Morning and Evening Effects of Guanfacine Extended Release Adjunctive to Psychostimulants in Pediatric ADHD: Results From a Phase III Multicenter Trial

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Abstract
Objective: To examine efficacy and safety of adjunctive guanfacine extended release (GXR) on morning and evening ADHD symptoms using the Conners’ Global Index-Parent (CGI-P) and Before-School Functioning Questionnaire (BSFQ).
Method: Participants 6 to 17 years with ADHD (N = 461) and suboptimal psychostimulant response were maintained on current psychostimulants and randomized to dose-optimized GXR (≤4 mg/d) in the morning (GXR AM) or evening (GXR PM), or placebo. Results: CGI-P scores improved with GXR (morning assessment, GXR AM, placebo-adjusted least squares [LS] mean = -1.7, GXR PM = -2.6; evening assessment, GXR AM = -2.4, GXR PM = -3.0; all p < .01). Parent-rated BSFQ scores reflected improved morning functioning with GXR (GXR AM, placebo-adjusted LS mean = -5.1; GXR PM = -4.7; both p < .01). Most adverse events were mild or moderate. Conclusion: Adjunctive GXR AM or GXR PM was associated with improvements in morning and evening ADHD symptoms in children and adolescents. (J. of Att. Dis. 2017; 21(2) 110-119)

Keywords
Intuniv, guanfacine XR, functioning, before school, after school

Introduction
ADHD occurs in 6% to 9% of youths worldwide (Biederman & Faraone, 2005; Kessler et al., 2005; Pliszka, 2007; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and is a significant clinical and public health problem (Pliszka, 2007; Wilens et al., 2002; Wilens et al., 2010a). While school behavior and academic performance remain the major focus of treatment, before- and after-school behaviors are also affected by ADHD (Coghill et al., 2008; Whalen et al., 2006). For example, getting ready for school in the morning or engaging in social activities, completing homework, or participating in athletics, both after school and into the evening, may be affected adversely by ADHD (Biederman et al., 2006). Hence, effective treatment of ADHD needs to be evaluated with regard to patient functioning on a variety of before-, during-, and after-school behaviors.

Despite extensive literature on medications in school-age youths with ADHD, there is little information available on the effect of medications on before- and after-school activities (Buitelaar & Medori, 2010; Coghill et al., 2008). Whalen et al. (2006), using electronic diaries, showed important differences in a number of before- and after-school ADHD symptoms, behaviors, and negative mood states with maternal and child reports in psychostimulant-treated children relative to non-ADHD controls. Wilens et al. (2010a) used the Before-School Functioning Questionnaire (BSFQ) to assess school-related activities in the time frame from 6:00 a.m. to 9:00 a.m. in youths with ADHD receiving psychostimulant treatment. This crossover study found notable improvements in these children’s early morning functioning while on a psychostimulant compared with placebo.

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An extended-release formulation of guanfacine (GXR; Intuniv®, Shire Development Inc., Wayne, Pennsylvania) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD as monotherapy and adjunctive to psychostimulants (INTUNIV, 2011). In a prior Phase II, open-label, 9-week study of children and adolescents with ADHD with suboptimal response to a psychostimulant, adjunctive morning-administered GXR with a psychostimulant resulted in significant improvements in ADHD symptoms and no unique adverse events (AEs) compared with those historically reported AEs for either treatment alone (Spencer, Greenbaum, Ginsberg, & Murphy, 2009). However, the small sample size (*n* = 75) and open-label nature of the study mitigate broad-scale generalizability of these data. Furthermore, although clinical trials of GXR prior to this current study restricted administration of GXR to the morning, this is not consistent with clinical practice. Anecdotally, it is known that some prescribers with an extended-release psychostimulant with improvement but continued mild to moderate symptoms of ADHD (ADHD-RS-IV total score of ≥24 and a CGI-S indicative of at least mild impairment [≥3]). The psychostimulants consisted of FDA-approved extended-release preparations of mixed amphetamine salts, lisdexamfetamine dimesylate, methylphenidate HCl, or dexmethylphenidate HCl (either proprietary or generic formulation). Exclusion criteria included the presence of cardiovascular abnormalities, body weight of <55 or >176 pounds, or any current, controlled or uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder), including any severe comorbid Axis II disorders or severe Axis I disorders.

