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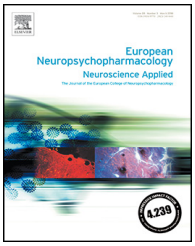

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Distinguishing the efficacy and sedative effects of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder

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Abstract
The present study investigated whether symptom reduction in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) treated with guanfacine extended release (GXR) can be explained by sedative effects of the medication. Data from four double-blind, randomized, placebo-controlled, phase 3 trials of GXR monotherapy (1–7 mg/day; morning administration) in children (aged 6–12 years) and adolescents (aged 13–17 years) with ADHD were analyzed *post hoc*. Two studies used forced-dose titration and two used flexible-dose titration. Efficacy was determined using ADHD Rating Scale IV (ADHD-RS-IV) scores. Sedative treatment-emergent adverse events (TEAEs) included somnolence, sedation and hypersomnia. The proportion of responders (≥ 30% reduction in ADHD-RS-IV total score) increased from weeks 1 to 4 and remained stable to study endpoint. Sedative TEAEs generally peaked at the first week

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in which the target dose was achieved and then declined. In subgroup analyses, significant placebo-adjusted improvements in ADHD-RS-IV total scores were observed in participants without any sedative TEAEs in the forced-dose and flexible-dose studies (nominal $p < 0.001$). In addition, GXR was associated with significant improvements in both inattentive and hyperactive-impulsive symptoms, as assessed by the ADHD-RS-IV subscale scores (nominal $p < 0.001$) and by the ADHD-RS-IV total score in participants with different ADHD subtypes (nominal $p < 0.05$). Thus, the efficacy of GXR in children and adolescents with ADHD is not primarily due to sedation, although some contribution to symptom reduction cannot be excluded, especially early in treatment when rates of sedative TEAEs are at their highest.

1. Introduction

Pharmacotherapy reduces the symptoms of attention-deficit/hyperactivity disorder (ADHD) and improves functional outcomes such as academic performance and social function (Arnold et al., 2015). Stimulants are usually the first-line treatment option for children and adolescents with ADHD but may be ineffective, poorly tolerated, contraindicated, or undesirable in some patients.

Guanfacine extended release (GXR) is a non-stimulant medication used for the treatment of ADHD in children (aged 6–12 years) and adolescents (aged 13–17 years). Guanfacine binds to the α_{2A} adrenergic receptor, and preclinical data indicate that stimulation of post-synaptic α_{2A} receptors by α_2-agonist non-stimulant medications modulates noradrenergic neurotransmission in the prefrontal cortex, thereby strengthening cognitive function, which is typically impaired in children and adolescents with ADHD (Arnsten and Jin, 2012; Huss et al., 2016; Wang et al., 2007). In Europe, GXR is approved as a monotherapy when stimulants are not suitable, not tolerated or ineffective (Shire Pharmaceuticals LTD, December 2015). GXR is also approved in the USA and Canada as a monotherapy and as an adjunct to stimulant therapy.

The efficacy of GXR monotherapy has been established in a series of double-blind, randomized, placebo-controlled phase 3 trials in children and adolescents with ADHD. SPD503-301 and SPD503-304 were pivotal studies of forced-dose GXR (1–4 mg/day) for 5–6 weeks (Biederman et al., 2008b; Sallee et al., 2009b); SPD503-312 (adolescents only) and SPD503-316 were studies of flexible-dose GXR (1–7 mg/day) for 10–13 weeks (Hervas et al., 2014; Wilens et al., 2015). In these studies, GXR resulted in statistically significant and clinically relevant reductions in ADHD Rating Scale IV (ADHD-RS-IV) total scores compared with placebo, with effect sizes ranging from 0.43 to 0.86 (Biederman et al., 2008b; Hervas et al., 2014; Sallee et al., 2009b; Wilens et al., 2015).

Sedative effects are common in patients treated with α_2-adrenergic receptor agonists (Connor et al., 2010; Hazell and Stuart, 2003; Palumbo et al., 2008), and somnolence was the most frequently reported treatment-emergent adverse event (TEAE) in phase 3 trials of GXR (24–44% of participants) (Biederman et al., 2008b; Hervas et al., 2014; Sallee et al., 2009b; Wilens et al., 2015). Sedative TEAEs generally occurred within the first few weeks after initiation of GXR but decreased with continued treatment (Biederman et al., 2008b; Sallee et al., 2009b). Indeed, a predictor analysis of sedative TEAEs identified treatment duration as the only factor that predicted emergence and magnitude of sedative TEAEs with GXR, with the likelihood of sedation decreasing with increasing time on GXR (Faraone and Glatt, 2010).

The present *post hoc* analyses investigated whether the reduction in ADHD symptoms observed with GXR treatment is primarily related to sedation. Three different approaches were applied using data from four double-blind, randomized, placebo-controlled studies of GXR (SPD503-301, SPD503-304, SPD503-312, and SPD503-316): first, the temporal profiles of symptom reduction and the prevalence of sedative TEAEs were compared; second, the efficacy of GXR was evaluated based on the presence or absence of sedative TEAEs; third, the efficacy of GXR on different symptom types, especially inattention, was assessed based on ADHD-RS-IV subscale scores in all participants and ADHD-RS-IV total scores in participants with different ADHD subtypes.

2. Experimental procedures

2.1. Ethics and conduct

The study protocols, protocol amendments, protocol administrative changes, informed consent and assent documents, and all relevant recruitment information, were approved by the study centers' ethics committees and regulatory agencies before study initiation (protocol) or implementation (amendments). The studies were performed in accordance with the International Conference on Harmonization of Good Clinical Practice under the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant's parent or legal guardian before enrolment in each study and written assent was obtained from each participant (where applicable).

2.2. Participants

The present *post hoc* analyses used data from four double-blind, randomized, placebo-controlled, multicenter, phase 3 studies that assessed the efficacy and safety of GXR monotherapy (administered in the morning) in children (aged 6–12 years) and/or adolescents (aged 13–17

years) with ADHD (SPD503-301, SPD503-304, SPD503-312 and SPD503-316; Fig. S1). Full participant inclusion and exclusion criteria for all four studies have been published previously (Biederman et al., 2008b; Hervas et al., 2014; Sallee et al., 2009b; Wilens et al., 2015). In brief, in all four studies individuals were eligible for inclusion if they met criteria for a primary diagnosis of ADHD set out in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. In all four studies, key exclusion criteria included the presence of a current comorbid psychiatric diagnosis other than oppositional defiant disorder.

