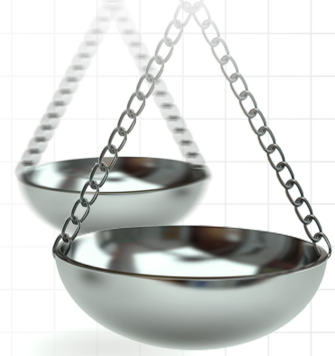
Research Article



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The impact of adjunctive guanfacine extended release on stimulant adherence in children/adolescents with attention-deficit/hyperactivity disorder

Aim: To assess stimulant adherence among children/adolescents with attention-deficit/hyperactivity disorder (ADHD) augmenting stimulants with guanfacine extended-release (GXR). **Patients & methods:** Inclusion criteria: 6–17 years, ≥1 ADHD diagnosis, ≥1 long-acting and/or short-acting stimulant with GXR augmentation. Modified medication possession ratio (mMPR; days medication available/days in period, excluding medication holidays) was assessed; mMPR <0.80 nonadherent. Regression models assessed change in mMPR adjusting for demographic and clinical characteristics. **Results:** Among patients nonadherent to stimulants pre-augmentation (n = 165), unadjusted mean (SD) pre- and post-stimulant mMPRs were 0.68 (0.11) and 0.87 (0.16). Adjusted mean change in mMPR was 0.20 for long-acting versus 0.18 for short-acting stimulants (p = 0.34). **Conclusion**: Among patients nonadherent to stimulants, GXR augmentation was associated with increased stimulant adherence.

Juliana Meyers*[,1], Kavita Gajria[2], Sean D Candrilli[1], Moshe Fridman[3] & Vanja Sikirica[2]

[1]RTI Health Solutions, 3040 Cornwallis Road, Post Office Box 12194, Research Triangle Park, NC 27709, USA

[2]Shire, 725 Chesterbrook Boulevard, Wayne, PA 19087, USA

[3]AMF Consulting, 846 S Citrus Avenue, Los Angeles, CA 90036, USA

*Author for correspondence

Tel.: +1 202 506 6944

jmeyers@rti.org

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Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder with an estimated prevalence of 6–9% in children and adolescents in the USA [1]. Although most commonly seen in childhood and adolescence, ADHD can often extend into adulthood [2], and symptoms include inattention, hyperactivity and impulsivity [3]. Children and adolescents with ADHD have difficulties in the areas of academic functioning, self-esteem and interpersonal relationships [4–6]. ADHD often occurs with other mental health conditions [7–10]; symptoms of ADHD and comorbidities may overlap and exacerbate each other [11–13].

ADHD symptoms can be treated with medications that include stimulants (short-acting [SA] and long-acting [LA] methylphenidates and amphetamines) and nonstimulants (guanfacine extended release [GXR], atomoxetine and extended-release clonidine), as well as behavioral therapy. GXR is the only selective α-2 agonist approved as once-daily monotherapy or as adjunctive therapy (with stimulants) for children and adolescents aged 6–17 years with ADHD in the USA [14]. In a randomized placebo-controlled study, GXR adjunctive to a stimulant was associated with reductions in core ADHD symptoms [15] and in comorbid oppositional symptoms [16], and greater response and remission rates [17]. Although any adjunctive medication has the potential for increased or new treatment-emergent adverse events, no unique adverse events emerged following short-term administration of GXR with stimulant versus stimulant alone [15]. GXR represents a different treatment option that may help address previously unmet medical needs in children and adolescents with ADHD who have suboptimal response to their base stimulant therapy [15,16,18].

In the clinical context, adherence has been defined as the degree to which a patient's

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behavior (e.g., taking medication, following a diet, modifying habits or attending clinics) coincides with advice received from a healthcare professional [19]. Previous research has shown that adherence is a vital element to successful treatment of medical disorders [20]. Additionally, many clinicians consider medication nonadherence to be one of the most serious problems facing current medical practice [21,22]: typical compliance rates for prescribed medications for chronic conditions are reported to be only approximately 50% [23,24]. To the extent that treatment response is related to the treatment's dosage and regimen, nonadherence reduces treatment benefits [25] and can bias assessments of treatment effectiveness [26]. Furthermore, nonadherence has been associated with poorer disease prognosis [27,28] and greater healthcare costs to patients and society [29]. The cost of medication nonadherence in the USA has been estimated to be approximately US$300 billion per year across all diseases [30].

ADHD is one of many conditions in which treatment nonadherence has been shown to be a problem. Nonadherence to treatment in ADHD is thought to be widespread [31], with previous studies estimating the prevalence of medication discontinuation or nonadherence to be 13–64% [32]. Nonadherence to treatment can be further compounded with polypharmacy, as evidenced in the general literature [33,34]. The association between adjunctive GXR treatment and adherence to stimulant therapy among children and adolescents with ADHD has not been previously investigated, with initial literature searches not revealing any empirical studies on the subject; however, anecdotal findings suggested that patients receiving GXR in combination with stimulant therapy may be more likely to be adherent to their stimulant medication.

This retrospective cohort study was designed to assess whether stimulant therapy adherence is affected by the addition of GXR treatment. The study objective was to examine the effect of adjunctive GXR treatment on stimulant adherence among children and adolescents diagnosed with ADHD who were initially nonadherent to stimulant therapy and subsequently augmented stimulant treatment with GXR, using a pre–post study design; effects of the impact of patterns of adjunctive GXR use on healthcare utilization and costs were also explored.

Methods & patients

This retrospective study used data from the MarketScan Commercial Claims and Encounters database, maintained by Truven Health Analytics (Truven, MI, USA), which includes information from employer- and health-plan-sourced claims for nearly 40 million unique individuals, with representation from more than 100 large employers and 12 unique health plans throughout the USA. The database contains medical and drug utilization data and healthcare information, including diagnoses, procedures, healthcare utilization, pharmacy claims and copayments for employees and their dependents covered under fee-for-service and capitated health plans, including preferred provider organizations, point-of-service plans and health maintenance organizations.

All data used in this study were pre-existing and de-identified, with no risk of patient identification by the researchers. Therefore, RTI International's institutional review board, Research Triangle Park, NC, USA, determined that this study met all criteria for exemption from institutional review board review.

In accordance with the approved label for GXR in the USA [14], all children (6–12 years) and adolescents (13–17 years) in the database who had at least one inpatient or outpatient primary or nonprimary diagnosis of ADHD (International Classification of Diseases, Ninth Revision, Clinical Modification codes 314.00 or 314.01) and who filled at least one LA or SA stimulant prescription were initially selected for study inclusion. From this initial sample, data from children and adolescents who remained on stimulant therapy and subsequently augmented it with GXR (adjunctive therapy) were analyzed. All patients were required to be aged 6–17 years on their GXR index date, designated as the date of the first prescription claim for GXR, between September 2009 and June 2011. For the inclusion criteria, adjunctive therapy was defined as stimulant therapy taken for a minimum of 30 days both prior to and following augmentation with GXR. A gap in stimulant treatment of up to 7 days in either time period was permitted. Furthermore, there was some flexibility in the selection criteria as patients were not required to retain the same stimulant or stimulant dose pre- and post-GXR augmentation.