**Method**

**Participants**

Participants were aged 6 to 17 years with a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000) diagnosis of ADHD with a suboptimal response to an extended-release oral preparation of methylphenidate or amphetamine. Suboptimal response was defined as ≥4 weeks of treatment with an extended-release psychostimulant with improvement but continued mild to moderate symptoms of ADHD (ADHD-RS-IV total score of ≥24 and a CGI-S indicative of at least mild impairment [≥3]). The psychostimulants consisted of FDA-approved extended-release preparations of mixed amphetamine salts, lisdexamfetamine dimesylate, methylphenidate HCl, or dexmethylphenidate HCl (either proprietary or generic formulation). Exclusion criteria included the presence of cardiovascular abnormalities, body weight of <55 or >176 pounds, or any current, controlled or uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder), including any severe comorbid Axis II disorders or severe Axis I disorders.

Institutional Review Board approval was obtained prior to study initiation. Parents or legal guardians provided informed consent and the participant provided additional assent as per site requirements.

**Study Design**

This 9-week, double-blind, placebo-controlled adjunctive study was conducted at 59 sites in the United States. Details of the study design have been described previously (Wilens et al., 2012). In brief, once participant eligibility was confirmed, participants were randomized at baseline in a 1:1:1 ratio to receive GXR (1-4 mg/d) in the morning (GXR AM), GXR at bedtime (GXR PM), or placebo, in addition to their current stable dose of psychostimulant. Randomization was stratified by psychostimulant type (amphetamine or methylphenidate).

Visits were scheduled 7 (±2) days apart during the 5-week dose-optimization period and the 3-week dose-maintenance period. At the start of the 5-week dose-optimization period, participants received GXR or placebo, and were maintained at their optimal dose of GXR during the 3-week dose-maintenance period. Participants’ doses were optimized at the discretion of the investigator based on a

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reduction in ADHD symptoms and acceptable tolerability and safety. Participants could have a one-time 1-mg/d reduction in their dosing for tolerability reasons. Beginning at Visit 10, the dose of GXR or placebo was tapered over the subsequent week following a schedule based on the participant's specific dose prior to Visit 10. Psychostimulant doses remained fixed throughout the study.

**Assessments**

This report details results from the two secondary measures of efficacy that specifically evaluated symptomatology or function before or after school: the CGI-P (Conners, 1997) and the BSFQ (Wilens et al., 2010a).

The CGI-P contains 10 items of a global nature and has been used to assess a child's ADHD symptoms at different time points during the day. Parents completed 2 CGI-P assessments at each weekly visit (Visits 1-11), one assessing morning symptoms (i.e., prior to leaving for school) and the other assessing evening symptoms (i.e., prior to bedtime) over the last week. Each item on the CGI-P was scored from 0 (reflecting never, seldom) to 3 (reflecting very often, very frequent). The 10 items were also grouped into two subscales: Restless-Impulsive (7 items) and Emotional Lability (3 items).

The BSFQ is a questionnaire that was generated from commonly reported areas of dysfunction in early morning, before-school activities associated with ADHD (e.g., breakfast, hygiene, time awareness, getting to school; Wilens et al., 2010a). There are two components of the BSFQ: a 20-item questionnaire that was completed by the parent, and a 14-item self-report section completed collaboratively by the participant with assistance from the parent or legally authorized representative, if needed. The parent-rated questionnaire assesses ADHD symptomatology and functioning on a severity scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; and 3 = severe) and focuses primarily on the early morning, before-school activities noted above. The 14-item self-report section is split into two subscales (7 items each), Feelings and Behaviors, and assesses how the child felt, his or her relationship with parents and siblings, his or her success with morning activities or problems, and whether the child was proud of himself or herself over the past week during the hours of 6:00 a.m. through 9:00 a.m. The self-report questions ranged from 0 = no to 2 = a lot. The BSFQ was administered at screening (Visit 1), baseline (Visit 2), Visits 8 and 10 (endpoint for efficacy), and Visit 11 (end of tapering) with respect to symptoms occurring during the previous week.

**Data Analysis**

Efficacy and safety analyses were performed using the full analysis set (FAS) and safety population, respectively. Both populations were defined to include all participants who were randomized and received ≥1 dose of study medication.

The mean CGI-P score and change from baseline score were summarized at each time point (i.e., morning and evening), at each visit, and at endpoint (i.e., last valid CGI-P obtained on-treatment, postbaseline, and before dose taper) by treatment group. Changes from baseline in CGI-P score were assessed using an analysis of covariance (ANCOVA) model that included terms for treatment group (the effect of interest), psychostimulant type (blocking factor: amphetamine or methylphenidate), and the corresponding baseline score (the covariate). Comparisons were made between each GXR group (i.e., GXR AM + psychostimulant and GXR PM + psychostimulant) versus placebo.