2.3. Study designs

SPD503-301 (NCT00152009; USA) (Biederman et al., 2008b) and SPD503-304 (NCT00150618; USA) (Sallee et al., 2009b) were forced-dose titration studies in which participants were randomized 1:1:1:1 to receive GXR 2, 3 or 4 mg/day or placebo (SPD503-301), or 1:1:1:1:1 to receive GXR 1, 2, 3 or 4 mg/day or placebo (SPD503-304). The double-blind treatment period was 8 weeks (SPD503-301) or 9 weeks (SPD503-304) and included up to 3 weeks of dose escalation and 3 weeks of dose tapering. During dose escalation, GXR was initiated at 1 mg/day and increased weekly by 1 mg increments until the randomized dose was reached (see Fig. S1 for details of dosing schedules).

SPD503-312 (NCT01081132; USA) (Wilens et al., 2015) and SPD503-316 (NCT01244490; USA, Canada and Europe) (Hervas et al., 2014) were flexible-dose titration studies in which participants were randomized 1:1 to receive GXR or placebo (SPD503-312), or 1:1:1 to receive GXR, placebo or atomoxetine (SPD503-316). Atomoxetine was included as a reference therapy in SPD503-316 only so data from this treatment arm were excluded from the current pooled analyses. The double-blind treatment period consisted of 4 weeks (children) or 7 weeks (adolescents) of dose optimization, 6 weeks of dose maintenance and 2 weeks of dose tapering. GXR was initiated at 1 mg/day and increased weekly by 1 mg increments until an 'acceptable' response was achieved (defined as $\geq$ 30% reduction from baseline in ADHD-RS-IV total score and a Clinical Global Impressions-Improvement score of 1 or 2, with tolerable side effects). The maximum permitted GXR dose was 4 mg/day for children and 4–7 mg/day (depending on body weight) for adolescents.

2.4. Analyses

Three different analyses were performed to investigate whether symptom reduction is primarily related to sedation based on two pools of data derived from forced-dose titration (SPD503-301 and SPD503-304) and flexible-dose titration (SPD503-312 and SPD503-316) trials of GXR.

1. Comparison of the temporal profiles of the proportion of patients with a treatment response and the prevalence of sedative TEAEs. Treatment response was defined as $\geq$ 30% reduction from baseline in ADHD-RS-IV total score, and was assessed at each week through to endpoint (defined as the last post-randomization week before dose tapering for which a valid ADHD-RS-IV score was obtained). The prevalence of new or ongoing sedative TEAEs was analyzed at each week from baseline through to the last post-randomization, on-treatment week including dose tapering. Sedative TEAEs were defined by the sponsor as somnolence, sedation or hypersomnia, were assessed by the investigator, and were coded using the Medical Dictionary for Regulatory Activities version 12.1. Both time-course analyses assessed outcomes by individual GXR dosing groups (randomized dose); the time-course analysis of sedative TEAEs was also assessed by actual GXR dose received. Pooled data from the forced-dose studies (SPD503-301 and SPD503-304) were used for these analyses; data from the flexible-dose studies (SPD503-312 and SPD503-316) were not included because of the personalized response- and tolerability-guided GXR dosing scheme in these trials which would have made it difficult to observe clear temporal trends.
2. Efficacy of GXR in subgroups of patients with and without sedative TEAEs, based on change from baseline to endpoint in ADHD-RS-IV total scores. The presence of sedative TEAEs was assessed cumulatively through to the last post-randomization, on-treatment week including dose tapering.
3. Efficacy of GXR on symptoms of inattention and hyperactivity-impulsivity, based on change from baseline to endpoint in i) ADHD-RS-IV subscale scores in all participants, and ii) ADHD-RS-IV total scores in subgroups of patients with different ADHD subtypes. Because the number of patients with the predominantly hyperactive–impulsive subtype was low, these patients were assessed together with patients of the combined subtype.

Analyses 2 and 3 were performed for the pooled forced-dose studies SPD503-301 and SPD503-304, and the pooled flexible-dose studies SPD503-312 and SPD503-316. GXR dosing groups were combined in each dataset.

2.5. Statistical analysis

The analysis of sedative TEAEs from baseline to the last on-treatment assessment was based on the safety populations of the two pooled datasets, defined as all randomized participants who received at least one dose of the investigational drug. For the overall summary of sedative TEAEs, cumulative occurrence through to the last on-treatment week, mean day of onset, and mean duration were analyzed descriptively.

Efficacy analyses were based on the full analysis set (FAS), defined as all randomized participants with at least one post-baseline assessment (pooled SPD503-301 and SPD503-304), or all randomized participants who received at least one dose of the investigational drug (pooled SPD503-312 and SPD503-316). Missing data were handled using the last observation carried forward (LOCF) method to ensure that treatment response was not overestimated when individuals discontinued treatment because of lack of effect. LOCF was not applicable for the safety analyses.

The change from baseline to endpoint in ADHD-RS-IV scores (analyses 2 and 3) was analyzed using an analysis of covariance model, with the baseline value as a covariate and the treatment group, age group and study as fixed ef-

fects; in the pooled flexible-dose studies, country was also included as a fixed effect. All *p* values are nominal (unadjusted for multiplicity).

3. Results

3.1. Participant disposition, demographics and disease characteristics

Participant disposition and baseline characteristics for each of the four individual GXR studies have been reported previously (Biederman et al., 2008b; Hervas et al., 2014; Sallee et al., 2009b; Wilens et al., 2015). In the present analyses, the safety population from the pooled forced-dose studies comprised 513 participants receiving GXR and 149 receiving placebo; two GXR-randomized and three placebo-randomized participants were never treated and were therefore excluded from the safety population. The FAS comprised 490 participants receiving GXR and 141 receiving placebo. In the pooled flexible-dose studies, the safety population and FAS both comprised 271 participants receiving GXR and 266 receiving placebo. Five GXR-treated participants in the FAS of the pooled flexible-dose studies had no post-baseline ADHD-RS-IV measurement and were excluded from the current efficacy analyses (based on LOCF).

Baseline demographics and disease characteristics were similar across GXR and placebo groups in both pooled datasets (Table S1). The majority of participants were male (64.9–77.5%), white (66.0–70.7%) and had the combined ADHD subtype (68.7–77.2%). Because the number of participants with the predominantly hyperactive-impulsive ADHD subtype was low, this group was merged with the combined ADHD subtype in subsequent analyses. The mean age in the pooled flexible-dose studies was higher (13.0–13.1 years) than in the pooled forced-dose studies (9.2–10.9 years) because study SPD503-312 enrolled only adolescents.

3.2. Sedative TEAEs in pooled forced-dose and pooled flexible-dose studies

The cumulative occurrence of sedative TEAEs reported in the pooled forced-dose studies is summarized in Table 1. Overall, sedative TEAEs were observed in 38.4% of participants receiving GXR and 12.1% receiving placebo. The proportion of participants with one or more sedative TEAEs increased with the GXR dose. Across all GXR doses, the mean day of reported onset of sedative TEAEs was 12.0 days after treatment initiation (placebo, 6.4 days), and most events resolved spontaneously by the end of the taper period. The mean duration of individual sedative TEAEs was 18.0 days in participants receiving GXR, compared with 27.0 days in those receiving placebo. The most common sedative TEAE was somnolence, which was reported in 29.2% of participants receiving GXR and 6.7% receiving placebo. Hypersomnia was rarely reported, with only two events recorded (one each with GXR and placebo). The proportion of sedative TEAEs that led to drug withdrawal was 11.8% for GXR and 5.3% for placebo.

