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Efficacy of Guanfacine Extended Release in the Treatment of Combined and Inattentive Only Subtypes of Attention-Deficit/Hyperactivity Disorder

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Abstract

Background: Extended-release guanfacine (GXR) is approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6–17 years. This *post-hoc* analysis further examines the effects of GXR on hyperactivity-impulsivity and inattentiveness.

Method: Data from two large double-blind placebo-controlled pivotal trials of GXR in the treatment of ADHD were analyzed. Using the pooled population to provide sufficient sample size and associated statistical power, the impact of GXR treatment on core ADHD symptoms was examined by comparing ADHD Rating Scale IV (ADHD-RS-IV) total scores in the overall GXR and placebo groups in subjects with each of the three ADHD subtypes. ADHD-RS-IV Hyperactivity-Impulsivity and Inattentiveness subscale scores in the overall study population by randomized dose group (vs. placebo) were also examined.

Results: The full analysis set included 631 subjects aged 6–17 years (GXR: $n = 490$; placebo: $n = 141$). Among subjects with the predominantly inattentive subtype of ADHD, differences in least squares (LS) mean reductions from baseline in ADHD-RS-IV total scores were significantly greater in GXR-treated subjects ($n = 127$) than in placebo-treated subjects ($n = 38$) at treatment weeks 3 through 5 and end point ($p \leq 0.020$). Among subjects with combined type ADHD, differences in LS mean ADHD-RS-IV total score reductions from baseline were significantly greater in the GXR group ($n = 354$) than in the placebo group ($n = 100$) at treatment weeks 1 through 5 and end point ($p \leq 0.011$). The dearth of predominantly hyperactive-impulsive type subjects ($n = 12$) precluded analysis of this subgroup. Each randomized GXR dose group in each trial demonstrated significantly greater reductions from baseline in ADHD-RS-IV Hyperactivity-Impulsivity and Inattentiveness subscale scores than did the respective placebo group at end point ($p \leq 0.05$ for all).

Conclusions: The results support the use of GXR in the treatment of core ADHD symptoms as defined in the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision*, including hyperactivity, impulsivity, and inattention.

Introduction

The worldwide prevalence of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents has been estimated at ~ 5%, indicating the importance of this disorder as a public health problem (Polanczyk et al. 2007; Wittchen et al. 2011). The symptoms of ADHD are separated into two domains by the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision* (DSM-IV-TR): inattention and hyperactivity-impulsivity (American Psychiatric Association 2000). The DSM-IV-TR also describes three subtypes of ADHD: combined, predominantly inattentive, and predominantly hyperactive-impulsive (American Psychiatric Association 2000).

The United States Food and Drug Administration has approved an extended-release formulation of the selective α_{2A}-adrenergic receptor agonist guanfacine (GXR) for the treatment of ADHD in children and adolescents aged 6–17 years (Intuniv [package insert] 2011). In two large, randomized, double-blind, placebo-controlled, pivotal trials of children and adolescents aged 6–17 years, once-daily GXR significantly reduced the symptoms of ADHD compared with placebo, as assessed by several measures including the clinician-administered ADHD Rating Scale IV (ADHD-RS-IV), Clinical Global Impressions-Improvement, Parent's Global Assessment, and Conners' Parent Rating Scale–Revised: Short Form (Biederman et al. 2008; Sallee et al. 2009). In one trial, the most common treatment-emergent adverse events (TEAEs) occurring in ≥ 5% of subjects receiving GXR and at least twice the placebo rate

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were somnolence, fatigue, upper abdominal pain, sedation, dry mouth, nausea, lethargy, pyrexia, decreased appetite, dizziness, and irritability (Biederman et al. 2008). In the other trial, TEAEs that occurred in ≥5% of subjects taking GXR were sedation, somnolence, headache, fatigue, upper abdominal pain, dizziness, irritability, and nausea (Sallee et al. 2009). In both trials, most TEAEs were mild to moderate in severity (Biederman et al. 2008; Sallee et al. 2009).

The analysis presented in this article was conducted to further examine the effects of GXR on hyperactivity and impulsivity as well as on inattentiveness, the core symptoms of ADHD as defined by DSM-IV. To address these symptoms individually, this analysis examined the efficacy of GXR in subjects of each of the DSM-IV-defined subtypes of ADHD, using the pooled population to provide sufficient sample size and associated statistical power for the analysis. In addition, the efficacy of GXR, as measured by each subscale of the ADHD-RS-IV, was examined. For the analysis of each subtype of ADHD, data across both trials are collapsed because of the low numbers of subjects with the predominantly inattentive subtype of ADHD within each study. For examination of ADHD-RS-IV subscales, analyses are conducted within each study individually.

Methods

Subjects

The present analysis used data from two large, previously published multicenter, placebo-controlled, double-blind, pivotal trials of GXR in the treatment of ADHD in children and adolescents aged 6–17 years (Biederman et al. 2008).

Both trials enrolled subjects aged 6–17 years who met DSM-IV-TR criteria for a primary diagnosis of ADHD (Biederman et al. 2008; Sallee et al. 2009). Subjects in study 2 were also required to have a baseline ADHD-RS-IV score of at least 24. Subjects were excluded if they had hypertension, any current uncontrolled comorbid psychiatric diagnosis (excluding ADHD or oppositional defiant disorder), or a history of tic disorder or seizure (within 2 years). Subjects were excluded from enrolling in the trials if they were taking medications that affect the cardiovascular or central nervous systems, with the exception of ADHD treatments, which were washed out prior to baseline. Selective serotonin reuptake inhibitors and antipsychotics were also washed out prior to baseline. Anticonvulsant medications were not permitted in either study.

