Immediate-Release Versus Extended-Release Guanfacine for Treatment of Attention-Deficit/Hyperactivity Disorder

Vanja Sikirica, PharmD, MPH; Jipan Xie, MD, PhD; Tony Lizhang He, BS; M. Haim Erder, PhD; Paul Hodgkins, PhD, MSc; Hongbo Yang, PhD; Thomas Samuelson, BA; and Eric Q. Wu, PhD

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed pediatric psychiatric disorder in the United States, affecting about 7.2% of children and adolescents.[1] The core symptoms of ADHD include hyperactivity, impulsivity, and inattention.[2] If untreated, ADHD can delay social and academic development, with symptoms and dysfunction persisting into adulthood in approximately 70% of patients.[3-5] In addition, children and adolescents with ADHD are likely to have mental health comorbidities.[2] Attention-deficit/hyperactivity disorder poses a substantial economic burden, with estimated annual societal costs of $143 to $266 billion (2010 dollars) in the United States.[6] Furthermore, ADHD patients incur excess costs from treating mental health comorbidities that are commonly associated with ADHD.[7]

According to guidelines from the American Academy of Pediatrics, a school-aged child or adolescent diagnosed with ADHD should be treated with behavioral therapy and/or a stimulant as the first-line medication.[8] Although stimulants are the most frequently prescribed medications for ADHD up to 30% of patients using stimulants are intolerant to treatment or have an inadequate response.[9] For these patients, a nonstimulant medication may be used.[9] Nonstimulants approved by the US Food and Drug Administration (FDA) for ADHD treatment include atomoxetine, clonidine extended release, and guanfacine extended release (GXR).[10]

Guanfacine is a centrally acting slective alpha-2A adrenoceptor agonist that has been shown to improve prefrontal cortex neuronal firing and strengthen working memory in primates.[11] This pharmacologic action is the basis for treating human prefrontal cortex–related cognitive disorders.[11] Guanfacine extended release is used as monotherapy or adjunctive therapy to stimulants for ADHD treatment in children and adolescents.[12] It appears to be more efficacious than atomoxetine, a commonly used nonstimulant, at the target dose in indirect comparison studies.[13,14]

ABSTRACT

Objectives: To compare treatment patterns, resource utilization, and healthcare costs for guanfacine immediate release (GIR) versus guanfacine extended release (GXR) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Study Design: Retrospective claims analysis using the Truven Health MarketScan database.

Methods: Patients with ADHD aged 6 to17 years who initiated therapy with GIR or GXR between November 2009 and December 2010 were selected. Therapy adjustment rates (discontinuation, switching, augmentation), medication possession ratios (MPRs), resource utilization, and healthcare costs (2010 dollars) during the 6 months after therapy initiation were compared between GIR and GXR cohorts, using multivariate regressions controlling for baseline characteristics during the 6 months before therapy initiation.

Results: During the 6-month study period, GIR users (n = 743) had significantly higher rates of treatment discontinuation (adjusted hazard ratio [aHR] = 1.79; P <.001), switching (aHR = 2.32; P <.001), and augmentation (aHR = 1.55; P = .003) and significantly lower MPRs (0.50 vs 0.64; P <.001) than GXR users (n = 2344). GIR users had significantly more frequent all-cause inpatient admissions (P = .022) and emergency department visits (P = .016). GIR users incurred significantly lower all-cause pharmacy costs (P <.001) but significantly higher medical costs (P = .009), resulting in no significant difference in total all-cause healthcare costs (P = .068) between the 2 groups.

Conclusions: After adjustment, GIR users had significantly higher therapy adjustment rates, lower MPRs, and greater resource utilization than GXR users. Total all-cause healthcare costs were comparable between the 2 groups.

Am J Pharm Benefits. 2013;5(4):e85-e94

PRACTICAL IMPLICATIONS

Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) treated with guanfacine immediate-release (GIR) had significantly higher resource use than those treated with guanfacine extended-release (GXR):

- Significantly higher therapy adjustment rates and significantly higher resource utilization.
- While drug costs were lower for GIR users, they were offset by higher medical costs; total healthcare costs were comparable between the 2 groups.
- Further investigation is warranted on clinical outcomes associated with GIR's off-label use in ADHD relative to GXR.