Sedative TEAEs associated with GXR were more common in the pooled flexible-dose studies than in the pooled forced-dose studies (50.2% versus 38.4%; Table S2) whereas the mean day of reported onset (15.5 versus 12.0 days) and the mean duration (21.3 versus 18.0 days) of sedative TEAEs were similar in both pooled datasets. The proportion of sedative TEAEs that led to withdrawal of GXR was greater in the forced-dose studies than that in the flexible-dose studies (1.8%).

3.3. Time courses of treatment response and sedative TEAEs in the pooled forced-dose studies

To investigate whether symptomatic improvement was associated with the occurrence of sedative TEAEs, we first assessed whether these outcomes had similar temporal profiles during GXR treatment. Fig. 1 shows the time course of treatment response (as assessed/shown by the proportions of participants with $\geq$ 30% reduction from baseline in ADHD-RS-IV total score) in the pooled forced-dose studies (findings shown by randomized dose). In all GXR dose groups, the proportion of responders increased from weeks 1 to 4 and then remained stable through to study endpoint, when response rates were 66.7–72.2% (depending on dose group). In contrast, the prevalence of sedative TEAEs generally peaked during the first week in which the target dose was achieved, and subsequently decreased over the course of treatment to the end of the dose taper period (Fig. 2A shows findings by randomized dose; Fig. 2B shows findings by actual dose received at the indicated study visit).

3.4. ADHD-RS-IV total scores in participants with and without sedative TEAEs in the pooled forced-dose and pooled flexible-dose studies

If symptomatic improvement was secondary to sedation, limited improvement would be expected in the absence of any sedative TEAEs. We therefore assessed changes in ADHD-RS-IV total scores in subgroups of participants with and without sedative effects. In participants without any sedative TEAEs, the least-squares (LS) mean changes from baseline to endpoint in ADHD-RS-IV total scores were significantly greater with GXR than with placebo in both forced-dose (effect size [ES] 0.49; nominal $p < 0.001$) and flexible-dose studies (ES 0.67; nominal $p < 0.001$) (Fig. 3). In participants with sedative TEAEs, the placebo-adjusted LS mean changes in ADHD-RS-IV total scores with GXR were not significant. However it is important to note that in both pooled datasets, participants randomized to placebo who reported sedative TEAEs comprised a small subgroup that had large reductions in ADHD-RS-IV total scores.

3.5. ADHD-RS-IV subscale scores and ADHD-RS-IV total scores by ADHD subtype in the pooled forced-dose and pooled flexible-dose studies

Finally, we assessed the effect of GXR on symptoms of inattention (based on ADHD-RS-IV subscale scores in all par-

Table 1 Cumulative sedative TEAEs reported in the pooled forced-dose studies SPD503-301 and SPD503-304, by randomized dose of GXR (safety population).

	Placebo	GXR				
	($n = 149$)	1 mg[a] ($n = 61$)	2 mg ($n = 150$)	3 mg ($n = 151$)	4 mg ($n = 151$)	All doses ($n = 513$)
Sedative TEAEs (sedation, somnolence and hypersomnia)						
Total, *n*	19	20	62	73	100	255
Participants with ≥ 1, *n* (%)[b]	18 (12.1)	17 (27.9)	45 (30.0)	58 (38.4)	77 (51.0)	197 (38.4)
Day of onset, mean (SD)[c]	6.4 (5.90)	6.5 (5.78)	10.0 (11.54)	14.3 (10.86)	12.5 (10.03)	12.0 (10.54)
Duration of individual events, days, mean (SD)[d]	27.0 (20.57)	14.8 (16.65)	15.4 (16.29)	20.5 (18.19)	18.5 (15.17)	18.0 (16.50)
Severity *n* (%)[e,f]						
Mild	12 (63.2)	12 (60.0)	42 (67.7)	44 (60.3)	48 (48.0)	146 (57.3)
Moderate	6 (31.6)	7 (35.0)	19 (30.6)	26 (35.6)	42 (42.0)	94 (36.9)
Severe	1 (5.3)	1 (5.0)	1 (1.6)	3 (4.1)	10 (10.0)	15 (5.9)
Unresolved, *n* (%)[e]	5 (26.3)	5 (25.0)	8 (12.9)	8 (11.0)	11 (11.0)	32 (12.5)
Leading to drug withdrawal, *n* (%)[e]	1 (5.3)	2 (10.0)	5 (8.1)	6 (8.2)	17 (17.0)	30 (11.8)
Sedation						
Total, n	8	1	19	19	22	61
Participants with ≥ 1, *n* (%)[b]	7 (4.7)	1 (1.6)	15 (10.0)	15 (9.9)	20 (13.2)	51 (9.9)
Day of onset, mean (SD)[c]	8.0 (7.92)	9.0 (N/A)	6.5 (6.07)	12.7 (8.76)	12.9 (11.17)	10.9 (9.37)
Duration of individual events, days, mean (SD)[d]	18.6 (16.82)	24.0 (N/A)	20.5 (20.89)	22.2 (19.49)	14.3 (14.60)	18.8 (18.22)
Severity *n* (%)[e,f]						
Mild	5 (62.5)	1 (100)	12 (63.2)	14 (73.7)	6 (27.3)	33 (54.1)
Moderate	2 (25.0)	0 (0.0)	7 (36.8)	5 (26.3)	8 (36.4)	20 (32.8)
Severe	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (36.4)	8 (13.1)
Unresolved, *n* (%)[e]	1 (12.5)	0 (0.0)	3 (15.8)	1 (5.3)	0 (0.0)	4 (6.6)
Leading to drug withdrawal, *n* (%)[e]	1 (12.5)	0 (0.0)	2 (10.5)	1 (5.3)	8 (36.4)	11 (18.0)
Somnolence						
Total, n	10	19	42	54	78	193
Participants with ≥ 1, *n* (%)[b]	10 (6.7)	16 (26.2)	31 (20.7)	43 (28.5)	60 (39.7)	150 (29.2)
Day of onset, mean (SD)[c]	5.6 (4.48)	6.4 (5.93)	11.7 (13.00)	14.9 (11.55)	13.1 (10.15)	12.6 (11.04)
Duration of individual events, days, mean (SD)[d]	32.6 (22.71)	14.3 (16.96)	13.3 (13.63)	19.9 (17.87)	19.6 (15.21)	17.8 (16.00)
Severity *n* (%)[e,f]						
Mild	6 (60.0)	11 (57.9)	29 (69.0)	30 (55.6)	42 (53.8)	112 (58.0)
Moderate	4 (40.0)	7 (36.8)	12 (28.6)	21 (38.9)	34 (43.6)	74 (38.3)
Severe	0 (0.0)	1 (5.3)	1 (2.4)	3 (5.6)	2 (2.6)	7 (3.6)
Unresolved, *n* (%)[e]	3 (30.0)	5 (26.3)	5 (11.9)	7 (13.0)	11 (14.1)	28 (14.5)
Leading to drug withdrawal, *n* (%)[e]	0 (0.0)	2 (10.5)	3 (7.1)	5 (9.3)	9 (11.5)	19 (9.8)
Hypersomnia						
Total, n	1	0 (0.0)	1	0 (0.0)	0 (0.0)	1
Participants with ≥ 1, *n* (%)[b]	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Day of onset, mean (SD)[c]	3.0 (N/A)	-	15.0 (N/A)	-	-	15.0 (N/A)