For study 1 versus study 2, respectively, the cohorts were comparable across most overall baseline characteristics: age (10.5 vs. 11 years), male (74.5% vs. 72%), white (70.1% vs. 67%), weight (43.6 vs. 44 kg), ADHD subtype (Combined: 71.9% vs. 73%; Inattentive: 26.1% vs. 26%; Hyperactive-Impulsive: 2% vs. 2%) (Biederman et al. 2008; Sallee et al. 2009). The only exception was in the number of years since ADHD diagnosis (2.61 vs. 1.9 years for study 1 vs. study 2, respectively). Because of the overall similarity in baseline characteristics across the two study cohorts and the analytical approach taken, efficacy data were combined for the present study as discussed subsequently.

Study designs

Both trials had similar study designs. Each began with a screening period lasting up to 2 weeks while subject eligibility was determined. Eligible subjects proceeded to a washout period lasting ~1 week, while all psychoactive medications were discontinued. At the baseline visit, subjects were randomized to a treatment group and began the double-blind treatment period. Subjects in study 1 were randomized to receive 2, 3, or 4 mg/day of GXR or placebo in a 1:1:1:1 ratio during an 8-week double-blind treatment period (Biederman et al. 2008). Subjects in study 2 were randomized in a 1:1:1:1:1 ratio to receive placebo or 1, 2, 3, or 4 mg/day GXR, although only subjects weighing <50 kg were eligible to be randomized into the 1 mg/day GXR treatment group. The double-blind treatment period of study 2 lasted 9 weeks (Sallee et al. 2009). Both trials used a forced dose-escalation design such that subjects randomized to receive 4 mg/day GXR had their dose increased in weekly 1-mg/day increments, reaching their randomized dose after 3 weeks. The precise medication schedule for the 2 and 3 mg/day GXR treatment groups differed slightly between the trials (Fig. 1). After a period of dose maintenance, subjects underwent a 1- to 3-week period of dose tapering, based on whether they chose to participate in a long-term, open-label extension study.

Efficacy Assessments

The primary efficacy assessment in each trial was the total score on the clinician-rated ADHD-RS-IV. The ADHD-RS-IV was originally designed to be completed by a child's parent or teacher (DuPaul et al. 1998). In the present studies, however, clinicians administered the scale to parents or caregivers of the subjects at baseline and at each study visit during the double-blind treatment

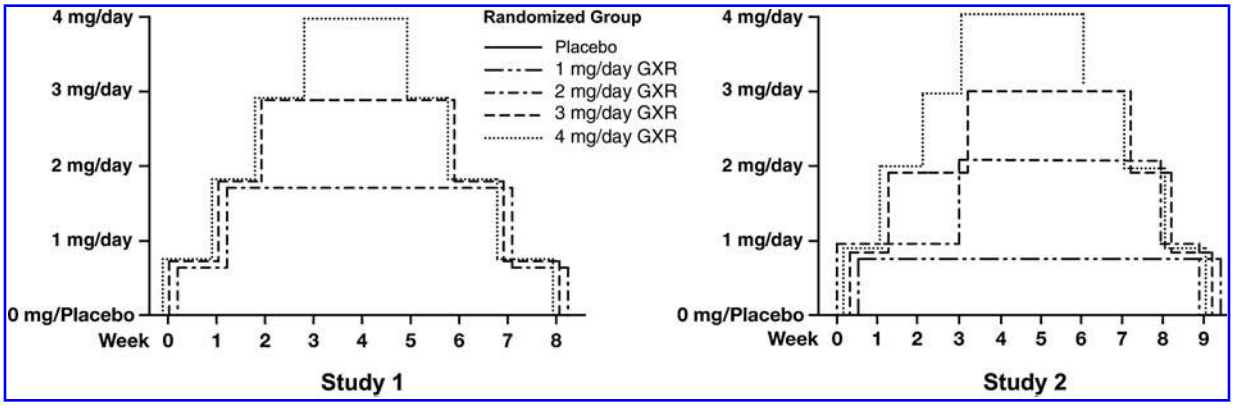

FIG. 1. Study designs of the analyzed trials. Subjects randomized to receive GXR began at the dose of 1 mg/day, and the dosage was escalated to match the randomized dose over a 3-week period. Following a period of dose maintenance, each trial ended with a period of dose tapering. GXR = guanfacine extended release.

period prior to dose tapering (ie, weeks 1 through 5 in study 1; weeks 1 through 6 in study 2) (Biederman et al. 2008; Sallee et al. 2009). The 18 items of the ADHD-RS-IV reflect DSM-IV-TR criteria for ADHD and are each scored on a 4-point Likert scale ranging from 0 (never or rarely) to 3 (very often) (DuPaul et al. 1998). Total scores range from 0 to 54. As previously mentioned, the ADHD-RS-IV also contains two subscales, Hyperactivity-Impulsivity and Inattentiveness, each containing nine items and ranging in score from 0 to 27. Both trials used the ADHD-RS-IV to assess the frequency of ADHD symptoms within the preceding week.