The mean parent-rated BSFQ total score (i.e., sum of 20 parent-rated items), the Feeling score, the Behavior score, and change from baseline score were summarized at each visit and endpoint (i.e., last valid score obtained on-treatment, postbaseline, and before dose taper) by treatment group including all active treatment groups pooled. In addition, the mean time to wake up and get out of bed and time to complete routines was summarized at each scheduled visit and endpoint, by treatment group, including all active treatment groups pooled. Similar to the CGI-P analyses, an ANCOVA model was used to compare BSFQ changes from baseline between GXR and placebo treatment groups for the FAS.

Missing data were handled as follows: If 20% or fewer of the items used to calculate the scale score were missing, the scale score was calculated as the mean of the nonmissing items multiplied by the number of items in the scale. If more than 20% of the items used for summing a score were missing, the score was set to missing. Incomplete data that resulted from either early study termination or unavailability were handled as endpoint analysis, which is equivalent to the last observation carried forward at Visit 10 approach for the primary efficacy analysis.

A post hoc analysis of the BSFQ data was performed to evaluate which, if any, of the individual items drove the overall response. The analysis assessed the distribution of severity ratings at endpoint on each of the 20 BSFQ items on the parent-rated portion. This analysis did not assess baseline to endpoint changes. Differences between groups at endpoint were assessed using the Cochran–Mantel–Haenszel test stratifying for psychostimulant type (amphetamine or methylphenidate).

The study was not designed or powered to make statistical comparisons between active treatment groups (i.e., GXR AM + psychostimulant vs. GXR PM + psychostimulant).

**Results**

Detailed analysis of demographic data and disposition of participants has been reported previously (Wilens et al.,
A total of 615 participants were screened and 461 were randomized. The FAS populations included 455 participants: 153 in the placebo + psychostimulant group, 150 in the GXR AM + psychostimulant group, and 152 in the GXR PM + psychostimulant group. Overall, 386 participants completed the dose-maintenance period (Visit 10) and 378 completed the study through the follow-up Visit 12.

Table 1. Demographics in the FAS/Safety Population (n = 455).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo + psychostimulant (n = 153)</th>
<th>GXR AM + psychostimulant (n = 150)</th>
<th>GXR PM + psychostimulant (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>10.8 (2.3)</td>
<td>11.0 (2.6)</td>
<td>10.6 (2.3)</td>
</tr>
<tr>
<td>6-12 years, n (%)</td>
<td>123 (80.4)</td>
<td>114 (76.0)</td>
<td>124 (81.6)</td>
</tr>
<tr>
<td>13-17 years, n (%)</td>
<td>30 (19.6)</td>
<td>36 (24.0)</td>
<td>28 (18.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>112 (73.2)</td>
<td>108 (72.0)</td>
<td>106 (69.7)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (26.8)</td>
<td>42 (28.0)</td>
<td>46 (30.3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>102 (66.7)</td>
<td>104 (69.3)</td>
<td>102 (67.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>35 (22.9)</td>
<td>28 (18.7)</td>
<td>37 (24.3)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.7)</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>0</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>14 (9.2)</td>
<td>14 (9.3)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>15 (9.8)</td>
<td>27 (18.0)</td>
<td>19 (12.5)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>138 (90.2)</td>
<td>123 (82.0)</td>
<td>133 (87.5)</td>
</tr>
<tr>
<td>Baseline CGI-P score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM assessment</td>
<td>17.1 (6.77)</td>
<td>16.7 (6.13)</td>
<td>17.5 (6.60)</td>
</tr>
<tr>
<td>PM assessment</td>
<td>18.2 (6.51)</td>
<td>17.7 (6.19)</td>
<td>17.8 (5.89)</td>
</tr>
<tr>
<td>Baseline BSFQ scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent-rated Total</td>
<td>35.9 (11.96)</td>
<td>35.9 (11.55)</td>
<td>36.7 (11.53)</td>
</tr>
<tr>
<td>Participant-rated Feelings</td>
<td>4.9 (2.73)</td>
<td>5.1 (2.89)</td>
<td>4.9 (3.00)</td>
</tr>
<tr>
<td>Participant-rated Behavior</td>
<td>6.2 (2.71)</td>
<td>6.2 (2.63)</td>
<td>6.3 (2.88)</td>
</tr>
<tr>
<td>Concomitant psychostimulant, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS XR</td>
<td>27 (17.6)</td>
<td>26 (17.3)</td>
<td>28 (18.4)</td>
</tr>
<tr>
<td>OROS® MPH</td>
<td>69 (45.1)</td>
<td>69 (46.0)</td>
<td>68 (44.7)</td>
</tr>
<tr>
<td>SODAS® d-MPH</td>
<td>9 (5.9)</td>
<td>9 (6.0)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>MPH CD</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>SODAS MPH</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>LDX</td>
<td>45 (29.4)</td>
<td>43 (28.7)</td>
<td>46 (30.3)</td>
</tr>
</tbody>
</table>