All prescriptions were identified using brand and generic drug names, with patients categorized into mutually exclusive cohorts based on the duration of action of the stimulant received during the study period (6 months pre- and post-GXR index date). Patients who received nothing other than LA stimulants during the study period were placed in the 'LA stimulant-only' cohort (n = 103). The 'SA stimulant-only' (n = 13) and 'SA + LA stimulant' (n = 49) cohorts were combined because of their small sample sizes and included patients who received an SA stimulant at any point during the study period, regardless of any previous, concurrent or later use of an LA stimulant (hereafter, these patients are referred to as the 'SA stimulant cohort'). Additionally, patients were classified in this

manner because SA stimulants have a shorter duration of action and therefore require more frequent administration than LA stimulants, and the combination of SA and LA stimulants would result in greater pill burden and polypharmacy, which could also impact adherence.

To ensure that each patient's GXR index date was a reasonable marker for treatment initiation and that any observed lack of healthcare events was not due to cessation of insurance, all patients were required to have at least 6 months of continuous health plan enrollment before and after their GXR index date.

Documented patient demographic characteristics included age in years, sex, geographic region and health plan type and year of GXR index date. The number and percentage of patients with relevant common childhood conditions was reported. Additionally, as it has previously been shown that ADHD typically overlaps with other psychiatric comorbidities in 60–70% of patients [35], the number and percentage of patients who had evidence of specific mental health comorbidities that commonly occur with ADHD at any point pre- or post-GXR index date, were also reported [36].

Treatment patterns during the study period for both stimulants and GXR were evaluated. The number and percentage of patients concomitantly treated with a mental health related medication and the class of concomitant medication (combination antipsychotics and antidepressants, antipsychotics, antidepressants, mood stabilizers, anticonvulsants and anti-anxiety medications) were reported.

Characteristics of GXR dose stabilization were reported for patients with at least two prescriptions (regardless of the days supplied on the prescription). Dose stabilization was achieved when the last observed dose was equal to the dose of the preceding prescription. Dosage was calculated as the total daily dose prescribed in mg. Among patients who achieved dose stabilization, the mean (standard deviation [SD]) time to the stabilized dose and the mean (SD) stabilized dose were reported. Among patients who never had their index dose titrated, the mean (SD) dose prescribed was reported.

The duration of stimulant treatment prior to augmentation (calculated as the number of days from the start of stimulant therapy to the GXR index date) and the duration of adjunctive therapy (calculated as index date to the earliest of either the GXR discontinuation date or the end of the 6-month follow-up period in days) were estimated. Treatment discontinuation was defined as a minimum 30-day refill gap between the last day of medication from a prescription claim and either the end of the patient's follow-up period (a minimum of 6 months, defined by health plan disenrollment or the end of the database [September 2011]) or the date of receipt of the next medication claim. The number and percentage of patients who discontinued GXR, discontinued all stimulants and discontinued their index stimulant class were reported, along with the mean (SD) days to discontinuation.

For a variety of reasons (e.g., physician recommendation, parental preference) children and adolescents with ADHD may take medication vacations or so-called drug holidays (e.g., weekends or school vacation periods) [32]. As noted in other studies among patients with ADHD [37], information provided in administrative claims databases does not allow researchers to definitively determine which patients were instructed to take a drug holiday, leading to a medication treatment gap. Therefore, an algorithm was developed to identify those patients who were likely to have a medication treatment gap. Specifically, patients followed during the summer months (June, July and August) with an observed gap in treatment of more than 30 days but not more than 90 days were not considered to have discontinued medication (however, patients with a medication treatment gap of more than 90 days during the summer months were considered to have discontinued therapy). To be considered a medication treatment gap, patients were required to restart a stimulant of the same duration and class (LA amphetamine, SA amphetamine, LA methamphetamine, SA methamphetamine) as that last prescribed, as a switch in medication class or treatment duration would have represented the start of a new treatment regimen, indicating the old treatment was discontinued rather than temporarily stopped.

Adherence was assessed using a pre–post-design. Adherence to stimulant therapy pre-GXR index date was measured from the start of stimulant treatment to the GXR index date. Post-GXR index date, adherence to stimulant and GXR treatment was measured by patients' cumulative exposure to the stimulant during the 6-month postindex date period or stimulant discontinuation date (whichever came first). Adherence was assessed by a modified version of the medication possession ratio (mMPR), which accounted for medication treatment gaps observed during the summer months.

The mMPR was defined as the proportion of days within an observation period that a particular study stimulant within that observation period was available. The use of mMPR was appropriate as it allowed for potential medication treatment gaps during the summer months. Specifically, these medication treatment gaps were not factored into adherence estimates, so did not count against adherence, provided these patients recommenced medication of the same duration and stimulant class. The mMPR was calculated

$$\text{mMPR (pre-index date)} = \frac{\text{Sum of days' supply in observation period - medication treatment gap days}}{\text{Days in observation period (i.e., days from start of stimulant therapy to the GXR index date) - medication treatment gap days}}$$

as follows:

$$\text{mMPR (post-index date)} = \frac{\text{Sum of days' supply in observation period - medication treatment gap days}}{\text{Days in observation period (i.e., the number of days from the GXR index date to discontinuation of the stimulant or the length of the follow-up period [6 months] among patients who did not discontinue stimulant therapy) - medication treatment gap days}}$$

In the calculation of mMPR for stimulant medications, patients were considered to have a covered day if they had at least one stimulant available, with either SA or LA stimulant counting for those patients receiving both types. Four mMPR categories (<0.40, 0.40–0.59, 0.60–0.79 and ≥0.80) were documented. Additionally, a dichotomous indicator of adherence was computed, where an mMPR value of ≥0.80 was considered adherent and a value of <0.80 was considered nonadherent [37].

For each patient, all-cause healthcare utilization and costs were aggregated across the 6-month pre- and post-index date periods. Utilization and costs were stratified by the major service sector (inpatient, emergency department, office visit, pharmacy, other outpatient or ancillary encounters, and total). Other outpatient or ancillary resource utilization included all healthcare encounters not identified as inpatient, emergency department, office visits or pharmacy, and includes such items as lab tests, visits in other healthcare settings (e.g., outpatient hospital) and durable medical equipment. All costs were adjusted to 2012 currency using the medical care component of the US Consumer Price Index.

Descriptive statistics of continuous variables (means, medians, ranges and SDs) and frequency distributions of categorical variables of interest were tabulated. Paired *t*-tests for continuous outcomes of interest were used to compare within group univariate differences across the pre- and postindex periods. To compare outcomes among study cohorts, Student's *t*-tests for two samples for continuous, and chi-squared or Cochran–Mantel–Haenszel tests for categorical measures were employed. No multiplicity adjustments were performed for any of the analyses. All analyses were conducted using SAS version 9.3 (SAS, Cary, NC, USA).