Statistical analysis

ADHD subtype. Analyses of the efficacy of GXR for the predominantly inattentive and combined ADHD subtypes were performed on the pooled samples for each study using the full analysis set, defined as all subjects randomized to treatment who had a baseline and at least 1 postrandomization ADHD-RS-IV assessment. The pooled population was used in order to have a sufficient sample size and associated statistical power for the analysis by ADHD subtype, based on the similarities in baseline characteristics of the study cohorts. Because the number of subjects across the studies with the predominantly hyperactive-impulsive subtype of ADHD was low (see Results), pooled efficacy analyses were not conducted for this subtype. The ADHD-RS-IV total score and change from baseline were reported by visit and for end point, with end point defined as the last postrandomization treatment week prior to dose tapering for which a score was available. Pairwise comparisons of the placebo and active treatment groups were analyzed using an analysis of covariance (ANCOVA) model for weeks 1 through 5 and end point. Because there were no corresponding data from study 1, data from week 6 of study 2 were used to derive end point values but are not presented individually. The ANCOVA model included the study, the treatment group (the effect of interest) and the corresponding baseline score (the covariate). For all analyses, the least squares (LS) mean, difference in LS mean between active (or randomized dose) and placebo groups, and 95% confidence intervals for the difference were summarized.

ADHD-RS-IV subscales. Analyses of the efficacy of GXR on each subscale of the ADHD-RS-IV were also performed on the full analysis set and included subjects with any of the three subtypes of ADHD. Because of the larger data set that was available for analysis of ADHD-RS-IV subscale results, the randomized dose groups from each study were not pooled to avoid overpowering the analysis; results are presented independently for each study. An ANCOVA model that included treatment group (the effect of interest) and the corresponding baseline score (the covariate) was used. For all analyses, the LS mean, difference in LS mean between active (or randomized dose) and placebo groups, and 95% confidence intervals for the difference were summarized.

Results

Subject demographics and disposition

Studies 1 and 2 enrolled 345 and 329 subjects, respectively. The safety population of the combined study cohort included 662 subjects; 513 were randomized to receive GXR and 149 were randomized to receive placebo. Demographic characteristics for the active and placebo treatment groups were similar (Table 1). Of the 662 subjects in the safety population, 426 completed the trial: 64.7% ($n = 332$) of subjects randomized to receive GXR and 63.1% ($n = 94$) of subjects randomized to receive placebo. In the active treatment group, reasons for discontinuation included adverse events (AEs) ($n = 61$; 11.9%), withdrawn consent ($n = 32$; 6.2%), loss to follow-up ($n = 27$; 5.3%), protocol violation ($n = 4$; 0.8%), and other ($n = 57$; 11.1%). AEs that led to discontinuation in at least two subjects in the active treatment group were somnolence ($n = 19$; 3.7%), sedation ($n = 11$; 2.1%), fatigue ($n = 8$; 1.6%), headache ($n = 5$; 1.0%), hypotension ($n = 4$; 0.8%), dizziness ($n = 3$; 0.6%), diastolic blood pressure decreased ($n = 2$; 0.4%), prolonged corrected QT interval ($n = 2$; 0.4%), affect lability ($n = 2$; 0.4%), depression ($n = 2$; 0.4%), and upper abdominal pain ($n = 2$; 0.4%). Reasons for discontinuation in the placebo group included withdrawn consent ($n = 13$; 8.7%), AEs ($n = 6$; 4.0%), loss to follow-up ($n = 5$; 3.4%), protocol violation ($n = 2$; 1.3%), and other ($n = 29$; 19.5%); of the 29 subjects in the ''other'' category, 21 (72%) discontinued because of lack of efficacy. Further details on the safety results of these two studies can be found in Biederman et al. (study 1) (Biederman et al. 2008) and Sallee et al. (study 2) (Sallee et al. 2009).

Table 1. Subject Demographics (Safety Population)

Characteristics	*GXR* (n = *513*)	*Placebo* (n = *149*)
Age (years)		
Mean (SD)	10.4 (2.69)	10.7 (2.76)
Gender, *n* (%)		
Male	379 (73.9)	107 (71.8)
Female	134 (26.1)	42 (28.2)
Ethnic origin, *n* (%)[a]		
White	351 (68.4)	102 (68.5)
Black	79 (15.4)	22 (14.8)
Hispanic	48 (9.4)	14 (9.4)
Asian/Pacific Islander	9 (1.8)	1 (0.7)
Native American	2 (0.4)	0
Other	24 (4.7)	10 (6.7)
Weight (kg)		
Mean (SD)	43.6 (16.23)	43.8 (15.45)
ADHD Subtype, *n* (%)		
Inattentive	130 (25.3)	41 (27.5)
Hyperactive-Impulsive	9 (1.8)	3 (2.0)
Combined	374 (72.9)	105 (70.5)

[a]Percentages may total > 100 as a result of rounding.
GXR = guanfacine extended release; SD = standard deviation; ADHD = attention-deficit/hyperactivity disorder.