Note. FAS = full analysis set; GXR = guanfacine extended release; SD = standard deviation; CGI-P = Connor’s Global Index–Parent version; BSFQ = Before-School Functioning Questionnaire; MAS XR = mixed amphetamine salts extended release; OROS MPH = osmotic-release oral system methylphenidate; SODAS d-MPH = spheroidal oral drug absorption system dexmethylphenidate; MPH CD = methylphenidate controlled-delivery; SODAS MPH = spheroidal oral drug absorption system methylphenidate; LDX = lisdexamfetamine dimesylate.

2012). A total of 615 participants were screened and 461 were randomized. The FAS populations included 455 participants: 153 in the placebo + psychostimulant group, 150 in the GXR AM + psychostimulant group, and 152 in the GXR PM + psychostimulant group. Overall, 386 participants completed the dose-maintenance period (Visit 10) and 378 completed the study through the follow-up Visit 12.

Demographic characteristics and current psychostimulant treatment were generally similar among treatment groups for the FAS population (Table 1). The mean (standard deviation [SD]) optimal dose of GXR was 3.2 (1.0) mg/d and mean optimal doses were similar between the GXR AM + psychostimulant (3.3 [1.0] mg/d) and GXR PM + psychostimulant (3.2 [1.0] mg/d) groups. Similarly, the mean (SD) weight-adjusted optimal dose of GXR was 0.088 (0.04) mg/kg and mean optimal weight-adjusted doses were similar between the GXR AM + psychostimulant (0.088 [0.0366] mg/kg) and GXR PM + psychostimulant (0.089 [0.0347] mg/kg) groups.

Efficacy

CGI-P morning assessment. Participants who received GXR along with their current stable dose of psychostimulant exhibited significantly greater improvement from baseline at endpoint on the morning assessment of the CGI-P than participants who received placebo + psychostimulant (GXR AM, placebo-adjusted least squares [LS] mean [95% confidence interval; CI] = –1.7 [–3.2, –0.3], p = .019; GXR PM, placebo-adjusted LS mean = –2.6 [–4.0, –1.1], p < .001; Figure 1a). For morning CGI-P assessment, participants in the GXR PM + psychostimulant group showed significant
improvement compared with placebo consistently from Visit 5 (3 weeks on treatment, during dose optimization) through Visit 10 ($p < .022$). Participants in the GXR AM + psychostimulant group showed significant improvement compared with placebo at Visits 5 and 6 and then consistently starting at Visit 8 (6 weeks on treatment) through Visit 10 ($p < .011$).

**CGI-P evening assessment.** Participants receiving GXR in combination with psychostimulants demonstrated significantly greater improvements from baseline at endpoint on the evening assessment of the CGI-P than participants receiving placebo + psychostimulants (GXR AM, placebo-adjusted LS mean [95% CI] = $-2.4 [-4.0, -0.9]$, $p = .002$; GXR PM, placebo-adjusted LS mean = $-3.0 [-4.5, -1.5]$, $p < .001$; Figure 1b). For evening CGI-P assessment, participants in the GXR PM + psychostimulant group showed significant improvement compared with the placebo group at Visit 5 ($p = .002$) and then consistently starting at Visit 7 (5 weeks on treatment, end of dose optimization) through Visit 10 ($p < .05$). Participants in the GXR AM + psychostimulant group showed significant improvement compared with placebo consistently from Visit 8 (6 weeks on treatment) through Visit 10 ($p < .05$).