(*continued on next page*)

Table 1 (*continued*)

	Placebo	GXR				
	($n=149$)	1 mg[a] ($n=61$)	2 mg ($n=150$)	3 mg ($n=151$)	4 mg ($n=151$)	All doses ($n=513$)
Duration of individual events, days, mean (SD)[d]	38.0 (N/A)	-	9.0 (N/A)	-	-	9.0 (N/A)
Severity *n* (%)[e,f]						
Mild	1 (100)	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	1 (100)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unresolved, *n* (%)[e]	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug withdrawal, *n* (%)[e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Cumulative TEAEs were assessed through the last post-randomization, on-treatment week including dose tapering.
GXR, guanfacine extended release; N/A, not applicable; SD, standard deviation; TEAE, treatment-emergent adverse event.
[a] Participants from study SPD503-304 only.
[b] Percentages are based on the number of participants in the safety population for each group.
[c] For participants with more than one sedative TEAE, only the day of onset of the first event was included in the mean.
[d] The duration of an individual sedative TEAE was defined as the total number of days between the start of the first event and the end of the last event.
[e] Percentages are based on the total number of sedative TEAEs in each group.
[f] TEAEs were considered mild if they were easily tolerated and did not interfere with usual activity; moderate if they interfered with daily activities but participants were still able to function; or severe if they were incapacitating and participants were unable to work or complete usual activities.

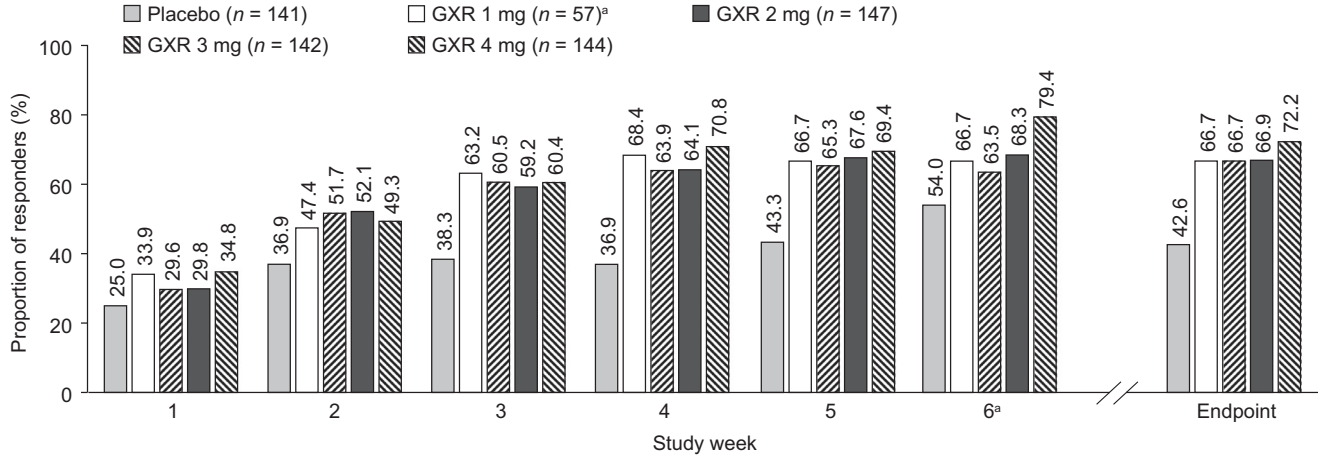
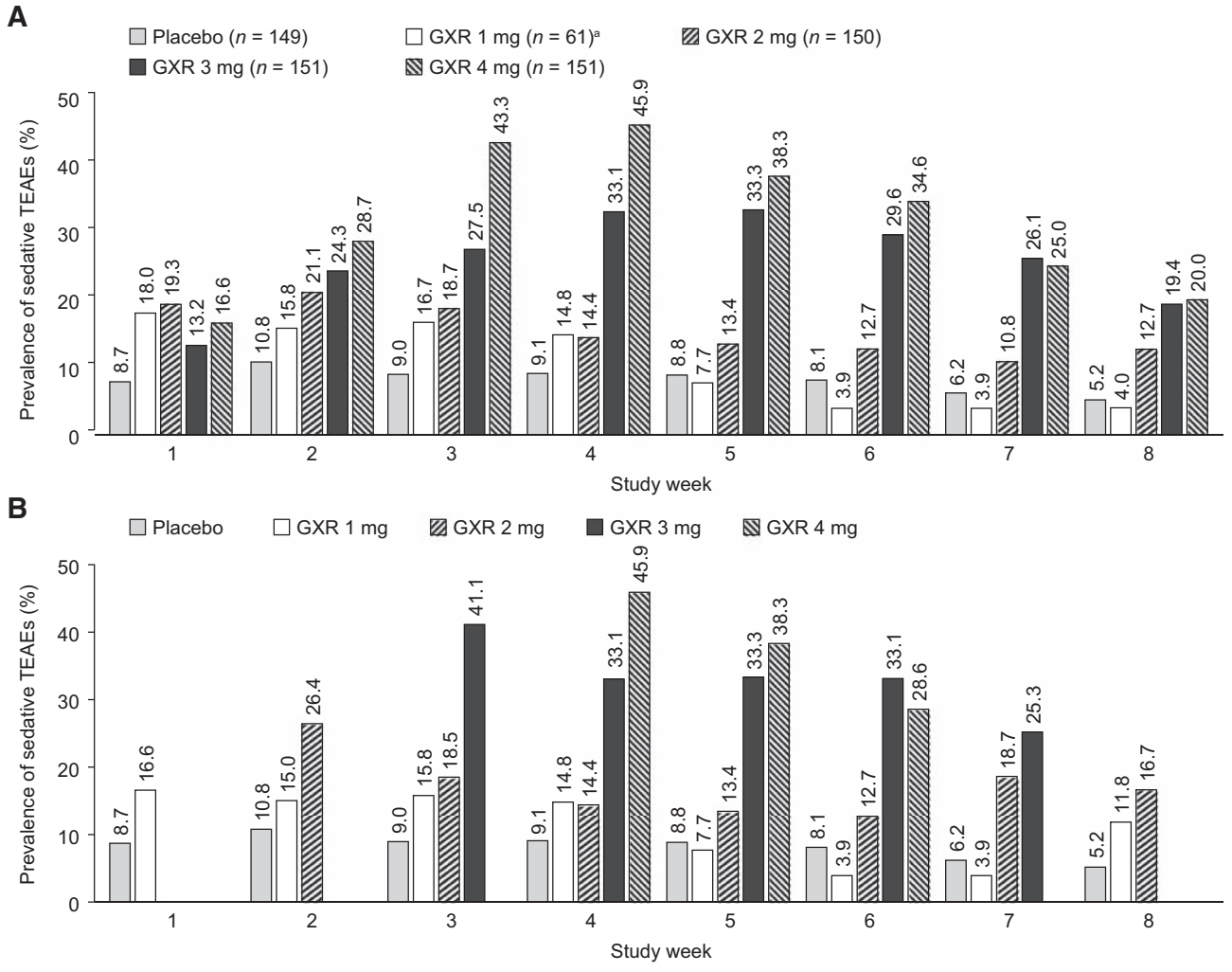