The full analysis set, which was used for all efficacy analyses, included 631 subjects; 490 received GXR and 141 received placebo. Only nine subjects in the GXR group and three subjects in the placebo group were identified with the predominantly hyperactive-impulsive subtype of ADHD, precluding further analysis regarding the efficacy of GXR in this subgroup. Of subjects who were identified as having the predominantly inattentive subtype of ADHD, 127 subjects received GXR and 38 received placebo. Of subjects who were identified as having the combined type ADHD, 354 received GXR and 100 received placebo.

Efficacy by ADHD subtype

To characterize the efficacy of GXR in reducing the core symptoms of ADHD in subjects with different subtypes of ADHD, the effects of treatment with GXR on ADHD-RS-IV total scores were examined in each subtype for which adequate data were available. Subjects in both the active treatment and placebo groups with predominantly inattentive ADHD had similar mean (SD)

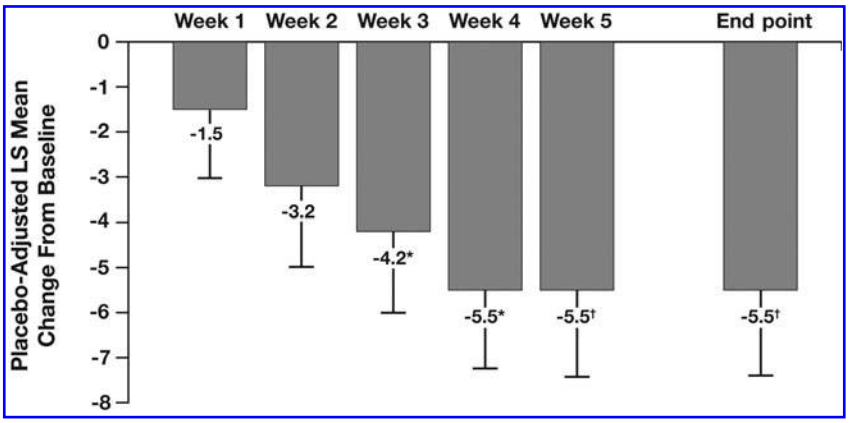

FIG. 2. Placebo-adjusted LS mean changes from baseline in ADHD-RS-IV total score among subjects with ADHD, predominantly the inattentive type. Significant improvements favoring GXR were seen at weeks 3, 4, and 5, and at end point. Plot represents data from subjects identified as predominantly having inattentive ADHD subtype in the full analysis set (placebo: $n = 38$ subjects; GXR: $n = 127$ subjects). A negative difference indicates a positive effect of the active treatment over placebo. End point is the last valid ADHD-RS-IV total score obtained post-baseline, before dose tapering. End point included data from visit 6 of study 2, although data from this visit are not presented individually because of the lack of corresponding data from study 1. *$p < 0.05$; †$p < 0.01$ (vs. placebo). LS = least squares; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; ADHD = attention-deficit/hyperactivity disorder; GXR = guanfacine extended release.

baseline ADHD-RS-IV total scores: 31.4 (7.93) in the placebo group and 30.9 (7.80) in the GXR group. Among the 127 subjects with this subtype of ADHD, significantly greater LS mean reductions from baseline in ADHD-RS-IV total scores were seen in the GXR group than in the placebo group at treatment weeks 3, 4, and 5 as well as at end point. Differences in LS mean changes from baseline between the GXR and placebo groups are shown in Fig. 2. At end point, subjects with predominantly inattentive ADHD receiving GXR exhibited an LS mean (SE) change from baseline of −14.7 (0.91) compared with −9.2 (1.67) for subjects receiving placebo ($p = 0.005$). At end point, the mean (SD) ADHD-RS-IV total score was 16.3 (10.02) for the GXR group and 22.0 (12.99) for the placebo group. The treatment effect size for GXR versus placebo in subjects with the inattentive subtype was 0.53.

More than two-thirds of subjects in the full analysis set were identified as having the combined subtype of ADHD. Baseline mean (SD) ADHD-RS-IV total scores for these subjects were similar between the GXR (41.6 [7.79]) and placebo (41.3 [7.93]) groups. At all time points analyzed (ie, weeks 1 to 5 and end point), treatment with GXR was associated with significantly greater LS mean improvements in ADHD-RS-IV total scores than was placebo. Differences in LS mean changes from baseline between the GXR and placebo groups are shown in Fig. 3. At end point, subjects with combined type ADHD receiving GXR exhibited an LS mean (SE) change from baseline of −19.7 (0.71) compared with −11.0 (1.34) for subjects receiving placebo ($p < 0.001$). The mean (SD) ADHD-RS-IV total scores of the GXR and placebo groups at end point were 21.9 (13.38) and 30.7 (15.20), respectively. The treatment effect size for GXR versus placebo in subjects with the combined subtype was 0.65.