To quantify the relationship between underlying patient characteristics and the adjusted change in mMPR, we estimated an ordinary least squares regression model with the following general form:

$$\text{CHANGE IN ADHERENCE} = \beta_0 + \beta_1 X_i + \beta_2 \text{CLIN}_i + \beta_3 \text{TREAT}_i + \varepsilon$$

where CHANGE IN ADHERENCE was a continuous measure of the change in adherence with stimulant monotherapy (i.e., the post-GXR index date period mMPR value minus the pre-GXR index date period mMPR); β_0 was the estimated regression intercept; X_i was a vector of underlying patient characteristics including age, sex and geographic region; CLIN_i was a vector of clinical characteristics including the presence of chronic comorbidities observed at any point pre- or post-GXR index date period (i.e., asthma, vision problems, epilepsy, hereditary and degenerative diseases of the CNS or other disorders of the CNS, organic sleep disorders or insomnia, diabetes, depression, oppositional defiant disorder, obsessive-compulsive disorder, conduct disorder, anxiety disorder, bipolar disorder, learning disability, pervasive disruptive disorder, autism, Asperger's disorder, aggression, tics [excluding Tourette's syndrome] and Tourette's syndrome, but excluding iron deficiency anemia, accidents and injuries, and adjustment reaction); TREAT_i was a vector of treatment-related characteristics including whether the patient received LA stimulant only versus SA stimulant during follow-up, the GXR adherence in the post-GXR index date period, the last GXR dose received, whether or not patients achieved GXR dose stabilization, the stimulant mMPR pre-GXR index date and the year of GXR augmentation; and ε was the error term.

The adjusted change in all-cause healthcare costs for each care setting was evaluated using an ordinary least squares regression model with the following general form:

$$\text{CHANGE IN COST} = \beta_0 + \beta_1 X_i + \beta_2 \text{CLIN}_i + \beta_3 \text{TREAT}_i + \varepsilon$$

where CHANGE IN COST represented a continuous measure for the change in healthcare costs (i.e., the post-GXR index date healthcare costs minus the pre-GXR index date healthcare costs); β_0 was the estimated regression intercept; X_i was a vector of underlying patient characteristics including age, sex and geographic region; CLIN_i was a vector of clinical characteristics including the presence of acute comorbidities observed in the pre- and post-index date periods, separately (i.e., accidents and injuries, adjustment reaction and substance abuse); TREAT_i was a vector of treatment-related characteristics as described for the adherence regression model above, adding receipt of a mental health medication pre-GXR index date; and ε was the error term. Normality was assumed for the change in costs, as this represented the difference between pre- and post-GXR augmentation costs (rather than the skewed cost measure itself) and no log-transformation was undertaken. Chronic comorbidities were not included in the regression equations as these costs would have likely remained constant before and after augmentation, but acute comorbidi-

ties were included as these represented short-term events that may have increased costs. Patient achievement of GXR dose stabilization was included because these patients would have been more likely to respond to stimulant + GXR therapy and remain on this treatment than those patients who did not stabilize or never titrated their GXR dose. A binary indicator for a patient receiving mental health medication pre-GXR index date was included as it may have indicated both polypharmacy and ADHD severity. Year of GXR augmentation was included as a potential proxy measure for poor response as the learning and experience with the product early after its availability, versus later years, may have differed.

Results

A total of 612,323 patients were identified in the database as having an ADHD diagnosis, of whom 11,618 (1.9%) were prescribed GXR (Figure 1); of those prescribed GXR, 8173 (70.3%) were excluded from the study because they received GXR as monotherapy (i.e., they did not have at least 30 days of stimulant medication use both pre- and post-GXR initiation). Of the 1374 patients who met all inclusion criteria, 1209 (88.0%) patients were adherent and 165 (12.0%) patients were nonadherent to stimulant therapy before GXR augmentation (Figure 1). Patients adherent to stimulants pre-GXR augmentation were excluded from the analysis as they remained adherent post-GXR augmentation and therefore had little room for improvement (unadjusted mMPR: pre-GXR = 0.95; post-GXR = 0.92).

Among nonadherent patients, 103/165 (62.4%) were included in the LA stimulant-only cohort and 62/165 (37.6%) were included in the SA stimulant cohort (Table 1). Mean age and percentage of male patients were similar in both cohorts (p = 0.39 and p = 0.91, respectively). Also similar was geographic location, with the largest percentage of patients coming from the South, and coverage by a preferred provider organization health plan. In both cohorts, approximately two-thirds of patients received their first GXR prescription in 2010.

There were no statistically significant differences between cohorts for any concomitant childhood conditions or mental health comorbidities. An asthma diagnosis was observed at any point pre- or post-GXR index date in 6/103 (5.83%) patients in the LA stimulant-only cohort and 5/62 (8.06%) in the SA stimulant cohort. Disorders of the CNS (excluding organic sleep disorders and hereditary and degenerative CNS diseases) were present in 6/103 (5.83%) of the LA stimulant-only cohort and 4/62 (6.45%) of the SA stimulant groups. Accidents and injuries occurred at any point during the pre- or post-index date periods in 33/103 (32.04%) and 19/62 (30.65%) of each cohort, respectively. Mental health comorbidities that occurred in more than 5% of patients in either cohort were oppositional defiant disorder (12/103 [11.65%]; 8/62 [12.90%]), adjustment reaction (11/103 [10.68%]; 6/62 [9.68%]), anxiety disorder (11/103 [10.68%]; 6/62 [9.68%]), conduct disorder (10/103 [9.71%]; 4/62 [6.45%]), depression (8/103 [7.77%]; 6/62 [9.68%]), bipolar disorder (8/103 [7.77%]; 3/62 [4.84%]), aggression (6/103 [5.83%]; 2/62 [3.23%]) and learning disability (4/103 [3.88%]; 5/62 [8.06%]) in the LA stimulant-only and SA stimulant cohorts, respectively.

Regardless of cohort, patients filled slightly more stimulant prescriptions succeeding the GXR index date than preceding it (mean [SD]: 3.96 [1.93] and 3.66 [1.27], respectively, in the LA stimulant-only cohort and 5.34 [2.80] and 4.42 [1.70], respectively, in the SA stimulant cohort) (Table 2). Patients in both cohorts filled similar numbers of prescriptions (approximately four) for GXR following augmentation (p = 0.64). Slightly more than a third of patients in both cohorts received treatment for a concomitant mental health disorder during the pre-GXR index date period (p = 0.82). The most common concomitant medications received in both cohorts were antidepressants (21/103 [20.39%] patients in the LA stimulant-only cohort and 15/62 [24.19%] patients in the SA stimulant cohort), and antipsychotics (20/103 [19.42%] patients in the LA stimulant-only cohort and 17/62 [27.42%] patients in the SA stimulant cohort).

Characteristics of GXR treatment are presented in Table 3. The number of patients with a GXR holiday was low (two in each cohort; p = 0.60), and the duration of GXR treatment was similar between patients in both cohorts (124.1 [66.9] days among patients in the LA stimulant-only cohort and 119.0 [64.8] days among patients in the SA stimulant cohort; p = 0.64). A total of 47/103 (45.63%) patients in the LA stimulant-only cohort and 32/62 (51.61%) patients in the SA stimulant cohort (p = 0.46) discontinued GXR. Regardless of cohort, average time to GXR discontinuation was about 2 months (p = 0.55).