**BSFQ assessment: Parent-rated items.** At endpoint, participants who received GXR + psychostimulant showed significantly greater improvement on the parent-rated BSFQ compared with participants who received placebo + psychostimulant (GXR AM, placebo-adjusted LS mean = $-5.1$, $P < .001$; GXR PM, placebo-adjusted LS mean = $-4.7$, $p = .002$; Figure 2). Participants who received GXR AM + psychostimulant or GXR PM + psychostimulant showed significantly greater improvement on the parent-rated BSFQ compared with participants who received placebo + psychostimulant showed significantly greater improvement on the parent-rated BSFQ compared with participants who received placebo + psychostimulant at all postbaseline, pretaper visits at which the BSFQ was measured (Visits 8, 10, and endpoint). More individual items of the BSFQ showed significant ($p < .05$) differences from placebo in the distribution of severity of each parent-rated item at endpoint in the GXR AM + psychostimulant group (14/20 items) compared with the GXR PM + psychostimulant group (6/20 items; Figure 3). No single item or group of items appeared to drive the response of the total score.

**BSFQ assessment: Participant-rated items.** The BSFQ participant-rated Feeling score LS mean placebo-adjusted difference (95% CI) did not demonstrate a significant change for GXR AM + psychostimulant ($-0.5 [-1.0, 0.1]$, $p = .116$) or GXR PM + psychostimulant ($-0.3 [-0.9, 0.2]$, $p = .239$) at
Figure 3. Severity at endpoint of 20 BSFQ parent-rated items in participants receiving GXR AM + psychostimulant, GXR PM + psychostimulant and placebo + psychostimulant n (%). a. The first 10 items on the BSFQ. b. The remaining 10 items on the BSFQ.
Note. BSFQ = Before-School Functioning Questionnaire; GXR = guanfacine extended release.
endpoint. The participant-rated BSFQ Behavior score LS mean placebo-adjusted difference (95% CI) also did not demonstrate a significant change at endpoint for either GXR AM + psychostimulant (–0.2 [–0.8, 0.3]; \( p = .429 \)) or GXR PM + psychostimulant (–0.5 [–1.1, 0.1]; \( p = .104 \)).

### Safety

Detailed safety analyses have been previously reported (Wilens et al., 2012). In brief, treatment-emergent AEs (TEAEs) were reported by 76.8% (232/302) and 63.4% (97/153) of participants in the GXR + psychostimulant treatment groups combined and placebo + psychostimulant group, respectively. Among GXR-treated participants, TEAEs with incidence ≥5% were upper abdominal pain (8.3%), cough (5.3%), decreased appetite (6.6%), fatigue (9.6%), headache (21.2%), irritability (5.0%), nausea (5.0%), insomnia (8.6%), somnolence (13.6%), and upper respiratory tract infection (9.9%). Among placebo-treated participants, TEAEs with incidence ≥5% were headache (13.1%), irritability (7.2%), and upper respiratory tract infection (7.8%). Most TEAEs were mild or moderate in severity. Severe TEAEs were reported by 2.0% (\( n = 3 \)), 6.6% (\( n = 10 \)), and 0.7% (\( n = 1 \)) of participants in the GXR AM + psychostimulant, GXR PM + psychostimulant, and placebo + psychostimulant groups, respectively. Serious AEs occurred in 1.0% (\( n = 3 \)) of participants receiving GXR + psychostimulant; 0.7% (\( n = 1 \)) and 1.3% (\( n = 2 \)) of participants in the GXR AM + psychostimulant and GXR PM + psychostimulant groups, respectively. All three events were deemed unrelated to study medication by the investigators: One participant experienced syncope in the context of nausea, vomiting, and sinusitis; one participant reported self-injurious behavior, aggression, homicidal ideation, and adjustment disorder with mixed disturbance of emotions and conduct, and had exhibited similar behaviors prior to study start; and one participant had a serious AE related to poison ivy. The rate of discontinuation due to TEAEs was 2.7% (4/150) in the GXR AM + psychostimulant group, 3.9% (6/152) in the GXR PM + psychostimulant group, and 0.7% (1/153) in the placebo + psychostimulant group.

### Discussion

These results show that GXR administered adjunctively in either the morning or evening with a psychostimulant was associated with significant improvements in morning and evening parent-reported symptoms and functioning compared with placebo plus psychostimulant in participants with a suboptimal response to a long-acting psychostimulant. Specifically, adjunctive GXR administered in either the morning or evening with psychostimulants resulted in significantly improved parent ratings over placebo plus psychostimulants on the morning and evening CGI-P and on the parent-rated morning measure of the BSFQ. The current findings suggest that GXR adjunctive to psychostimulants results in improvement of ADHD symptoms throughout the day (Wilens, Lyne, & Youcha, 2010b). In addition, as psychostimulants are generally taken in the morning, it could be postulated that morning administration of GXR with psychostimulants might be beneficial in simplifying treatment for patients with ADHD.