At baseline, the nine subjects with predominantly hyperactive-impulsive ADHD who were treated with GXR exhibited a mean

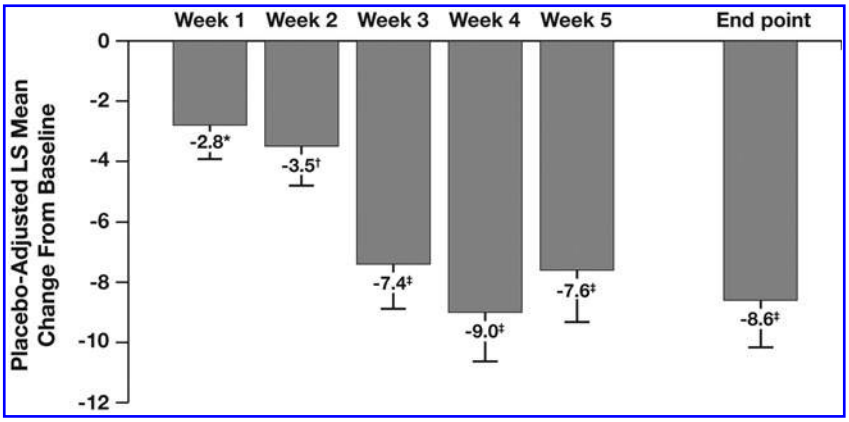

FIG. 3. Placebo-adjusted LS mean changes from baseline in ADHD-RS-IV total score among subjects with ADHD, combined type. Significant improvements favoring GXR were seen at all analyzed time points. Plot represents data from subjects identified as having combined ADHD subtype in the full analysis set (placebo: $n = 100$ subjects; GXR: $n = 354$ subjects). A negative difference indicates a positive effect of the active treatment over placebo. End point is the last valid ADHD-RS-IV total score obtained post-baseline, before dose tapering. End point included data from visit 6 of study 2, although data from this visit are not presented individually because of the lack of corresponding data from study 1. *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ (vs. placebo). LS = least squares; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; ADHD = attention-deficit/hyperactivity disorder; GXR = guanfacine extended release.

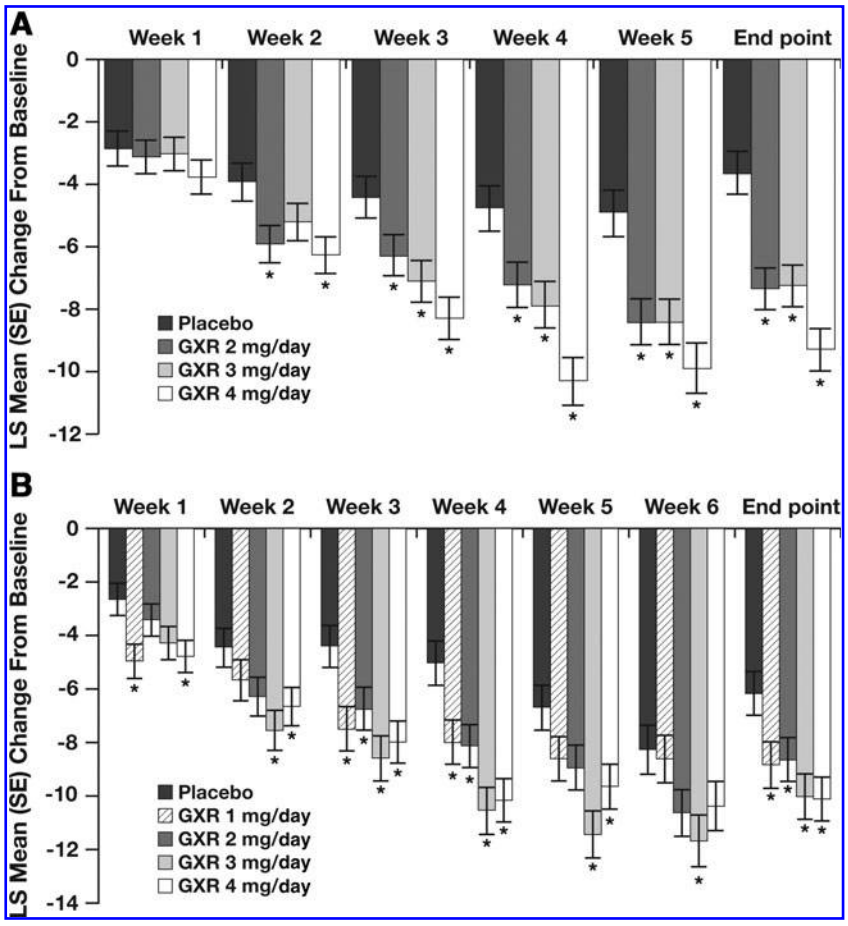

FIG. 4. LS mean (SE) change from baseline in ADHD-RS-IV Hyperactivity-Impulsivity subscale scores by randomized treatment group in **(A)** study 1 (placebo: $n=78$ subjects; GXR 2 mg/day: $n=84$ subjects; GXR 3 mg/day: $n=82$ subjects; GXR 4 mg/day: $n=81$ subjects [ITT population]) and **(B)** study 2 (placebo: $n=63$ subjects; GXR 1 mg/day: $n=57$ subjects; GXR 2 mg/day: $n=63$ subjects; GXR 3 mg/day: $n=60$ subjects; GXR 4 mg/day: $n=63$ subjects [ITT populations]). A reduction in ADHD-RS-IV subscale score from baseline indicates improvement. End point is the last valid ADHD-RS-IV Hyperactivity-Impulsivity subscale score obtained post-baseline, before dose tapering. *$p<0.05$ (vs. placebo). Only subjects weighing < 50 kg were eligible to be randomized into the 1 mg/day GXR treatment group (Sallee et al. 2009). LS = least squares; SE = standard error; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; ITT = intent-to-treat; GXR = guanfacine extended release.

