the PFC may include enhanced cognitive and attentional control over dysregulated emotions (Arnsten et al. 2012).

Our sample had a high prevalence of comorbid ADHD, and significant inattentive and hyperactive/impulsive symptoms. GXR is FDA approved for the treatment of ADHD in 6–17-year-olds. One question of clinical importance is whether the presence of significant PTSD symptoms will attenuate an ADHD response to GXR therapy. Within the limitations of our open-label methodology, we did not find support for this. ADHD symptoms significantly improved in addition to improvement in PTSD symptoms. Although further controlled research is needed, this suggests that the presence of traumatic stress symptoms does not diminish the response of ADHD symptoms to GXR therapy in comorbid youths.

In general, GXR was well tolerated. Patients did report AEs including sedation, headache, dry mouth, and feelings of dizziness/faintness on drug. However, severity was generally mild, and only one patient discontinued the drug because of side effects (worsening depressive symptoms). For example, as the GXR daily dose increased, there was no significant change in the mean number of side effects reported across 8 weeks, nor was there a significant change in mean side effect severity across treatment. As anticipated, diastolic blood pressure declined on drug relative to baseline, supporting the necessity of vital sign monitoring while on GXR. Weight gain appeared consistent with normal growth and development across the 8 study weeks.

Limitations

Our study has limitations. Designed as an open-label hypothesis-generating pilot study with a small number of subjects, our results cannot be taken as conclusive. More definitive results await the completion of controlled methodological research. Given the high prevalence of ADHD symptoms in our patients, it is possible that reported clinical improvement could be caused by the efficacy of GXR for the treatment of comorbid ADHD, and not caused by improvement in PTSD symptoms (i.e., a halo effect). Similarity between the ADHD symptoms of hyperactivity/impulsivity and the symptoms of PTSD cluster D (overarousal) may have been conflated by parent reporters. However, our results show significant improvement in PTSD clusters B (re-experiencing) and C (avoidance), which are unlikely to be confused with ADHD symptoms. This suggests that GXR may have an effect on PTSD symptoms independently of its efficacy for ADHD symptoms. Another limitation is that the clinician-rated CGI severity and improvement measures were not specific for PTSD symptoms, but were an overall assessment that also included ADHD symptoms. As such, improvement in ADHD symptoms may account for some of the improvement in overall CGI scores. However, significant improvement in symptoms of PTSD and anxiety, not assessed by the ADHD-RS-IV, suggest that improvement in CGI scores also occurred because of improvement in PTSD and anxiety symptoms. A strength of our study is the use of GXR monotherapy and exclusion of all other psychiatric medications, the use of which might have further confounded results.

Clinical Significance

In summary, our pilot results suggest that the α_{2A} -adrenoceptor agonist GXR may have therapeutic effects in the treatment of PTSD symptoms in traumatically stressed children and adolescents. Although trauma-focused cognitive behavioral therapies have methodologically controlled evidence for efficacy and should be the first line of treatment for this condition, medications that alter noradrenergic functioning may be clinically useful as adjunctive agents to ongoing psychotherapy.

Conclusions

Medications that facilitate central noradrenergic neurotransmission may be important in the treatment of early-onset PTSD. Our pilot study supports the need for further controlled research on the effects of GXR and other α_{2A} -adrenoceptor agonists in pediatric disorders of traumatic stress.

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