The proportion of patients who achieved GXR dose stabilization (22/103 [21.36%]; 17/62 [27.42%]), did not achieve GXR dose stabilization (7/103 [6.80%]; 4/62 [6.45%]), never titrated the GXR index dose (53/103 [51.46%]; 23/62 [37.10%]) and received only one GXR prescription (21/103 [20.39%], 18/62 [29.03%]) were comparable between patients in the two cohorts (LA stimulant-only and SA stimulant cohorts, respectively; all p > 0.05). For patients who achieved dose stabilization, the mean GXR dose (SD) was 2.55 (0.86) mg and 3.0 (0.71) mg for LA stimulant-only and SA stimulant cohorts, respectively. For

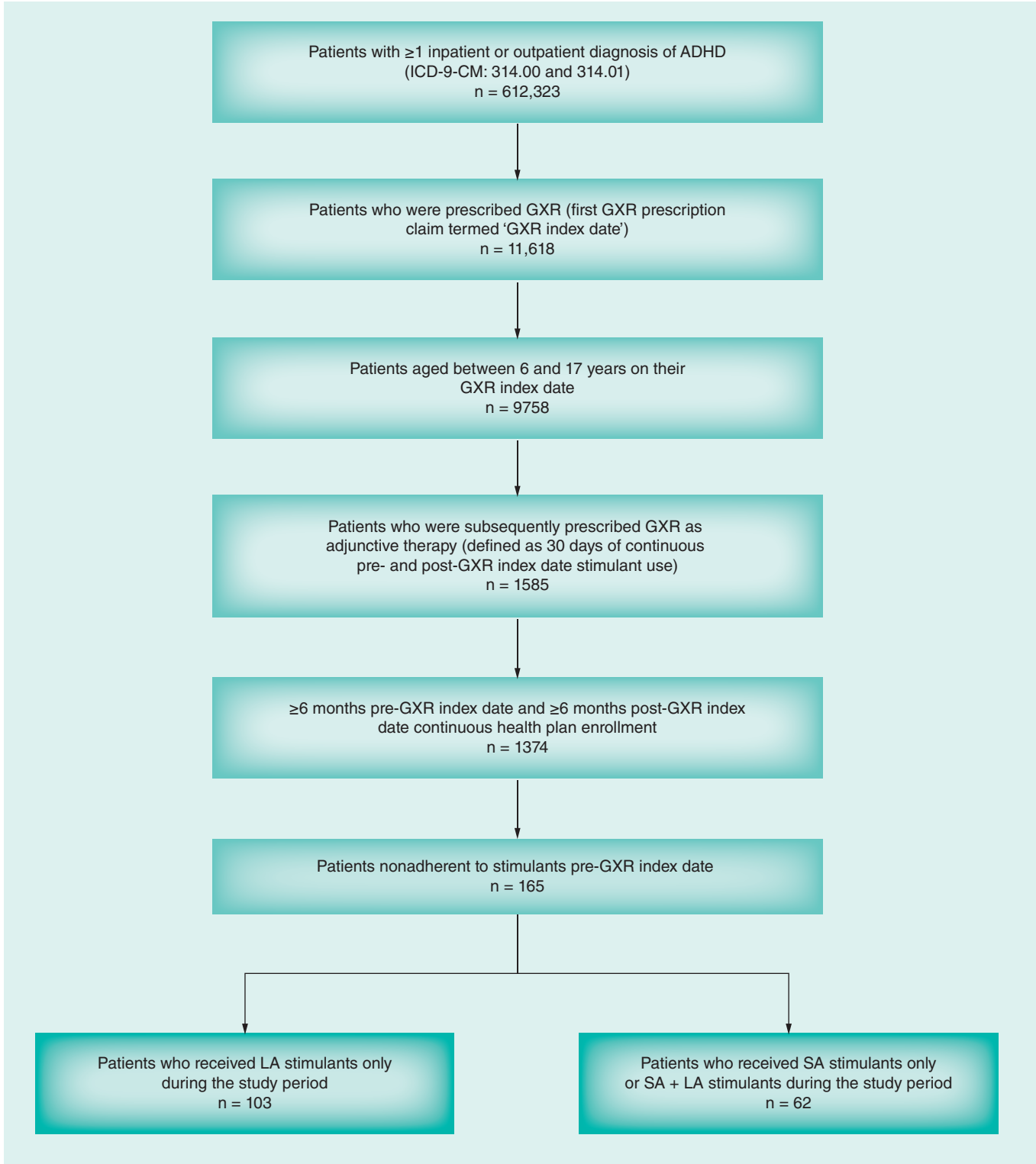

Figure 1. Sample attrition chart.
ADHD: Attention-deficit/hyperactivity disorder; GXR: Guanfacine extended release; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; LA: Long acting; SA: Short acting.

those without a titrated index dose, mean (SD) GXR doses were 2.26 (0.94) mg (LA stimulant-only cohort) and 2.22 (0.85) mg (SA stimulant cohort).

The duration of stimulant treatment during the pre- and post-GXR index date periods was similar between patients in both cohorts (pre-GXR index

date, p = 0.05; post-GXR index date, p = 0.14; Table 4). Discontinuation of all stimulants post-GXR index date occurred in 37/103 (35.92%) patients in the LA stimulant-only cohort and 17/62 (27.42%) patients in the SA stimulant cohort (p = 0.26).

Mean (SD) stimulant mMPR (based on stimulant availability on each day) during the pre-GXR index date period was 0.67 (0.11) in the LA stimulant-only cohort compared with 0.68 (0.10) in the SA stimulant cohort (Table 4). Stimulant mMPR increased significantly in the post-GXR index date period in both cohorts (both p < 0.001), with a mean (SD) mMPR of 0.88 (0.16) in the LA stimulant-only cohort and 0.86 (0.16) in the SA stimulant cohort. The proportion of patients with an mMPR ≥0.80 was 81% (83/103) in the LA stimulant-only cohort and 74% (46/62) in the SA stimulant cohort.

Prior to discontinuing GXR, the mean (SD) GXR mMPR was 0.91 (0.21) in the LA stimulant-only cohort and 0.91 (0.25) in the SA stimulant cohort. Of patients in the LA stimulant-only cohort, 80% (82/103) had a GXR mMPR ≥0.80 in the post-GXR index date period, compared with 77% (48/62) in the SA stimulant cohort (p = 0.74; Table 4).

Among all patients, the adjusted mean (SD) change in stimulant mMPR for the pre- to post-GXR index date periods was 0.19 (0.14) (p < 0.001). There was no significant difference between the individual cohorts, with adjusted mean (SD) change in mMPR of 0.20 (0.15) in the LA stimulant-only cohort and 0.18 (0.13) in the SA stimulant cohort (p = 0.34).