(SD) ADHD-RS-IV total score of 31.7 (7.5) whereas the three subjects receiving placebo exhibited considerably higher baseline scores (41.3 [13.01]). At end point, the GXR-treated subjects exhibited a mean (SD) ADHD-RS-IV total score change from baseline of −9.8 (15.34) compared with −11.0 (8.89) among the three subjects with this subtype who were treated with placebo. The limited number of subjects with predominantly hyperactive-impulsive ADHD prevented formal statistical analysis of this group of subjects, as low sample sizes would provide unreliable estimates of treatment effects.

ADHD-RS-IV subscale analysis – efficacy by randomized dose groups

In study 1, mean (SD) ADHD-RS-IV Hyperactivity-Impulsivity subscale scores were similar among all treatment groups at baseline. All dose groups also exhibited significant changes (vs. placebo; $p<0.05$ for all) from week 3 through end point (Fig. 4A). At end point, placebo-adjusted LS mean changes from baseline were significant for all randomized dose groups: −3.68 in the 2 mg/day group ($p=0.0002$), −3.58 in the 3 mg/day group ($p=0.0003$), and −5.62 in the 4 mg/day group ($p<0.0001$). Effect sizes were 0.60, 0.59, and 0.92 for the 2, 3, and 4 mg/day groups, respectively. In study 2, ADHD-RS-IV Hyperactivity-Impulsivity subscale scores were largely similar among randomized treatment groups, although the 1 mg/day GXR group had an LS mean baseline score that was greater than that of the placebo group (19.6 vs. 17.1; $p=0.04$). At end point, placebo-adjusted LS mean changes from baseline were significant for all randomized dose groups: −2.65 ($p=0.0280$), −2.48 ($p=0.0340$), −3.85 ($p=0.0012$), and −3.94 ($p=0.0008$) for the 1, 2, 3, and 4 mg/day groups, respectively. Effect sizes were 0.41, 0.38, 0.59, and 0.60 for the 1, 2, 3, and 4 mg/day groups, respectively. Significant improvements were also observed in all dose groups at weeks 3 and 4 ($p<0.05$ for all) (Fig. 4B).

In study 1, all doses of GXR were associated with significantly greater LS mean reductions in ADHD-RS-IV Inattentiveness subscale scores than was placebo at weeks 3, 4, and 5, and end point (Fig. 5A). At end point, placebo-adjusted LS mean changes from baseline were −3.74 ($p=0.0009$), −3.94 ($p=0.0005$), and −4.26 ($p=0.0002$) in the 2, 3, and 4 mg/day dose groups, respectively. Effect sizes were 0.53, 0.55, and 0.60 for the 2, 3, and 4 mg/day groups, respectively. Among subjects in study 2, all GXR doses