Guanfacine is also marketed in an immediate-release formulation in the United States. Guanfacine immediate release (GIR) was approved by the FDA in 1986 for hypertension treatment only.[15] However, its off-label use to treat psychiatric disorders, including ADHD, is common.[11,16] Although GIR has the same active moiety as GXR, there is limited clinical evidence supporting GIR use in the treatment of ADHD. Only 1 small (n = 34) placebo-controlled trial has been conducted to evaluate GIR's efficacy and safety in children with concomitant tic disorders and ADHD.[15,17]

The 2 formulations of guanfacine have distinct pharmacokinetic profiles and dosing requirements.[15] While GIR is metabolized quickly in children,[11,16,18] GXR is synthesized with rate-controlling polymers and organic acids that lead to a prolonged half-life.[19] Despite differences between GIR and GXR, payers and other decision makers (parents/caregivers) may treat the 2 drugs equally. Some payers who reimburse GXR may require a step-edit with GIR or a prior authorization prior to use of GXR.[20,21] This policy assumes that GIR and GXR are reasonable substitutes in ADHD treatment, but this assumption needs to be tested in terms of efficacy, tolerability profiles, usage patterns, and economic outcomes.

To date, no study has directly compared the impact of GIR use versus GXR use among ADHD patients. To better understand the real-world differences between the 2 drugs with respect to their impact on patients, this retrospective cohort study compared the treatment patterns, resource utilization, and healthcare costs associated with GIR therapy versus GXR therapy in patients with ADHD.

METHODS

Data Source

Data were extracted from the Truven Health MarketScan Commercial Claims & Encounters database for the period of 2009 to 2010. The database contains de-identified enrollment data and inpatient and outpatient medical and outpatient pharmacy claims from large employers and health plans across the United States.

Sample Selection

The study sample consisted of ADHD patients who initiated therapy with GIR or GXR from November 2009 to December 2010 (GXR was launched in November 2009). The first fill of either drug during this period was defined as the index drug, and the date of the fill was defined as the index date. The 6 months before and the 6 months after the index date were defined as the preindex period and the study period, respectively. Patients were further required to meet the following criteria: (1) to have at least 1 primary diagnosis of ADHD, identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 314.00 and 314.01, during the preindex period; (2) to be aged 6 to 17 years as of the index date; and (3) to have continuous eligibility during the preindex and study periods. Patients were excluded if they used GIR or GXR during the preindex period or were diagnosed with hypertension (*ICD-9-CM* codes 401.xx, 459.3x, 642.3x, 643.3x, and 997.91) during the preindex or study periods. Patients were allowed to take other ADHD medications during the preindex period.