Achieving dose stabilization (vs never titrating the index dose) was associated with a statistically significant increase in the change in stimulant mMPR (p = 0.04; Table 5). Both a higher stimulant mMPR prior to the GXR index date and female sex were associated with significantly smaller changes in stimulant mMPR than lower stimulant mMPR prior to the GXR index date and male sex (p < 0.001 and p = 0.05, respectively).

In both cohorts, the percentage of patients with an inpatient admission for any reason in the pre-GXR index date period was low and increased slightly (non-significantly) in the post-GXR index date period. There were no significant differences in the percentage of patients in either cohort with an emergency department visit in both index date periods, though there was a slight increase in mean (SD) emergency

Table 1. Baseline characteristics, by study cohort.

Characteristic	LA stimulant only†	SA stimulant†	p-value
n	103	62	
Age (years), n (%):			
– Mean (SD)	10.89 (2.95)	10.82 (3.25)	0.388
– Median, range (minimum, maximum)	10 (4, 17)	10 (6, 17)	
Sex (male/female), n (%)	64/39 (62.14/37.86)	38/24 (61.29/38.71)	0.914
Geographic region, n (%):			0.1079
– Northeast	7 (6.80)	12 (19.35)	
– North Central	21 (20.39)	15 (24.19)	
– South	59 (57.28)	22 (35.48)	
– West	14 (13.59)	12 (19.35)	
– Unknown	2 (1.94)	1 (1.61)	
Health plan type, n (%):			0.370
– Preferred provider organization	78 (75.73)	43 (69.35)	
– Other‡	25 (24.27)	19 (30.64)	
Year of GXR index date, n (%):			0.0476
– Year 2009	13 (12.62)	4 (6.45)	
– Year 2010	72 (69.90)	40 (64.52)	
– Year 2011	18 (17.48)	18 (29.03)	

No multiplicity adjustment was performed.
†The LA stimulant-only cohort included patients who received only LA stimulants throughout the pre- and postindex date periods. The SA stimulant cohort included patients who received only SA stimulants and patients who received both SA and LA stimulants at any point in the pre- or postindex date periods.
‡Includes health maintenance organization, point of service, basic or major medical, comprehensive plans, consumer-driven health plans and high-deductible health plans.
GXR: Guanfacine extended release; LA: Long acting; SA: Short acting; SD: Standard deviation.

Table 2. Summary of treatment-related characteristics, by study cohort.

Characteristic	LA stimulant only†	SA stimulant†	p-value
n	103	62	
Stimulant ADHD medications received during the pre-GXR index date period, n (%):			
– LA amphetamine	6 (5.83)	6 (9.68)	
– SA amphetamine	0 (0)	25 (40.32)	
– LA methylphenidate	63 (61.17)	29 (46.77)	
– SA methylphenidate	0 (0)	20 (32.26)	
– Lisdexamfetamine dimesylate	51 (49.51)	20 (32.26)	
Stimulant ADHD medication received on the GXR index date, n (%):			
– LA amphetamine	3 (2.91)	3 (4.84)	
– SA amphetamine	0 (0)	18 (29.03)	
– LA methylphenidate	52 (50.49)	20 (32.26)	
– SA methylphenidate	0 (0)	12 (19.35)	
– Lisdexamfetamine dimesylate	46 (44.66)	16 (25.81)	
Number of stimulant prescriptions filled during the pre-GXR index date period:			
– Mean (SD)	3.66 (1.27)	4.42 (1.70)	
– Median, range (minimum, maximum)	4 (1, 8)	4 (1, 8)	
Number of stimulant prescriptions filled during the post-GXR index date period:			
– Mean (SD)	3.96 (1.93)	5.34 (2.80)	<0.001
– Median, range (minimum, maximum)	4 (0, 9)	5 (0, 12)	
Number of GXR prescriptions filled during the post-GXR index date period:			
– Mean (SD)	3.83 (2.11)	3.66 (2.30)	0.641
– Median, range (minimum, maximum)	4 (1, 8)	4 (1, 8)	
Received concomitant mental disorder treatment at GXR index date or during pre-GXR index date period, n (%):	38 (36.89)	24 (38.71)	0.816
Among those concomitantly treated, class of medication treated with at GXR index date or during the pre-GXR index date period, n (%):			
– Combination antipsychotic and antidepressant medication	0 (0)	0 (0)	–
– Antipsychotic medication	20 (19.42)	17 (27.42)	0.233
– Antidepressant medication	21 (20.39)	15 (24.19)	0.567
– Mood stabilizing and anticonvulsant medication	8 (7.77)	7 (11.29)	0.270
– Anxiety medication	3 (2.91)	1 (1.61)	0.446

No multiplicity adjustment was performed.
†The LA stimulant-only cohort included patients who received only LA stimulants throughout the pre- and postindex date periods. The SA stimulant cohort included patients who received only SA stimulants or both SA and LA stimulants at any point in the pre- or post-index date periods.
ADHD: Attention-deficit/hyperactivity disorder; GXR: Guanfacine extended release; LA: Long acting; SA: Short acting; SD: Standard deviation.

department visit costs in the pre- compared with the post-GXR index date period (US$101 [US$270] vs US$114 [$379]; p = 0.025). Over 90% of patients in both cohorts and in both index date periods had at least one all-cause physician office visit (pre-GXR index date, 98/103 and 57/62; post-GXR index data

95/103 and 58/62; LA and SA stimulant cohorts, respectively). The number of all-cause prescription claims increased significantly in both cohorts from the pre- to post-GXR index date periods ($p < 0.001$).

Unadjusted all-cause healthcare costs increased from the pre- to the post-GXR index date periods for both cohorts, with median values for the LA stimulant-only cohort increasing from $1193 to $1871 and those for the SA stimulant cohort increasing from $1455 to $3044.

Adjusted analyses found that among patients in the LA stimulant-only cohort, mean total all-cause healthcare costs increased by $1171 (95% CI: $738, $1604), and mean total all-cause healthcare costs excluding pharmacy costs increased by $468 (95% CI: $50, $886) in the post-GXR index date period (Table 6). Similarly, among patients in the SA stimulant cohort, total all-cause healthcare costs increased by $2430 (95% CI: $1812, $3048), and adjusted total all-cause healthcare costs excluding pharmacy costs increased by $1916 (95% CI: $1337, $2495) in the post-GXR index date period. In the LA stimulant-only cohort, adjusted all-cause pharmacy costs accounted for 60% ($703/$1171) of the increase in all-cause total healthcare costs from the pre- to post-GXR index date periods. In the SA stimulant cohort, adjusted all-cause pharmacy costs accounted for just 21% ($514/$2430) of the total healthcare cost increase from the pre- to post-GXR index date periods, while adjusted other medical visits (primarily composed of outpatient hospital visits, laboratory claims and visits in other outpatient settings) accounted for about 59% ($1423/$2430) of the increase.

Discussion

The aim of adjunctive therapy for ADHD is to provide additional ADHD symptom control when stimulant therapy alone does not control symptoms sufficiently. This study evaluated the adherence and cost impact of adding adjunctive GXR therapy to stimulant therapy among children and adolescents with ADHD. As patients who were adherent to stimulant therapy pre-GXR augmentation had little room for improvement, only those patients who were nonadherent to stimulant treatment prior to starting GXR were studied.