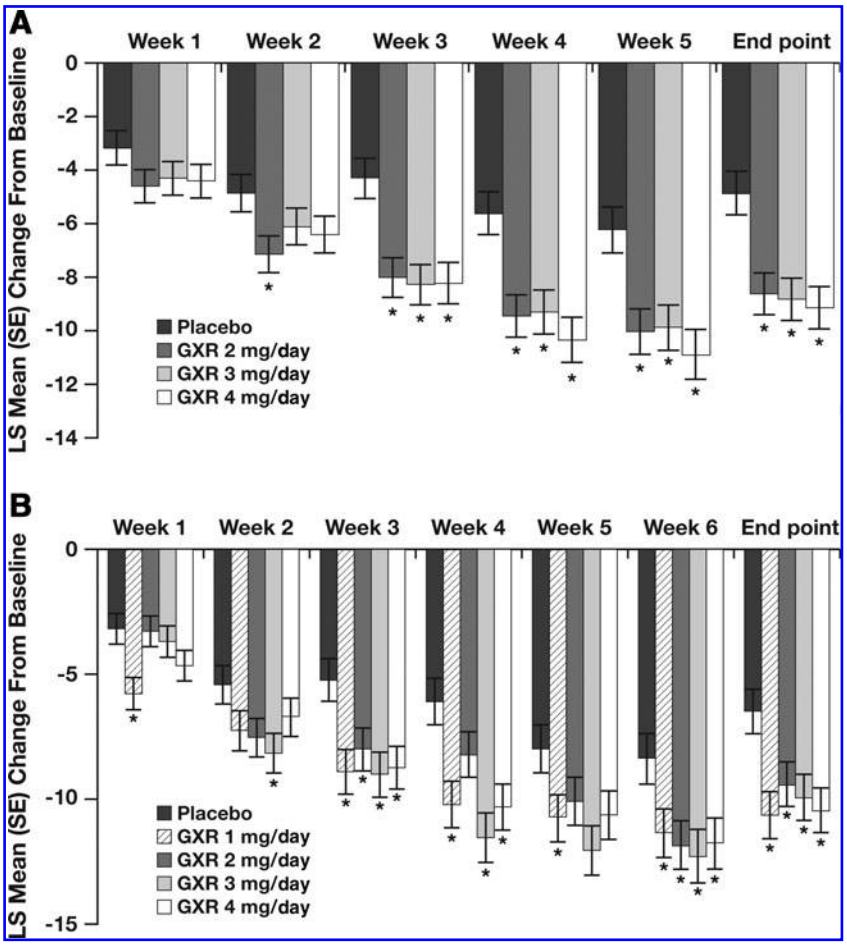

FIG. 5. LS mean (SE) change from baseline in ADHD-RS-IV Inattentiveness subscale scores by randomized treatment group in **(A)** study 1 (placebo: $n=78$ subjects; GXR 2 mg/day: $n=84$ subjects; GXR 3 mg/day: $n=82$ subjects; GXR 4 mg/day: $n=81$ subjects [ITT population]) and **(B)** study 2 (placebo: $n=63$ subjects; GXR 1 mg/day: $n=57$ subjects; GXR 2 mg/day: $n=63$ subjects; GXR 3 mg/day: $n=60$ subjects; GXR 4 mg/day: $n=63$ subjects [ITT populations]). A reduction in ADHD-RS-IV subscale score from baseline indicates improvement. End point is the last valid ADHD-RS-IV Inattentiveness subscale score obtained post-baseline, before dose tapering. $^*p<0.05$ (vs placebo). Only subjects weighing <50 kg were eligible to be randomized into the 1 mg/day GXR treatment group (Sallee et al. 2009). LS = least squares; SE = standard error; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; ITT = intent-to-treat; GXR = guanfacine extended release.

were associated with significantly greater LS mean reductions in ADHD-RS-IV Inattentiveness subscale scores than was placebo at weeks 3 and 6, in addition to end point (Fig. 5B). At end point, subjects receiving 1, 2, 3, and 4 mg/day of GXR exhibited placebo-adjusted LS mean changes from baseline of -4.16 ($p=0.0015$), -2.96 ($p=0.0197$), -3.47 ($p=0.0070$), and -3.99 ($p=0.0017$), respectively. Effect sizes were 0.59, 0.42, 0.49, and 0.56 for the 1, 2, 3, and 4 mg/day groups, respectively.

Discussion

Using a study population derived from two large pivotal trials, this analysis demonstrated that GXR reduced symptoms of both hyperactivity-impulsivity and inattentiveness as assessed by ADHD-RS-IV subscale scores. Compared with placebo, significant improvements in both subscales were evident for all GXR dose groups at end point.

The ability of GXR to help reduce the core symptoms of ADHD was also demonstrated across ADHD subtypes. The pooled population derived from two large pivotal trials was used to provide sufficient sample size and associated statistical power for the analysis. By week 3, subjects with either the combined or predominantly inattentive subtype of ADHD treated with GXR demonstrated significantly greater improvements than those given placebo. Whereas GXR-treated subjects with combined type ADHD had greater LS mean placebo-adjusted improvements from baseline at all time points than subjects with the predominantly inattentive subtype, such differences may represent dissimilarity of baseline symptoms of the two groups. At baseline, subjects with combined type ADHD had greater ADHD-RS-IV total scores than did subjects with the predominantly inattentive type. This pattern is consistent with data obtained during development of the ADHD-RS-IV, in which subjects with the combined subtype of ADHD who had not received treatment for ADHD or a related disorder within 6 months of evaluation had significantly higher Hyperactivity-Impulsivity subscale scores than did subjects with the predominantly inattentive subtype (DuPaul et al. 1998). These higher Hyperactivity-Impulsivity subscale scores could have contributed to higher total scores despite a lack of significant differences in inattentive subscale scores between the two subtypes. The ability of

GXR to reduce symptoms of inattention is also highlighted by the fact that most subjects with predominantly inattentive ADHD receiving treatment with GXR had end point ADHD-RS-IV total scores < 18 (median = 15), a cutoff frequently used to define remission (Steele et al. 2006).

Overall, significant improvements in symptoms of inattention were observed with GXR treatment as demonstrated by reductions in both ADHD-RS-IV Inattention subscale scores in the full analysis set as well as reductions in ADHD-RS-IV total scores in subjects with the predominantly inattentive subtype of ADHD. These improvements contradict suggestions that GXR might diminish the symptoms of ADHD through sedative effects. These results are also consistent with data from a prior laboratory classroom study which, based on results from a series of cognitive tasks, concluded that the beneficial effects of GXR on ADHD symptoms are unlikely to be caused by sedative side effects (Kollins et al. 2011). Similarly, a small study ($n = 34$) of children and adolescents with ADHD and tic disorders found that treatment with immediate-release guanfacine (0.5 mg in the morning, afternoon, and at bedtime; total dose of 1.5 mg/day) was associated with significant reductions in ADHD-RS total scores as well as Hyperactivity-Impulsivity and Inattentiveness subscale scores (Scahill et al. 2001). In addition, errors of both commission and omission were reduced on the Continuous Performance Test.

Further support for the separation between the sedative effects and the efficacy of guanfacine can be gleaned from the results of the individual pivotal trials of GXR (Biederman et al. 2008; Sallee et al. 2009). Both trials found that GXR was efficacious as monotherapy for ADHD. In both studies, treatment with GXR resulted in significant reductions in ADHD-RS-IV total scores as well as Hyperactivity-Impulsivity and Inattentiveness subscale scores. One of the pivotal trials (study 2) also showed no difference between GXR and placebo in terms of sleepiness, as measured by the Pediatric Daytime Sleepiness Scale (Sallee et al. 2009).