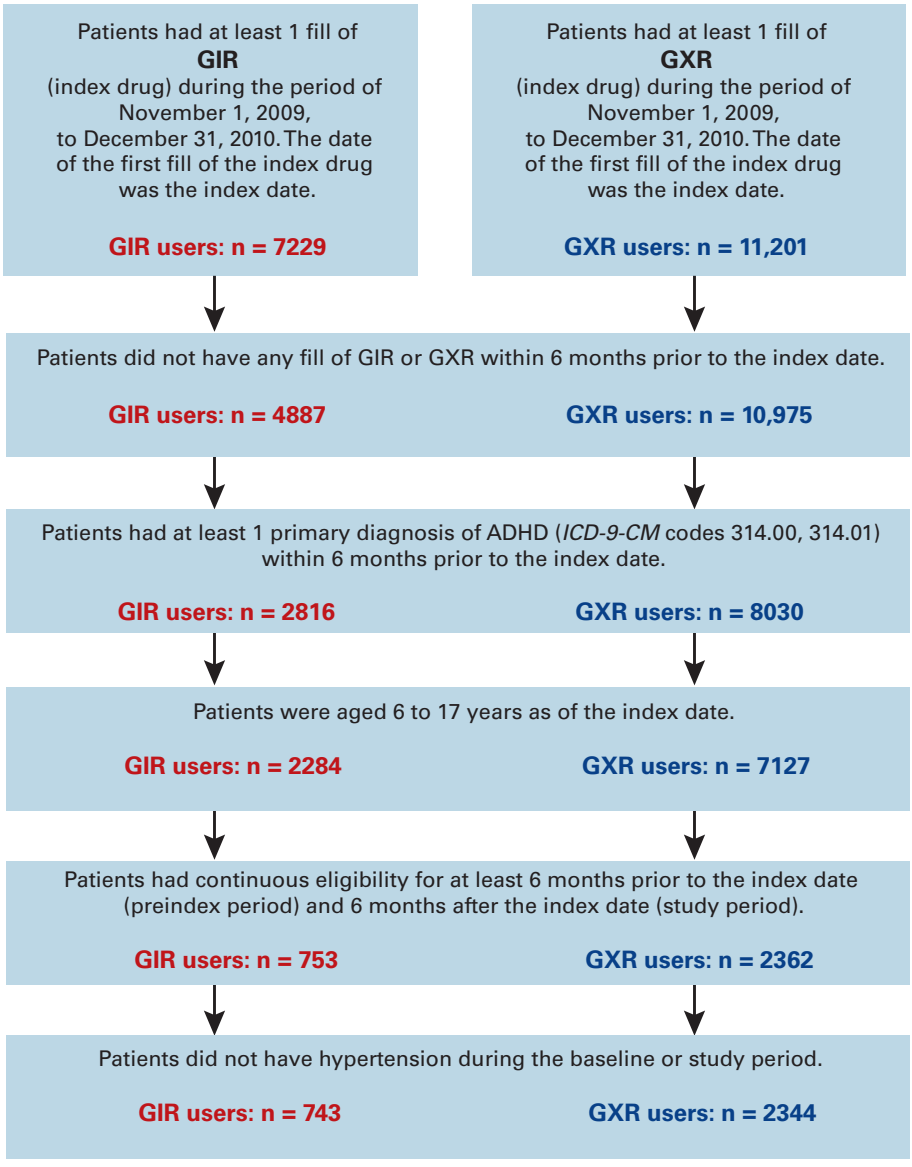
Study Outcomes

Outcomes categories measured during the 6-month study period included treatment patterns, resource utilization, and healthcare costs.

Treatment Patterns. Treatment patterns included medication possession ratio (MPR), daily average consumption (DACON), discontinuation, switching, and augmentation. Definitions of treatment patterns used in this study are in concordance with International Society for Pharmacoeconomics and Outcomes Research guidelines[22] and have been used previously.[23,24] Medication possession ratio, defined as the total number of days of drug supply divided by the total number of days in the study period (ie, 6 months), was used to measure adherence to the index drug. Daily average consumption was defined as the quantity of pills supplied during the study period divided by total number of days supplied within the study period.

Discontinuation of the index drug was defined as a gap of more than 30 days since the last day of supply

Figure. Sample Selection Flow Chart



ADHD indicates attention-deficit/hyperactivity disorder; GIR, guanfacine immediate release; GXR, guanfacine extended release; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

of the previous index drug fill. Switching was defined as the initiation of a new ADHD medication not used during the preindex period within 30 days before or after the discontinuation of the index drug. The switched-to ADHD medication had to be taken for 30 days or longer. Augmentation was defined as the initiation of a new ADHD medication not used during the preindex period before the discontinuation of the index drug. The augmenting drug must have at least 30 days of supply overlap with the index drug. The ADHD medications considered for switching and augmentation included the 2 comparators, GIR and GXR, and other FDA-approved ADHD medications (stimulants, atomoxetine, clonidine extended release).

Sensitivity analyses for switching and augmentation were conducted by expanding the list to include other medications that are not FDA approved for treatment of ADHD, but are sometimes used for ADHD treatment: clonidine immediate release, bupropion, typical and atypical antipsychotics, selective serotonin reuptake inhibitors, and tricyclic antidepressants. In addition, switching required the new ADHD medication be taken for 60 days or longer, and augmentation required the

augmenting drug to have 60 days or more of supply overlap with the index drug.

Resource Utilization. Types of resource utilization measured during the study period included inpatient, emergency department (ED), and outpatient visits. The mean numbers of inpatient, ED, and outpatient visits per patient were calculated for each cohort. Both all-cause utilization and utilization related to mental health (MH) were measured. Utilization related to MH was identified based on claims associated with a primary diagnosis of an MH condition (*ICD-9-CM* codes 290-319).

Healthcare Costs. Healthcare costs measured during the study period included medical service and prescription drug costs. Both all-cause and MH-related costs were estimated. Mental health–related medical costs were defined as costs associated with an MH-related utilization, and MH-related drug costs were identified using therapeutic class codes. Cost analyses were conducted from a third-party payer's perspective (ie, the amount paid by third-party payers). Costs were inflated to December 2010 US dollars using the medical component of the Consumer Price Index.[25]

Statistical Analyses

Baseline characteristics were compared between the GIR and GXR cohorts using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Baseline characteristics include demographics, baseline medications and psychotherapies, comorbidities, resource utilizations, healthcare costs, and use of the index therapy as combination therapy or monotherapy. Combination therapy with the index drug was defined as fills of the same nonindex ADHD drug during the preindex period and within 30 days after GIR or GXR initiation; the nonindex drug must have 30 days or more of overlapping use with the index drug.

Rates of therapy discontinuation, switching, and augmentation during the study period were estimated using Kaplan-Meier survival analysis and compared descriptively between the 2 cohorts using log-rank tests. The hazard ratios of discontinuation, switching, and augmentation between GIR and GXR users were calculated using multivariate Cox proportional hazards models. Medication possession ratio and DACON were compared between GIR and GXR users by using generalized linear models.