Information on adherence to polypharmacy in psychiatric disorders is scarce; however, polypharmacy has been shown to decrease adherence in other chronic conditions [33,34,38,39]. Our study found that for patients previously nonadherent to stimulants, the relative increase in adherence was between 27% (SA stimulant cohort) and 30% (LA stimulant-only cohort) following the addition of GXR. One may speculate that the increased adherence may be driven by patients experiencing improved symptom control following GXR augmentation and therefore being more likely to continue taking their medications. Even though only about 20% of the patients were stabilized on their GXR dose, the presence of GXR seemed to be associated with improved adherence in the short term. Longer-term studies would be needed to determine whether stable dosing leads to continued adherence, or greater improvements in adherence.

In examining adherence to stimulant medications before and after initiating GXR, patients were not required to receive stimulant medications for the

Table 3. Summary of adjunctive guanfacine extended release treatment patterns during the 6-month period following the guanfacine extended release index date, by study cohort.

Characteristic	LA stimulant only†	SA stimulant†	p-value
n	103	62	
Duration of GXR treatment (days)‡:			
– Mean (SD)	124.05 (66.89)	119.03 (64.84)	0.638
– Median, range (minimum, maximum)	181 (31, 181)	127.5 (31, 181)	
Had a GXR holiday, n (%)	2 (1.94)	2 (3.23)	0.604
Discontinued GXR, n (%)§	47 (45.63)	32 (51.61)	0.456
Time to discontinuation of GXR (days)¶:			
– Mean (SD)	56.19 (35.60)	60.94 (32.76)	0.550
– Median, range (minimum, maximum)	31 (31, 149)	56.5 (31, 140)	

No multiplicity adjustment was performed.
†The LA stimulant-only cohort included patients who received only LA stimulants throughout the pre- and postindex date periods. The SA stimulant cohort included patients who received only SA stimulants or both SA and LA stimulants at any point in the pre- or post-index date periods.
‡Determined from the index date until the date of the first discontinuation.
§Discontinuation defined as 30 consecutive days without GXR available.
¶Time to discontinuation calculated among those patients who discontinued GXR.
GXR: Guanfacine extended release; LA: Long acting; SA: Short acting; SD: Standard deviation.

Table 4. Summary of stimulant treatment patterns and adherence characteristics, by study cohort.

Characteristic	Pre-GXR index date			Post-GXR index date		
	LA stimulant only†	SA stimulant†	p-value	LA stimulant only†	SA stimulant†	p-value
n	103	62		103	62	
Duration of stimulant treatment (days), mean (SD)	165.15 (29.65)	173.45 (20.24)	0.053	134.13 (65.38)	149.05 (56.06)	0.137
Median, range (minimum, maximum)	181 (69, 181)	181 (83, 181)		181 (23, 181)	181 (25, 181)	
Had a stimulant holiday, among patients followed during the summer months, n (%)	5 (4.85)	9 (14.52)	0.031			
Discontinued all stimulant use, n (%)‡				37 (35.92)	17 (27.42)	0.260
Time to discontinuation of all stimulant use (days), mean (SD)				50.51 (29.94)	64.47 (38.84)	0.154
Median, range (minimum, maximum)				32 (23, 131)	55 (25, 145)	
Discontinued index stimulant class, n (%)				39 (37.86)	30 (48.39)	0.184
Time to discontinuation of index stimulant class (days), mean (SD)				51.64 (30.04)	58.03 (31.20)	0.707
Median, range (minimum, maximum)				36 (23, 131)	48.5 (25, 133)	
Stimulant mMPR:			0.698			0.534
– <0.40	3 (2.91)	0 (0)		3 (2.91)	1 (1.61)	
– 0.40–0.59	22 (21.36)	15 (24.19)		5 (4.85)	5 (8.06)	
– 0.60–0.79	78 (75.73)	47 (75.81)		12 (11.65)	10 (16.13)	
– ≥0.80	0 (0)	0 (0)		83 (80.58)	46 (74.19)	
– Mean (SD)	0.67 (0.11)	0.68 (0.10)	0.745	0.88 (0.16)	0.86 (0.16)	
– Median, range (minimum, maximum)	0.71 (0.34, 0.80)	0.71 (0.42, 0.80)		0.93 (0.28, 1.00)	0.92 (0.26, 1.00)	
Stimulant mMPR ≥0.80, n (%):	0 (0)	0 (0)	–	83 (80.58)	46 (74.19)	0.336
GXR mMPR:						0.194
– <0.40				4 (3.88)	6 (9.68)	
– 0.40–0.59				3 (2.91)	4 (6.45)	
– 0.60–0.79				14 (13.59)	4 (6.45)	
– ≥0.80				82 (79.61)	48 (77.42)	
– Mean (SD)				0.91 (0.21)	0.91 (0.25)	
– Median, range (minimum, maximum)				0.97 (0.28, 1.59)	1 (0.29, 1.34)	
GXR mMPR ≥0.80, n (%)				82 (79.61)	48 (77.42)	0.739

No multiplicity adjustment was performed.
†The LA stimulant-only cohort included patients who received only LA stimulants throughout the pre- and post-index date periods. The SA stimulant cohort included patients who received only SA stimulants or both SA and LA stimulants at any point in the pre- or post-index date periods.
‡Discontinuation defined as 30 consecutive days without any stimulant medication available.
GXR: Guanfacine extended release; LA: Long acting; mMPR: Modified medication possession ratio; SA: Short acting; SD: Standard deviation.

entire 6-month period before the GXR index date. This is because they may not have been diagnosed with ADHD or they may have been trying psychotherapy or other nonprescription treatments. There-

fore, calculating adherence to stimulant therapy began with the patient's first prescription fill within the pre-GXR index date period. However, we did not require that patients be newly initiating stimulant therapy during the 6-month pre-GXR index date period, therefore patients may have been followed from the start of the 6-month period onward if they were prevalent stimulant users. Adherence during the post-GXR index date period was calculated from the GXR index date until the date of stimulant discon-

Table 5. Factors associated with a change in adherence (pre- to post-guanfacine extended release index date difference) to stimulant treatment among nonadherent patients: ordinary least squares regression results.