Limitations

The results of the present analysis should be viewed in light of several limitations. Inter-rater reliability checks were not performed in either study. Both trials analyzed used a fixed dose-escalation design that does not reflect clinical practice in which doses are titrated to optimal efficacy, tolerability, and safety. Additionally, whereas in community samples of patients with ADHD, clinicians encounter psychiatric comorbidities, cardiovascular dysfunction, blood pressure abnormalities, and other medical conditions (e.g., seizures), subjects with these conditions were excluded from the pivotal trials of GXR. Furthermore, the low number of hyperactive-impulsive subtype subjects ($n = 12$) precluded statistical analysis of that group, and suggests the need for future studies focused on this ADHD subtype. Given that only 426 of the 662 subjects in the combined safety population completed the trials, as well as the limitations of combining two studies in a *post-hoc* analysis, it should also be noted that the findings of this analysis are exploratory rather than confirmatory.

Because of differences in dose-titration schedules and the need to achieve adequate sample sizes to ensure statistical power, efficacy analyses were limited to comparing the active treatment group with the placebo group, thereby preventing evaluation of dose response in subjects with either the predominantly inattentive or combined subtype of ADHD. In addition, when individual GXR dose groups were examined, all groups reached statistical significance compared with placebo, limiting the utility of these data in providing clinical guidance with regard to appropriate doses of GXR. Prior analyses, however, have suggested a positive dose-response relationship for GXR when results were analyzed by actual weight-adjusted dose (Biederman et al. 2008; Sallee et al. 2009). Finally, because the included trials were short term in design, conclusions regarding the long-term safety and efficacy of GXR cannot be inferred from this data set.

Notably, the validity of this analysis is limited by the validity of the DSM-IV-defined subtypes of ADHD. Although the DSM-IV-TR is routinely used in clinical practice and some studies support the current classification system (Willcutt et al. 2001; Lahey et al. 2005, 2008), several concerns regarding the DSM-IV classification system have been raised. Specifically, the view that ADHD subtypes are discrete entities, which remain stable over time, has been challenged (Lahey et al. 2005; Solanto et al. 2007; Todd et al. 2008). For example, in an 8-year longitudinal study, Lahey et al. demonstrated that although the diagnosis of ADHD was stable over time, shifts in subtypes were common, occurring at least once in more than two-thirds of patients (Lahey et al. 2005). Data from adults also suggest instability of ADHD subtypes over time (Sobanski et al. 2008). The tendency for children initially diagnosed as predominantly hyperactive-impulsive to later meet criteria for the combined subtype in concert with functional similarities between the two subtypes has led to suggestions that the hyperactive-impulsive subtype is an early form of the combined subtype, rather than representing a distinct subtype (Riley et al. 2008). At the other end of the spectrum, researchers have proposed that the combined and inattentive subtypes of ADHD may be distinct unrelated disorders (Lahey 2001; Milich et al. 2001; Solanto et al. 2007). Data generated during the development of the forthcoming DSM-V may shed further light on the validity and utility of the current subtype classification.

Finally, the 30% attrition rate observed across GXR and placebo groups in the current report is within the range of dropout rates observed for a similar short-term study of extended-release clonidine for treating ADHD in children and adolescents (Jain et al. 2011), and is also consistent with some trials of amphetamine for treating adult ADHD (Castells et al. 2011). As has been discussed with regard to studies of psychostimulant treatments for ADHD, this dropout rate may indicate that some patients did not tolerate the intervention. However, these dropouts caused by side effects in the active drug groups should theoretically be balanced by dropouts caused by lack of efficacy in the placebo groups (Castells et al. 2011). This sentiment is supported by the current data that whereas there were three times as many dropouts caused by AEs reported for GXR than for placebo groups (11.9% vs. 4%, respectively), 72% of subjects leaving for ''other'' reasons in the placebo groups reported doing so because of lack of efficacy. Regardless, the end point analysis used in the current study should have mitigated any effects caused by study attrition that may have confounded interpretation of the data.

Conclusions

Notwithstanding the abovementioned limitations, the present analysis demonstrated the efficacy of GXR in the treatment of both hyperactive-impulsive and inattentive symptoms of ADHD by examining subjects with either the combined or predominantly inattentive subtypes of ADHD as well as by examining ADHD-RS-IV Hyperactivity-Impulsivity and Inattentiveness subscale scores. These analyses further support the efficacy of GXR in

treating all of the core symptoms of ADHD, including hyperactivity and impulsivity, as well as inattentiveness.

Clinical significance

GXR is approved by the United States Food and Drug Administration for the treatment of ADHD in children and adolescents aged 6–17 years (Intuniv [package insert] 2011). This pooled analysis, using study cohorts from two large pivotal trials (Biederman et al. 2008; Sallee et al. 2009), demonstrated that GXR reduced symptoms of both hyperactivity-impulsivity and inattentiveness as assessed by ADHD-RS-IV subscale scores. In addition, subjects with either the combined or predominantly inattentive subtype of ADHD treated with GXR demonstrated significantly greater improvements than those given placebo. Overall, this *post-hoc* analysis demonstrated the efficacy of GXR in the treatment of both hyperactive-impulsive and inattentive symptoms of ADHD.

Disclosures

Dr. Sallee is a grant awardee of Shire Development LLC and a consultant for AstraZeneca, NextWave Pharma, Otsuka America Pharmaceutical Inc., Sepracor, Shire Development Inc., and Shionogi Pharma. He is on the board of directors for P2D Inc. and is a shareholder in P2D Inc. He is also founder and principal in Satiety Solutions, LLC.

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