Fig. 1 Time course of the proportion of responders in the pooled forced-dose studies (SPD503-301 and SPD503-304), by randomized dose of GXR (LOCF; FAS).
GXR dosing was titrated to the randomized dose over a period of up to 3 weeks, and tapered from week 6 (SPD503-301) or week 7 (SPD503-304).
ADHD-RS-IV total score was assessed at each on-treatment visit before dose tapering. Response was defined as $\geq$ 30% reduction from baseline in ADHD Rating Scale IV total score. Percentages are based on the number of participants assessed at each visit.
[a]Participants from study SPD503-304 only.
ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; FAS, full analysis set; GXR, guanfacine extended release; LOCF, last observation carried forward.

ticipants and ADHD-RS-IV total scores in participants diagnosed with different subtypes of ADHD), because these would not be expected to improve substantially if the efficacy of GXR is primarily related to sedation. For GXR treatment, placebo-adjusted LS mean changes from baseline to endpoint in ADHD-RS-IV Inattentiveness (ES 0.50–0.54; nominal $p < 0.001$) and Hyperactivity-Impulsivity (ES 0.61–0.67; nominal $p < 0.001$) subscale scores were significant in both pooled forced-dose and pooled fixed-dose studies (Fig. 4). Likewise, placebo-adjusted LS mean changes from baseline to endpoint in ADHD-RS-IV total scores were significant with GXR in participants with the predominantly inattentive subtype (ES 0.50–0.52; nominal $p < 0.05$) as well as in those with either the predominantly hyperactive-impulsive



Placebo, *n*	149	139	134	121	113	111	113	58
GXR 1 mg, *n*	513	120[a]	114[a]	54[a]	52[a]	51[a]	51[a]	110
GXR 2 mg, *n*	–	367	135	125	119	118	252	138[a]
GXR 3 mg, *n*	–	–	209	118	111	166	95[a]	–
GXR 4 mg, *n*	–	–	–	122	107	49[a]	–	–

Fig. 2 Time course of the prevalence of sedative TEAEs in the pooled forced-dose studies (SPD503-301 and SPD503-304), by (A) randomized dose or (B) actual dose of GXR (new and ongoing events at each week; safety population).

GXR dosing was titrated to the randomized dose over a period of up to 3 weeks, and tapered from week 6 (SPD503-301) or week 7 (SPD503-304). In both studies, GXR was initiated at 1 mg/day. In study SPD503-301, GXR was increased weekly by 1 mg/day increments until the randomized dose was reached (2 mg/day at week 2, 3 mg/day at week 3 and 4 mg/day at week 4). In study SPD503-304, GXR was increased: to 2 mg/day at week 4 in participants randomized to GXR 2 mg; to 2 mg/day at week 2 and to 3 mg/day at week 4 in participants randomized to GXR 3 mg; or weekly by 1 mg/day increments until 4 mg/day was reached at week 4 in participants randomized to GXR 4 mg.

Sedative TEAEs were defined as somnolence, sedation and hypersomnia.

Prevalence of sedative TEAEs (participants with new and ongoing events) was assessed at each post-randomization, on-treatment week including dose tapering.

Percentages are based on the number of participants assessed at each visit.

[a]Participants from study SPD503-304 only.

GXR, guanfacine extended release; TEAE, treatment-emergent adverse event.