With a paucity of previous data assessing treatment response in the evening, the findings of significant improvement versus placebo in ADHD symptom coverage in the evening provide useful information for guiding clinician’s choices of treatment and suggest that children with ADHD treated with GXR as an adjunct to psychostimulant treatment may achieve symptom control into the time period prior to bedtime. The late afternoon/evening period is critically important to performance on after-school daily tasks (e.g., homework and extracurricular activities). The current findings with GXR as an adjunct to psychostimulant treatment may offer clinicians a practical and unique treatment option to enhance symptom coverage in the evening in children with ADHD. Further adequately designed studies will be needed to confirm these findings.

The current findings are qualitatively similar to those of previous monotherapy studies (Buitelaar & Medori, 2010). The CGI-P has been used as a measure of symptomatology at specific times of day (Biederman et al., 2002; Block et al., 2009; Wilens et al., 2010a). For example, controlled studies of extended-release mixed amphetamine salts administered in the morning showed efficacy on both morning (~10:00 a.m.) and early evening (after 4:00 p.m.) on the CGI-P (Biederman et al., 2002). Similarly, in a 6-week evaluation of atomoxetine, both morning- and evening-administered atomoxetine showed efficacy as measured by the CGI-P in both the morning and evening, although on the primary ADHD-RS endpoint, efficacy was observed for morning-administered, but not evening-administered, atomoxetine (Block et al., 2009). To our knowledge, this is the first study that attempts to specifically assess morning and evening symptomatology with a concomitant ADHD pharmacotherapy regimen.

The current study included a relatively novel scale capturing before-school functioning that can be impaired by ADHD (Wilens et al., 2010a). The BSFQ findings of this study are similar to a controlled monotherapy study with the methylphenidate transdermal system (MTS). Although participant ratings were not statistically significantly different from placebo in either the MTS monotherapy or this adjunctive study, significant reductions in morning symptoms were seen with MTS (applied 6:00 a.m. to 7:00 a.m.) compared with placebo on the BSFQ, overall and on 17 of 20 individual parent-reported items (Wilens et al., 2010a). Interestingly, however, in the MTS study, no significant reductions were seen with MTS compared with placebo on the CGI-P.
targeted for morning time period. In the present adjunctive therapy study, significant improvements in morning functioning were observed on the parent-rated BSFQ and CGI-P at endpoint for the GXR AM and PM plus psychostimulants groups versus placebo plus psychostimulants.

Improvements for the total parent-rated BSFQ scores were similar for morning or evening GXR administration (5.1 vs. 4.7, respectively). In the post hoc analysis examining the distribution of severity of each parent-rated item at endpoint, there did not appear to be a single item or group of items that drove the response. This analysis did not evaluate change from baseline and therefore did not account for possible differences in the distribution of severity of these parent-reported items at baseline between the GXR and placebo groups. With this caveat, there were apparently more items whose distribution at endpoint differed from placebo on the BSFQ in the GXR AM compared with the GXR PM groups. It could be postulated that adjunctive administration of GXR in the morning might have more robust effects on the specific morning functioning that is thought to be impaired by ADHD than adjunctive administration of GXR in the evening. Alternatively, adjunctive administration of GXR in the evening may have residual morning sedative effects that interfere with recognizing improvements due to reductions in ADHD symptoms. However, in this study, the incidence of treatment-emergent somnolence, sedation, and hypersomnia events combined was similar whether GXR was administered in the morning or evening (18.0% in the GXR AM + psychostimulant group and 18.4% in the GXR PM + psychostimulant group). A future study specifically designed to compare morning with evening GXR administration regimens could directly assess any potential differences in the distribution of severity of these parent-reported items at baseline between the GXR and placebo groups. With this caveat, there were apparently more items whose distribution at endpoint differed from placebo on the BSFQ in the GXR AM compared with the GXR PM groups. It could be postulated that adjunctive administration of GXR in the morning might have more robust effects on the specific morning functioning that is thought to be impaired by ADHD than adjunctive administration of GXR in the evening. Alternatively, adjunctive administration of GXR in the evening may have residual morning sedative effects that interfere with recognizing improvements due to reductions in ADHD symptoms. However, in this study, the incidence of treatment-emergent somnolence, sedation, and hypersomnia events combined was similar whether GXR was administered in the morning or evening (18.0% in the GXR AM + psychostimulant group and 18.4% in the GXR PM + psychostimulant group). A future study specifically designed to compare morning with evening GXR administration regimens could directly assess any potential differences. Further work, specifically with more frequent time-locked circadian assessments, is also necessary to better understand the duration of coverage of $\alpha_2$-adrenoceptor agonists and psychostimulants in the treatment of ADHD over the course of the day.

