A Randomized, Placebo-Controlled Trial of Guanfacine Extended Release in Adolescents With Attention-Deficit/Hyperactivity Disorder

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Objective: Despite the continuity of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known regarding use of nonstimulants to treat ADHD in adolescents. This phase 3 trial evaluated the safety and efficacy of guanfacine extended release (GXR) in adolescents with ADHD.

Method: This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included scores from the Clinical Global Impressions–Severity of Illness (CGI-S), and Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) at week 13.

Results: A total of 314 participants were randomized (GXR, n = 157; placebo, n = 157). The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with 46.5% of participants receiving an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo (least-squares mean score change, –24.55 [GXR] versus –18.53 [placebo]; effect size, 0.52; $p < .001$). More participants on GXR also showed significant improvement in CGI-S scores compared with placebo (50.6% versus 36.1%; $p = .010$). There was no statistically significant difference between treatments at week 13 in the 2 WFIRS-P domains. Most treatment-emergent adverse events were mild to moderate, with sedation-related events reported most commonly.

Conclusion: GXR was associated with statistically significant improvements in ADHD symptoms in adolescents. GXR was well tolerated, with no new safety signals reported.

Clinical Trial Registration Information—Dose-Optimization in Adolescents Aged 13-17 Diagnosed With Attention-Deficit/Hyperactivity Disorder (ADHD) Using Extended-Release Guanfacine HCl; http://ClinicalTrials.gov/; NCT01081132.

Key Words: attention-deficit/hyperactivity disorder, nonstimulants, guanfacine, GXR

J Am Acad Child Adolesc Psychiatry 2015;54(11):916–925.

Attention-deficit/hyperactivity disorder (ADHD) is among the most common neurobehavioral disorders presenting for treatment in children and adolescents.[1,2] A US Centers for Disease Control and Prevention and Health Resources and Services Administration report estimated the 2011 prevalence of US youth, aged 4 to 17 years with an ADHD diagnosis, to be 11%.[3] ADHD is often persistent, with more than 80% of children maintaining the disorder into adolescence.[4] Children and adolescents with ADHD share many characteristics of the disorder,[5] although inattention tends to be more common than overt hyperactivity in adolescents.[6,7]

Compared to unaffected peers, adolescents with ADHD manifest more dysfunction in psychiatric, social, academic, legal, and family functioning.[4,5,8] For example, adolescents with ADHD often experience difficulties interacting with peers, which may result in becoming associated with other disenfranchised adolescents.[9] Given the increasing demands, autonomy, and multitasking required of adolescents, academic failure is often accentuated.[8] Adolescents with ADHD have an increased risk of substance abuse, especially if they have psychiatric comorbidities (e.g., conduct or bipolar disorders).[10,11] In addition, adolescents with ADHD are more likely to be involved in driving-related offenses and accidents[12,13] as well as irresponsible sexual encounters leading to pregnancies and sexually transmitted diseases.[14] Children and adolescents with ADHD are also more likely to be exposed to a dysfunctional family environment, as evidenced by higher levels of family stress and marital discord.[15,16] Hence, ADHD in adolescence is a disorder of high clinical and public health significance.

Although stimulants have long been recognized among first-line therapies for ADHD,[17,18] approximately 30% of adolescents may not adequately respond to or tolerate stimulant

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medications. Stimulant use has been associated with reduced appetite, nausea, insomnia, and potential cardiovascular adverse events (AEs),[19-21] and may exacerbate comorbid conditions such as tics and anxiety, suggesting a need for nonstimulant medications.[18] Currently, US Food and Drug Administration (FDA)–approved nonstimulants for children and adolescents with ADHD include atomoxetine, guanfacine extended release (GXR), and clonidine extended release.[22-24]

The use of guanfacine in adolescents has not been extensively studied. GXR monotherapy (1–4 mg) for the treatment of ADHD was evaluated in 2 short-term, placebo-controlled, pivotal, fixed-dose efficacy studies.[25,26] Although both studies enrolled children (6–12 years) and adolescents (13–17 years), adolescents represented only ~25% of the participant pool. Subgroup analyses comparing treatment response stratified by age revealed numerical improvement, but no significant treatment effect, in adolescents. Compared with children, the adolescents in both studies totaled fewer participants and demonstrated higher placebo response rates. Furthermore, due to fixed-dose study designs and higher body weights, analyses of doses on a milligram-per-kilogram basis revealed that the majority of adolescent participants received doses <0.05 mg/kg, the lowest dose to show consistent, clinically relevant improvement on the ADHD Rating Scale–IV (ADHD-RS-IV) total score in these studies.[25,26]