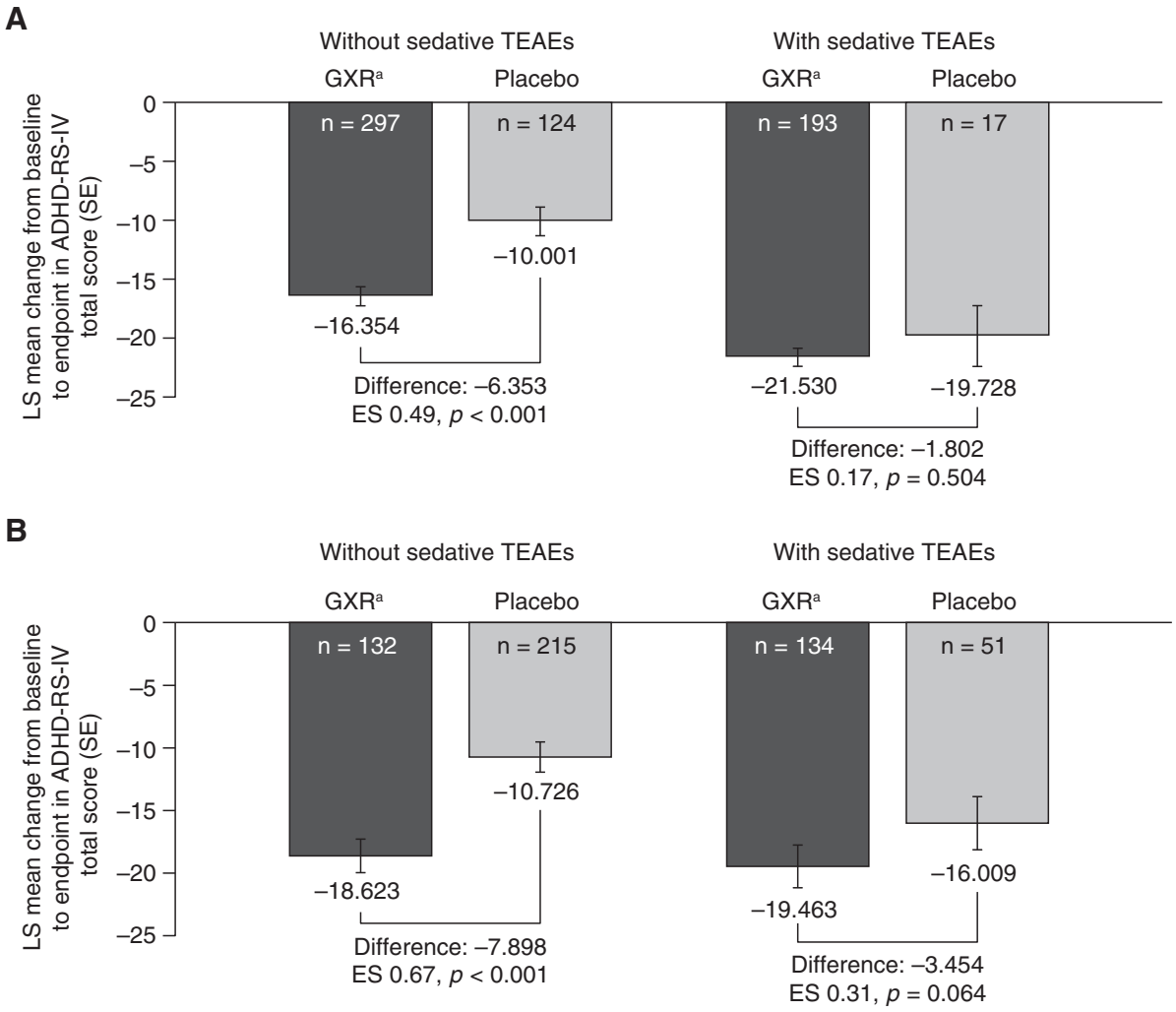


Fig. 3 Change from baseline to endpoint in ADHD-RS-IV total scores in subgroups of participants with and without sedative TEAEs in (A) the pooled forced-dose studies (SPD503-301 and SPD503-304; LOCF, FAS) and (B) the pooled flexible-dose studies (SPD503-312 and SPD503-316; LOCF, FAS).
All *p* values are nominal (unadjusted for multiplicity).
Sedative events were defined as somnolence, sedation and hypersomnia.
[a]All GXR doses combined.
ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; ES, effect size; FAS, full analysis set; LOCF, last observation carried forward; LS, least-squares; SE, standard error; TEAE, treatment-emergent adverse event.

or combined subtype (ES 0.64, nominal $p < 0.001$) in both pooled datasets (Fig. 5).

4. Discussion

The present *post hoc* analyses using data from four phase 3 studies in children and adolescents with ADHD were conducted with the aim of investigating whether symptomatic improvement following GXR treatment is primarily the result of sedative TEAEs associated with the medication. The temporal profiles of symptomatic response and sedative TEAEs were different, symptom reduction was observed in the absence of sedative TEAEs, and GXR treatment reduced symptoms of both inattention and hyperactivity–impulsivity. While some contribution of somnolence, sedation and hypersomnia to the efficacy of GXR cannot be excluded, particularly regarding early symptomatic improvement when sedation is greatest, the present results provide evidence that the reduction in symptoms seen with GXR is beyond what can be explained solely by sedation.

In the pooled forced-dose studies, the prevalence of sedative TEAEs peaked during the first week in which the target GXR dose was reached, and then decreased, whereas the proportion of participants with a treatment response increased to at least 60% in all dose groups during the dose-escalation period, and remained stable throughout dose maintenance to endpoint. The difference between the temporal profiles of symptomatic response and sedative TEAEs suggests that these effects are not directly linked. Although

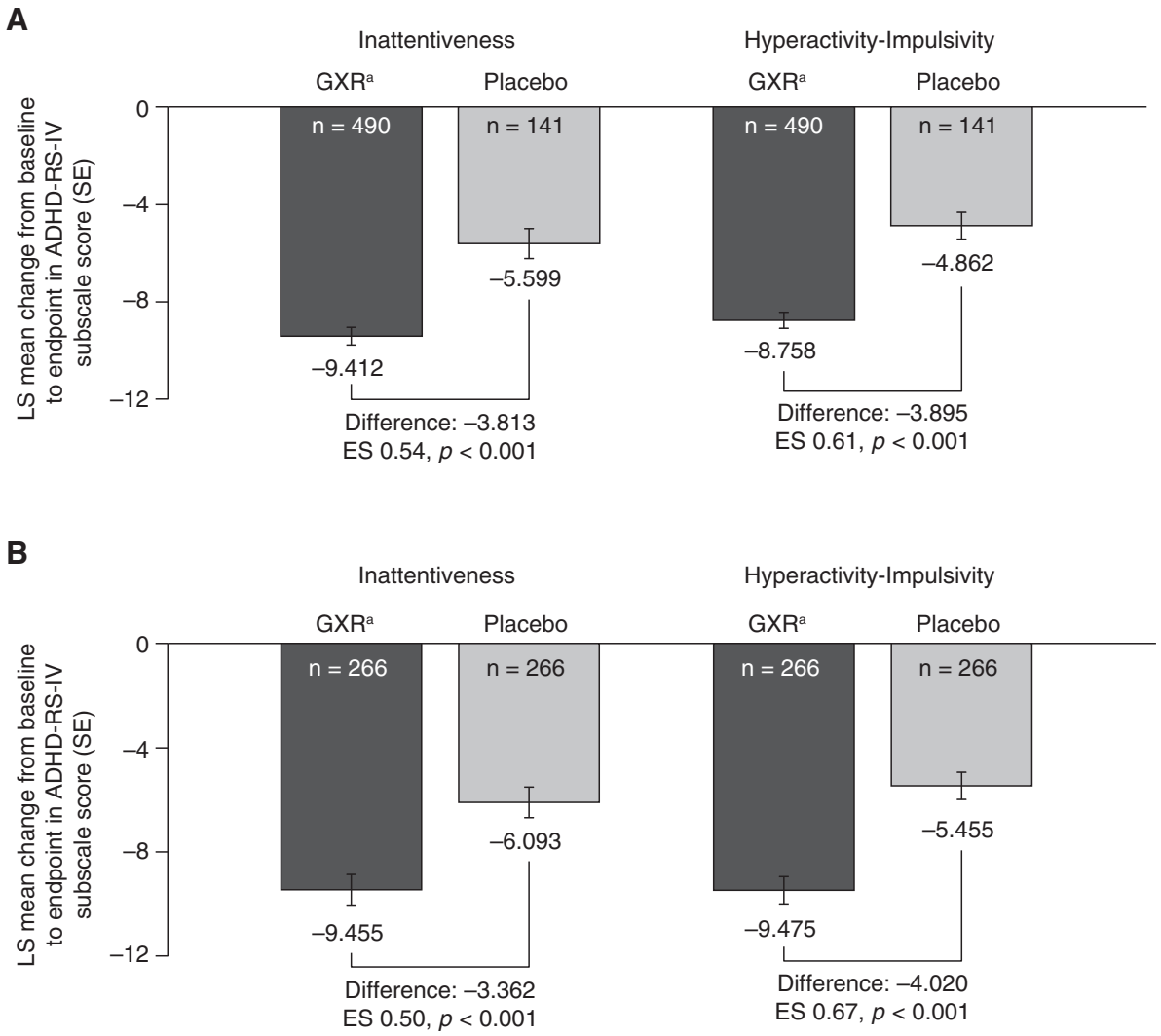


Fig. 4 Change from baseline to endpoint in ADHD-RS-IV subscale scores in (A) the pooled forced-dose studies (SPD503-301 and SPD503-304; LOCF, FAS) and (B) the pooled flexible-dose studies (SPD503-312 and SPD503-316; LOCF, FAS).
All *p* values are nominal (unadjusted for multiplicity).
[a]All GXR doses combined.
ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; ES, effect size; FAS, full analysis set; LOCF, last observation carried forward; LS, least-squares; SE, standard error.