Although the current study lacks a group of children without ADHD, the clear postbaseline differences in scores reflective of before-school functioning in those youths with GXR + psychostimulant compared with placebo + psycho-stimulant suggest significant, treatable psychopathology during this vulnerable circadian period. Overall, the current findings also suggest the potential utility of instruments such as the BSFQ in identifying before-school functioning and the importance of examining and addressing before-school dysfunction in ADHD.

Another important finding of the current study was the utility of either AM or PM administration of adjunctive GXR with resultant improvement in morning and evening ADHD symptoms as indicated by the CGI-P and BSFQ. Given that many parents report morning behavioral difficulties in children with ADHD (Coghill et al., 2008), administration of GXR at night or in the morning appeared to result in coverage of ADHD symptoms prior to school onset with resultant improvement in ADHD and before-school functioning.

One potential goal of future research is to determine the mechanisms by which the presence of ADHD produces the impairments on morning and evening behavior and their subsequent link to longer term outcomes that have been noted in previous studies (Biederman et al., 2006; Coghill et al., 2008).

There are a number of limitations in the current study. Participants were given GXR only upon awakening or at bedtime and the CGI-P was assessed only in the morning and evening. In addition, parents and participants were asked to evaluate symptoms retrospectively for the previous week. Therefore, whether dosing occurred before or after the evaluation may have an impact on the efficacy evaluation. Moreover, the study was of relatively short duration and not powered to evaluate differences between morning and evening dosing of GXR.

Moreover, the study did not incorporate psychostimulant optimization during the conduct of the study, although optimization may have occurred prior to study start. Although participants had to manifest some improvement in response to psychostimulant monotherapy to be included in the study, they were not assessed prior to beginning their psychostimulant regimen. Thus, the response attributable to the psychostimulant is unknown.

In addition, adherence with psychostimulant therapy prior to study start was not assessed, although adherence rates for psychostimulant therapy were high during this study. It is possible that participation in the study may have enhanced adherence to psychostimulants, resulting in an artificially enhanced placebo response in the psychostimulant plus placebo administration group. The relatively restricted inclusion and exclusion criteria—essential to reduce confounding noise caused by comorbid illnesses—nevertheless produced a select group of participants that may not be comparable with the general clinical population of which approximately 60% has comorbid mental or developmental illnesses. Given limited available expanded instruments for assessing morning and evening symptomatology and functioning, none of which are objective measures, the study relied upon a validated overall ADHD symptom scale, and a newly developed instrument assessing before-school functioning (i.e., BSFQ). While the BSFQ is promising in showing significant changes compared with placebo for early morning functioning in the current study, as well as in one other study of psychostimulant monotherapy (Wilens et al., 2010a), it has yet to be assessed by formal psychometric testing. In addition, unlike analog classroom-derived data, the instruments and assessments utilized in this study were not strictly time-locked; the current data do not allow determination of the time to onset of efficacy. Finally, it is not clear why, as in the MTS study,
significant changes were not seen on the participant-rated scores of the BSFQ. The results of this study do not provide insight into why significant changes were observed with adjunctive GXR treatment on the parent-rated BSFQ, but not on the participant-rated BSFQ scores, while significant changes were seen on the 20-item scores, which were parent-rated in this study.

Despite these limitations, the current study demonstrates that the addition of GXR to a stable psychostimulant regimen may provide additional benefits based on parent-rated measures during early morning and evening hours for children and adolescents aged 6 to 17 years with ADHD who exhibit suboptimal response to psychostimulant therapy. The current findings underscore the importance of understanding ADHD outside the context of what is typically a single, unitary rating scale (e.g., ADHD-RS-IV) and utilizing additional measures such as those in the current study to inform treatment planning and more fully assess patient response to medication over the day.

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