Parameter	β value	p-value
Intercept	0.801	<0.001
Received LA stimulant only (vs SA stimulant[†])	0.012	0.673
Post-GXR index date GXR adherence	0.115	0.076
Last GXR dose received (total daily dose, mg)	-0.005	0.748
GXR dose stabilization (vs never titrated index dose):		
– Achieved dose stabilization	0.068	0.041
– Did not achieve dose stabilization	0.057	0.315
Received a mental health medication pre-GXR index date (Yes/No)	0.004	0.201
Stimulant mMPR pre-GXR index date	-1.045	<0.001
Year of GXR initiation (vs 2011):		
– Initiated GXR in 2009	0.074	0.149
– Initiated GXR in 2010	0.001	0.978
Aged 6–12 years (vs 13–17 years)	-0.002	0.958
Female (vs male)	-0.057	0.046
Geographic region (vs northeast):		
– North Central	-0.072	0.157
– South	-0.004	0.938
– West	0.046	0.380
– Unknown	-0.061	0.582
Chronic comorbidities at any time pre- or post-GXR index date (vs did not have comorbidity):		
– Asthma	-0.036	0.537
– Vision problems	0.050	0.566
– Epilepsy	-0.058	0.531
– Hereditary and degenerative diseases, or other disorders of the CNS	-0.026	0.636
– Organic sleep disorders or insomnia	-0.076	0.538
– Diabetes	-0.015	0.894
– Depression	0.000	0.998
– Oppositional defiant disorder	-0.035	0.428
– Obsessive–compulsive disorder	0.116	0.197
– Conduct disorder	-0.047	0.578
– Anxiety disorder	0.047	0.327
– Bipolar disorder	-0.027	0.638
– Learning disability	-0.106	0.107
– Pervasive disruptive disorder	0.042	0.663
– Autism	0.007	0.929
– Asperger's disorder	-0.023	0.765
– Aggression	-0.017	0.855
– Tics (excluding Tourette's syndrome)	0.156	0.118
– Tourette's syndrome	-0.087	0.340

No multiplicity adjustment was performed.
[†]The SA stimulant cohort included patients who received only SA stimulants or both SA and LA stimulants at any time in the pre- or post-index date periods.
GXR: Guanfacine extended release; LA: Long acting; mMPR: Modified medication possession ratio; SA: Short acting.

Table 6. Summary of adjusted difference in all-cause healthcare costs, by study cohort.

Characteristic	All patients: pre- vs post-GXR index date difference (US$)		LA stimulant only†: pre- vs post-GXR index date difference (US$)		SA stimulant†: pre- vs post-GXR index date difference (US$)		Difference (LA stimulant only – SA stimulant) (US$)	p-value (LA stimulant only vs SA stimulant), (US$)
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
Inpatient	197 (1397)	-17, 412	57 (1181)	-173, 288	429 (1681)	3, 856	-372	0.098
ED visits	-8 (253)	-46, 31	13 (270)	-40, 66	-42 (219)	-97, 14	55	0.176
Physician office visits	4 (372)	-53, 61	-58 (346)	-125, 10	106 (394)	6, 206	-164	0.006
Pharmacy	632 (501)	555, 709	703 (493)	607, 799	514 (496)	388, 640	189	0.019
Other medical visits	819 (1250)	627, 1011	455 (1193)	222, 688	1423 (1107)	1141, 1704	-967	<0.001
Total healthcare utilization (excluding pharmacy)	1012 (2298)	659, 1365	468 (2141)	50, 886	1916 (2280)	1337, 2495	-1448	<0.001
Total healthcare utilization	1644 (2373)	1279, 2009	1171 (2216)	738, 1604	2430 (2433)	1812, 3048	-1259	0.001

No multiplicity adjustment was performed.
†The LA stimulant-only cohort included patients who received only LA stimulants throughout the pre- and post-index date periods. The SA stimulant cohort included patients who received only SA stimulants or both SA and LA stimulants at any point in the pre- or post-index date periods.
Note: Adjusted healthcare costs were assessed using an ordinary least squares regression model and will control for demographics, clinical characteristics and treatment characteristics.
ED: Emergency department; GXR: Guanfacine extended release; LA: Long acting; SA: Short acting.

tinuation, as patients may have had a clinical reason for discontinuing treatment after the 30-day window (e.g., medication side effects, lack of efficacy, misdiagnosis). Based on this rationale, the medication possession ratio with a variable follow-up time rather than the proportion of days covered with a fixed follow-up time was more appropriate for assessing adherence. Specifically, the adherence estimate reported in this study represents adherence to treatment while the medication was actively being taken, rather than persistence.

This methodology resulted in an average adherence estimate that is higher than that typically reported in the literature for an ADHD population. Sikirica and colleagues assessed adherence to GXR in children and adolescents in the same database and found an average mMPR during a 6-month follow-up period (mMPR = 0.64) lower than that estimated here (mean mMPR 0.91 for LA stimulant only, 0.91 for SA stimulant) [36]. To compare with adherence estimates in the literature, when mMPR in this study was calculated over the entire 6-month follow-up period, values ranged from 0.69 (among patients in the LA stimulant-only cohort) to 0.66 (among patients in the SA stimulant cohort), consistent with the estimates reported by Sikirica and colleagues.

After augmentation with GXR in nonadherent patients, we observed that between 74% (SA stimulant cohort) and 81% (LA stimulant-only cohort) of patients were adherent to stimulant therapy (defined as an mMPR ≥0.80). Although not directly comparable to our study population, Lachaine and colleagues studied a Canadian claims database and reported that in a 1-year follow-up period, approximately 39% of patients with ADHD were adherent to SA stimulants and 63% to LA stimulants [40]. Hodgkins and colleagues examined patients with ADHD receiving methylphenidate in a USA managed care claims database and found that 59% of children were adherent to their medication during a 1-year follow-up period [41]. The greater adherence observed in our analysis may be a function of measuring adherence for the time medication was being taken, as well as a time window of 6 versus 12 months.

This study found that a third of patients discontinued stimulant therapy while approximately half of patients discontinued GXR during the 6-month follow-up period. Patients remained on GXR therapy for an average of 2 months and stimulant therapy for an average of 4.7 months. The duration of stimulant therapy reported in this analysis is consistent with that reported previously [42,43]. As GXR was added to stimulants as adjunctive therapy, it is difficult to gauge what an appropriate rate of discontinuation or how long treatment duration would be. It is more likely that patients would discontinue the adjunctive therapy, intended to provide additional symptom control, rather than the initial stimulant treatment and the

higher discontinuation rate found in this analysis for GXR compared with stimulant therapy supports this.

Results were reported separately for patients in the LA stimulant-only cohort and for patients in the SA stimulant cohort. These cohorts were selected based on the duration of action of stimulant received and the assumption that patients receiving SA stimulants or both SA and LA stimulants concurrently would likely be taking more pills per day and therefore would have lower adherence than patients in the LA stimulant-only cohort. No significant differences in treatment patterns or stimulant adherence characteristics were noted between these two cohorts, with the change in stimulant mMPR from pre- to post-GXR index date periods similar for each cohort. In the SA stimulant cohort, the change in adherence could have been due partially to one of two potential biases. First, patients could have received SA stimulants pre-GXR augmentation and switched to an LA stimulant post-GXR augmentation, resulting in fewer pills per day and increased adherence. However, only a small proportion of patients (8.06% [n = 5]) received such a regimen, so this was unlikely to be a major factor contributing to the increase in mMPR observed in the post-GXR index date period. Second, patients receiving either LA or SA stimulants pre-GXR index date may have received both medications post-GXR index date and were then considered adherent to treatment if either stimulant was available. However, we found that approximately the same percentage of patients received concomitant SA + LA treatment in the pre-GXR index date (19.35%; 12 patients) and post-GXR index date (17.74%; 11 patients), making it unlikely that this was a major factor contributing to the observed increase in adherence in the post-GXR index date period. Furthermore, sensitivity analyses were conducted excluding the five patients who received an SA stimulant pre-GXR augmentation and an LA stimulant post-GXR initiation. Adjusted analyses found that stimulant adherence still increased significantly following GXR initiation.