the present analyses were limited to short-term studies, similar findings have been reported in two long-term, single-arm studies which showed that sedative TEAEs (defined as somnolence, sedation and fatigue) were highest in the first month of GXR monotherapy but then declined and remained low for the 2-year treatment period, whereas efficacy was maintained throughout (Biederman et al., 2008a; Sallee et al., 2009a). The findings from the present analyses are also consistent with a previous *post hoc* analysis using data from GXR studies SPD503-301, SPD503-304 and the randomized, placebo-controlled, flexible-dose, phase 2 study SPD503-206, which indicated that sedative effects (including, but not limited to, the sedative TEAEs described here) were associated with treatment duration, and that the likelihood of sedation-related adverse events decreased with continued GXR treatment (Faraone and Glatt, 2010).

A second thread of evidence from these *post hoc* analyses suggesting that the efficacy of GXR cannot be explained solely by sedative effects is the fact that clinically meaningful and significant improvements in ADHD symptoms are observed with GXR in the absence of any sedative TEAEs. In participants with sedative TEAEs, no statistical difference was observed between GXR and placebo. However, it is important to note that the subgroup of placebo-treated participants with sedative TEAEs was non-representative as it comprised a small number of individuals who demonstrated a high treatment response. In addition, because sedative TEAE status is acquired post-baseline and is related to treatment, this was not a conventional subgroup analysis aiming to compare efficacy between participants with and without sedative TEAEs, but was conducted solely to investigate the relationship between sedation and symptom reduction.

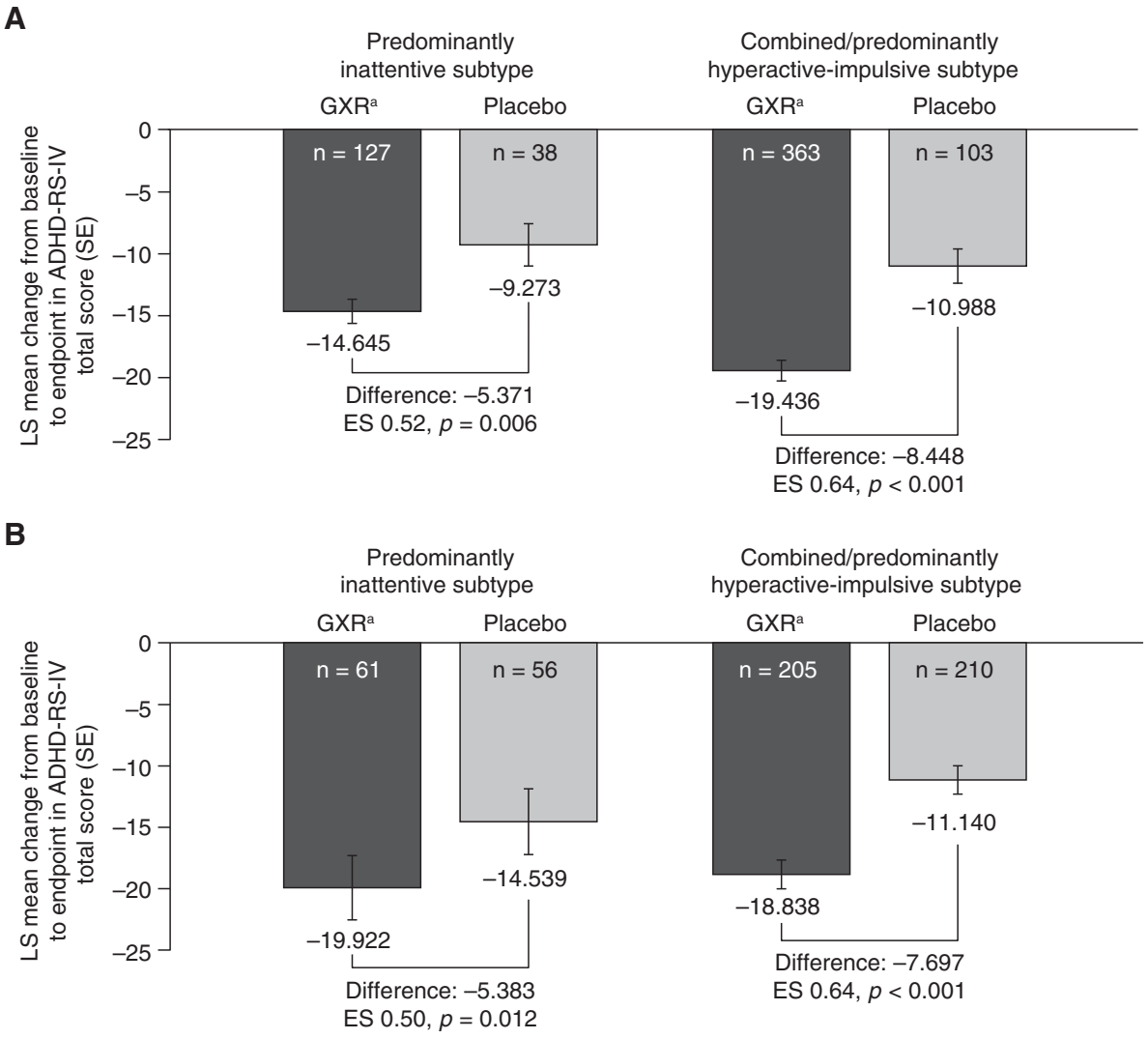


Fig. 5 Change from baseline to endpoint in ADHD-RS-IV total scores in subgroups of participants with predominantly inattentive and combined/predominantly hyperactive-impulsive ADHD subtypes in (A) the pooled forced-dose studies (SPD503-301 and SPD503-304; LOCF, FAS) and (B) the pooled flexible-dose studies (SPD503-312 and SPD503-316; LOCF, FAS).
All *p* values are nominal (unadjusted for multiplicity).
[a]All GXR doses combined.
ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale IV; GXR, guanfacine extended release; ES, effect size; FAS, full analysis set; LOCF, last observation carried forward; LS, least-squares; SE, standard error.