After evaluation of both GXR safety/pharmacokinetic data in adolescents (doses up to 9 mg per day[27]) and prescribing data from immediate-release guanfacine,[28] the dose range of GXR 1 to 7 mg was chosen for this study, allowing adolescent participants with ADHD to receive mg/kg doses within the efficacious range of 0.05 mg/kg per day to 0.12 mg/kg per day previously identified in the short-term pivotal studies. The primary objective of this study was to assess the efficacy of dose-optimized GXR versus placebo in the treatment of adolescents with ADHD, as measured by the ADHD-RS-IV. Key secondary objectives were to evaluate the effects of GXR on the Clinicians' Global Impressions–Severity of Illness (CGI-S) scale scores, and on changes in function associated with ADHD as measured by the Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P). Safety and tolerability of GXR in adolescents were also evaluated, adding to safety findings from the small adolescent cohorts in prior GXR studies.[25,26]

METHOD

Participants

Inclusion criteria included adolescent outpatients aged 13 to 17 years with a diagnosis of ADHD (any subtype). Consistent with *DSM-IV-TR* criteria, a primary ADHD diagnosis was confirmed by clinical evaluation using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL)[29] at screening (visit 1). Participants were also required to have a minimum ADHD-RS-IV total score of 32 and a minimum CGI-S score of 4 at baseline (visit 2). Supine and standing blood pressure measurements within the 95th percentile for age, sex, and height were also required.

Participants were excluded if they had any current controlled or uncontrolled comorbid psychiatric diagnosis (except oppositional defiant disorder), including severe comorbid Axis II disorders or severe Axis I disorders, such as anxiety disorder, posttraumatic stress disorder, depression, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder within 6 months, or other symptomatic manifestations or lifetime history of bipolar or unipolar illness (e.g., active suicidality), psychosis, or conduct disorder that, in the opinion of the investigator, contraindicated treatment with GXR or could confound efficacy or safety assessments. Other exclusion criteria included history/presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems, exercise-related cardiac events, orthostatic hypotension, history of controlled or uncontrolled hypertension, or clinically significant bradycardia. Participants who used any medications that affect blood pressure or heart rate, have central nervous system effects, or affect cognitive performance (such as sedating antihistamines) were also excluded. Psychosocial treatment was permitted during the study if it had been ongoing for >1 month at the time of the baseline visit, and any changes/modifications to psychosocial treatment during the study had to be cleared by medical staff.

Participants and their parent/legally authorized representative (LAR)/caregiver had to understand and be willing to fully comply with study procedures. Each parent/LAR/caregiver was required to give signed informed consent, and each participant was required to give written assent; forms were approved by the institutional review boards of participating centers. This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice under the principles of the Declaration of Helsinki.

Study Design

This phase 3, multicenter, double-blind, placebo-controlled, randomized study was designed to assess safety, efficacy, and tolerability of once-daily dosing of GXR in adolescents with a diagnosis of ADHD who were given doses ≤7 mg using a flexible dose-optimization design (ClinicalTrials.gov Identifier: NCT01081132). Participants were enrolled at 48 sites across the United States. This study consisted of 5 periods: screening, 7-week dose optimization (visits 3–9), 6-week dose maintenance (visits 10–13), 2-week dose taper (visits 14 and 15), and follow up (visit 16).

Eligible participants were randomized to GXR or placebo (1:1 ratio) on a studywide basis by automatic interactive response technology. At least 25% of randomized participants were to be female, and treatment assignments were balanced within weight groups (34.0–41.4, 41.5–49.4, 49.5–58.4, and 58.5–91.0 kg). After randomization, all participants underwent dose optimization (visits 3–9), with 1 dose reduction permitted if necessary. Starting the morning after baseline, all participants received 1 mg per day of GXR or placebo, and the dose was titrated up to the maximal permitted dose for a participant's respective weight group in the absence of any significant safety or tolerability issues. The dose was allowed to increase in 1-mg increments (after a minimum of 1 week on the current dose) on a weekly basis to a maximal dose based on the participant's baseline weight and tolerability (4 mg per day for those 34.0–41.4 kg to 7 mg per day for those 58.5–91.0 kg). Participants were considered at optimal dose if they achieved ≥30% reduction in ADHD-RS-IV total score from baseline and a CGI–Global Improvement (CGI-I) score of 1 or 2 at a given tolerated dose (defined as a "responder"; response to treatment was also analyzed throughout the dose maintenance phase). Investigators were encouraged to increase the dose if these criteria were not met, and the dose was tolerated. Furthermore, if a participant achieved a ≥30% reduction in ADHD-RS-IV total score, tolerated the optimal dose, and (in the opinion of the investigator) could potentially achieve additional symptom reduction, the dose could be increased.