This study found that, in both cohorts, healthcare costs were observed to increase following augmentation of stimulant therapy with GXR, for these patients who were nonadherent to stimulant treatment prior to starting GXR. The increase in costs was due, in a large part, to an increase in pharmacy expenditures and an increase in the number of physician office visits and other outpatient visits (primarily outpatient hospital visits, laboratory claims and visits in other outpatient settings), all of which are to be expected when adding a medication to an existing treatment regimen, regardless of treatment outcome. On the other hand, the observation of increased costs is counter-intuitive to the expectation that better symptom control with GXR augmentation could lead to reduced medical visit costs; cost analyses based on a larger patient sample with an appropriate length of follow-up are needed. In light of the observed increase in costs associated with GXR, it is important to note that previous clinical trials have shown that patients with a suboptimal response to stimulants experience significant symptom reduction following adjunctive GXR therapy [44,45]. This increased cost of adding GXR to LA stimulants was found to be cost effective [46]. Furthermore, families of children with ADHD experience both emotional and financial stressors [47–49], and their health-related quality of life has been shown to be negatively impacted [50]; thus, the potential benefits of improved adherence on these factors should not be dismissed. When viewed from a patient perspective, the increased costs associated with GXR therapy may be offset by the effects of improved adherence and greater symptom control (e.g., fewer missed work days for parents and better school performance for patients), but these effects were not assessed in this study. The immediate release formulation of guanfacine is not currently approved for ADHD and, although it might be considered as a less expensive option than GXR if comparing daily pharmacy costs, a retrospective claims analysis showed lower MPRs and greater resource utilization, as well as higher rates of discontinuation, switching and augmentation, among those receiving guanfacine immediate release versus GXR [36]. There was no significant difference in total all-cause healthcare costs between the two groups.

This study has limitations, including those common to retrospective database analyses using claims data, such as coding errors and incomplete claims. It must be acknowledged that the sample size analyzed (n = 165) was small. It was also not possible to confirm diagnoses of ADHD and other mental health conditions. Information on reasons why GXR was prescribed was not available, and these patients may represent a population with more severe ADHD as they were prescribed a second medication; alternatively, as cautiously noted by the current American Academy of Child and Adolescent Psychiatry practice parameter, α agonists (specifically clonidine) may be used to treat stimulant-induced insomnia [51], although GXR is not licensed for counteracting stimulant-induced insomnia. Additionally, it was not possible to determine the prescribing physician, and the corresponding specialty of the prescribing physician for medications. Furthermore, this study examined a unique subset of the ADHD population, specifically, only those patients who remained on stimulant therapy following addition of GXR. The selection of such patients may have led to the inclusion of only those patients who responded

suboptimally to stimulants, thereby limiting generalizability. Also, as these patients likely responded to stimulant therapy to some degree, they may have been more likely to be adherent to the stimulant after adding GXR, if the combined treatment led to optimal response. Next, it is unknown if adherence to stimulant therapy may have increased over time or remained constant due to factors such as treatment optimization. The study also included only children and adolescents covered by managed care plans. Study findings therefore may be limited in generalizability to Medicaid or uninsured patients. Finally, there are a large number of variables in this model with a small sample size, so there may be other differences not seen at a statistically significant level.

In this study, flexibility was allowed in the selection criteria in that patients were not required to have the same stimulant or stimulant dose pre- and post-GXR augmentation. As a result of this, patients may have switched stimulants on the date of augmentation with GXR. Therefore, it is not feasible to determine if the addition of GXR or a change in stimulant was the driver for the observed improved adherence. However, we observed that only ten patients changed stimulant medications within 30 days of GXR augmentation. As patient out-of-pocket expenses were not included in this analysis, the total healthcare costs incurred for patients with ADHD who are treated with GXR are likely underestimated. Finally, this study assessed direct healthcare costs incurred by patients receiving GXR. Using these data, it was not feasible to assess the impact of GXR on indirect costs (e.g., parental work loss impact) or on other nonpecuniary factors (e.g., academic achievement).

The results of this study can be used to generate hypotheses on adherence in patients covered by managed care plans whose stimulant therapy is augmented with GXR; further studies would be needed to test these hypotheses.

Conclusion

Our hypothesis-generating study found that, among patients who were nonadherent to stimulant therapy, adding GXR to their treatment regimen was associated with a significant increase in stimulant adherence and healthcare costs. The findings of this study appear to contradict previous results showing that polypharmacy is associated with decreased medication adherence [33,34], although studies of adherence to polypharmacy in psychiatric disorders are lacking. Given that treatment adherence is a critical component in the continuum of care, demonstrating potential mechanisms for improving adherence among patients who were previously nonadherent to therapy may be of interest to healthcare providers. Additional research is necessary to confirm the results presented in this study as more recent data, with correspondingly larger numbers of patients and longer periods of patient follow-up, become available. The noted study limitations notwithstanding (small sample size, reasons for GXR augmentation are lacking, limited generalizability), this analysis adds valuable information to the body of knowledge about ADHD-related medication adherence and use of GXR as adjunctive treatment for the condition.

Executive summary

- In this retrospective cohort study, we examined whether adjunctive guanfacine extended release (GXR) can influence adherence, healthcare utilization or cost in children/adolescents already receiving stimulant medication for attention-deficit/hyperactivity disorder (ADHD).
- Data, taken from a US commercial claims database, were analyzed for children and adolescents (6–17 years), with confirmed ADHD diagnosis, who remained on stimulant therapy (long or short acting) and subsequently augmented stimulant treatment with GXR (adjunctive therapy).
- Modified medication possession ratio (mMPR) was assessed; mMPR of <0.80 was interpreted as nonadherent. Regression models (adjusted for patient demographics and clinical characteristics) were used to assess change in mMPR.
- Patients with ADHD who were adherent to stimulant therapy pre-GXR augmentation were also adherent to stimulant therapy post-GXR augmentation (pre-augmentation unadjusted mean mMPR: 0.95; postaugmentation mMPR, 0.92).
- The addition of GXR to treatment in previously nonadherent patients increased adherence in the 6 months following treatment augmentation initiation (pre-augmentation mean mMPR: 0.68; postaugmentation mMPR: 0.87).
- In patients nonadherent prior to augmentation, adjusted mean change in mMPR was 0.20 for those on long-acting stimulants versus 0.18 for those on short-acting stimulants.
- Although GXR augmentation leads to improved treatment outcomes in these patients, thereby enabling better outcomes in school, family and other aspects of life, information is needed on why GXR was prescribed to fully understand the reasons for the increase in adherence observed.

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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical conduct of research

All data used in this study were de-identified, pre-existing and retrospective, with no risk of identifying patients. Therefore, RTI International's institutional review board (IRB), Research Triangle Park, North Carolina, determined that this study met all criteria for exemption from IRB review.

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