The observed improvement in inattentive and hyperactive–impulsive symptoms provides a third line of evidence supporting the idea that efficacy is not primarily a secondary effect of sedation: if efficacy were primarily due to sedation, hyperactivity–impulsivity would be expected to improve whereas inattention may stay the same or worsen. In the present analyses, symptoms of both inattention and hyperactivity–impulsivity improved in individuals receiving GXR. Similarly, GXR resulted in improvements in ADHD-RS-IV total scores in participants with the predominantly inattentive ADHD subtype as well as in those with either the predominantly hyperactive–impulsive or combined ADHD subtype. Interpretation of the ADHD subtype analysis is limited by the small number of participants with predominantly hyperactive–impulsive ADHD, such that these participants were grouped with those with the combined subtype. Nevertheless, it is noteworthy that effect sizes for GXR tended to be slightly larger for symptoms of hyperactivity–impulsivity than for those of inattention in the ADHD-RS-IV subscale analysis, with a similar trend observed in the ADHD subtype analysis. This suggests that a positive contribution of sedative TEAEs to the efficacy of GXR cannot be excluded, especially during the early stages of GXR treatment when the prevalence of sedative TEAEs is high. Equally, a negative impact of sedative TEAEs on inattentive symptoms cannot be ruled out as a contributory factor to the lower efficacy of GXR in reducing symptoms of inattention than hyperactivity–impulsivity.

Several findings of clinical relevance emerge from the present observations. The first is that although sedative

TEAEs were reported in 38.4% of participants receiving GXR in the forced-dose studies and 50.2% in the flexible-dose studies, such sedative effects were not a prerequisite for symptom reduction. The higher prevalence of sedative TEAEs in the flexible-dose studies most likely reflects the exposure to higher permitted doses of GXR in these studies (maximum allowed dose 4–7 mg) than in the forced-dose studies (1–4 mg). Next is the observation that sedative TEAEs associated with GXR tend to occur early in treatment and resolve with time, with an average duration of 3 weeks or less. Furthermore, the positive relationship between GXR dose and the prevalence of sedative TEAEs indicates that sedative TEAEs can be managed by dose reductions, and therefore do not invariably lead to treatment cessation. This highlights the importance of both careful dose titration when initiating GXR treatment, and ongoing monitoring of the tolerability of GXR during prolonged treatment in order to allow patients to derive the maximum therapeutic benefit of GXR while minimizing sedative side effects. While sedative TEAEs are generally mild or moderate and short-lived, and can often be managed by dose-reductions, it should be noted that sedative TEAEs may be prominent or long-lasting in some individuals, leading to discontinuation of treatment (Faraone et al., 2013). However, reported rates of discontinuation because of sedation-related adverse events have been as low as 6.3% in participants receiving GXR (Faraone and Glatt, 2010), suggesting that rates of GXR discontinuation resulting from sedative TEAEs in the present analyses are not too high. Finally, while GXR certainly is associated with sedative TEAEs, the impact of these events on daily life is less certain. For example, the sedative TEAEs reported in studies SPD503-304 and SPD503-312 did not appear to be associated with increased daytime sleepiness, as assessed using the self-reported Pediatric Daytime Sleepiness Scale (Sallee et al., 2009b; Wilens et al., 2015). In addition, in a 6-week classroom study in children and adolescents with ADHD, sedative TEAEs were reported by 47.8% of participants receiving GXR (1–3 mg), compared with 28.1% receiving placebo, and yet there was no significant differences in psychomotor functioning or alertness between GXR and placebo groups at the study endpoint (based on the Choice Reaction Time test of the Cambridge Neuropsychological Test Automated Battery) (Kollins et al., 2011). Likewise, in study SPD503-316, GXR resulted in statistically significant improvements from baseline to endpoint in the Learning and School domain of the Weiss Functional Impairment Rating Scale – Parent, an ADHD-specific measure of functional impairment (Hervas et al., 2014).

Strengths of the present investigation into the possible link between symptom reduction and sedative effects in children and adolescents receiving GXR include the size and variety of the data examined and the analytic approaches used. Three separate analyses were performed using data derived from four randomized, placebo-controlled, phase 3 studies of GXR conducted in the USA, Canada and Europe, which had different designs, including two different dosing schedules and included a total safety population of nearly 1200 participants. The present results should, however, be interpreted in light of a number of important caveats. The first is the risk of bias associated with *post hoc* analyses. Second, it is possible that the higher rates of sedative TEAEs in participants receiving GXR compared with placebo may have resulted in the partial unblinding of the randomized treatment and may therefore have confounded the reported efficacy outcomes. Third, the short-term nature of the studies included in these analyses limits assessment of possible long-term effects of sedation. However, long-term data from two published studies (Biederman et al., 2008a; Sallee et al., 2009a) and a recently completed study (NCT01500694; unpublished data) reported similar temporal profiles for efficacy and sedation with GXR to those reported here, with efficacy maintained during prolonged treatment over 2 years whereas sedative TEAEs occurred early and decreased with time. It is important to note when comparing temporal profiles that responders and sedative TEAEs were based on different study populations (FAS and safety population, respectively). Finally, the sample size and associated statistical power of the present dataset would have been increased if all studies had used an identical GXR titration scheme, ideally flexible-dose titration, as this is more relevant to clinical practice. Furthermore, all four studies employed dosing schemes of 1 mg/day adjustments, often at weekly intervals; therefore, the present report provides little information on the relationship between sedative TEAEs and efficacy when using alternative dosing strategies (e.g. faster or slower drug titration schedules).

5. Conclusion

Overall, the present *post hoc* analyses using pooled data from four phase 3 studies of GXR in children and adolescents with ADHD suggest that the efficacy of GXR is not primarily due to sedative effects, although some contribution to ADHD symptom reduction cannot be excluded, especially early in treatment when rates of sedative TEAEs are at their highest.

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Conflict of interest

C. Bliss and J. Gao are employees of Shire and own stock or stock options. B. Dirks is a former employee of Shire. The following authors have received compensation for serving as consultants or speakers for, or they or the institutions they work for have received research support or royalties from, the companies or organizations indicated: A.J. Cutler

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Author contributions

All authors participated in data analysis and interpretation, manuscript preparation and critical review. M. Huss, A.J. Cutler, A. Hervas, B. Dirks and J.H. Newcorn participated in study concept and design. M. Huss, K. McBurnett and A.J. Cutler participated in data acquisition. C. Bliss participated in statistical analyses. Although employees of the sponsor were involved in the design, collection, analysis, interpretation and fact-checking of information, the content of this manuscript, and the interpretation of the data, the decision to submit the manuscript for publication in European Neuropsychopharmacology was made by the authors independently.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.05.012.

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