The all-cause and MH-related incidence rate ratios for each resource utilization category, which measured the relative frequency of resource use for GIR users compared with GXR users, were calculated using univariate and multivariate negative binomial models.

Healthcare costs corresponding to each resource utilization category were compared descriptively between GIR and GXR users using Wilcoxon rank sum tests. In the multivariate models, cost outcomes for which 95% or more of patients had nonzero values were compared using generalized linear models with gamma distribution and log link. The cost outcomes for which less than 95% of patients had a nonzero value were estimated using 2-part models. Adjusted cost differences between the 2 groups were calculated. *P* values for the 2-part models were estimated via bootstrapping (500 iterations of sampling with replacement).

Multivariate models adjusted for baseline variables that were statistically different between the 2 cohorts. Specifically, baseline characteristics that were adjusted for included age, sex, region, healthcare provider type, use of index drug in combination therapy, use of baseline treatments, MH comorbidities, and the corresponding baseline utilization or cost.

Sensitivity analyses were performed for all multivariate regression analyses, where use of the index drug in combination therapy was redefined as at least 1 nonindex ADHD drug fill during the preindex period, coupled with any nonindex ADHD drug fill within 30 days of the index date. The nonindex ADHD drug used in the study period must have 30 days or more of supply overlap with the index drug.

All analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina). The significance for all statistical tests was assessed based on a type I error of .05.

RESULTS

Baseline Characteristics

The GIR and GXR cohorts included 743 and 2344 patients, respectively (**Figure**). At baseline, a higher proportion of GIR users were prescribed short-acting stimulants (23.96% vs 18.47%; $P = .001$), antidepressants (28.80% vs 24.74%; $P = .027$), and antipsychotics (24.76% vs 21.33%; $P = .050$), and a smaller proportion of GIR users were prescribed long-acting stimulants (66.89% vs 76.66%; $P < .001$). The GIR users had a higher prevalence of any MH comorbidity (47.11% vs 39.16%; $P < .001$). In the baseline period, GIR users had significantly higher means of all-cause inpatient visits per patient (0.11 vs 0.06; $P < .001$), ED visits per patient (0.24 vs 0.19; $P = .034$), inpatient costs per patient ($926 vs $598; $P < .001$), and ED costs per patient ($142 vs $131; $P = .020$). The results were similar for MH-related baseline inpatient utilization and costs, but MH-related baseline ED utilization and costs were not significantly different (**Table 1**).

Table 1. Comparison of Baseline Characteristics

Baseline Characteristics	GIR Users (n = 743)	GXR Users (n = 2344)	*P*
Demographics			
Age[a] mean ± SD, y	10.38 ± 3.01	10.76 ± 2.96	.002[b]
Female, n (%)	158 (21.27)	510 (21.76)	.776
Region, n (%)			<.001[b]
Northeast	86 (11.57)	182 (7.76)	
North Central	259 (34.86)	700 (29.86)	
South	252 (33.92)	1243 (53.03)	
West	144 (19.38)	211 (9.00)	
National (unknown)	2 (0.27)	8 (0.34)	
Healthcare provider type, n (%)			<.001[b]
Preferred provider organization	407 (54.78)	1464 (62.46)	
Health maintenance organization	176 (23.69)	320 (13.65)	
Noncapitated point-of-service	52 (7.00)	206 (8.79)	
Other	108 (14.54)	354 (15.10)	
Index therapy use pattern, n (%)			
Base definition			.231
Combination therapy[c]	225 (30.28)	765 (32.64)	
Monotherapy[c]	518 (69.72)	1579 (67.36)	
Sensitivity definition			.041[b]
Combination therapy—sensitivity[d]	273 (36.74)	960 (40.96)	
Monotherapy—sensitivity[d]	470 (63.26)	1384 (59.04)	
ADHD medications, n (%)			
Short-acting stimulants	178 (23.96)	433 (18.47)	.001[b]
Long-acting stimulants	497 (66.89)	1797 (76.66)	<.001[b]
Nonstimulants	167 (22.48)	560 (23.89)	.429
Concomitant mental health medications, n (%)			
Antidepressants	214 (28.80)	580 (24.74)	.027[b]
Antipsychotics/antimanics	184 (24.76)	500 (21.33)	.050[b]
Benzodiazepines	8 (1.08)	38 (1.62)	.286
Other sedatives, hypnotics, and anxiolytics	24 (3.23)	54 (2.30)	.161
Anticholinergics	8 (1.08)	13 (0.55)	.131
Nonmedication psychotherapies, n (%)			
Nonmedication psychotherapy[e]	524 (70.52)	1375 (58.66)	<.001[b]
Psychiatrist visits	392 (52.76)	922 (39.33)	<.001[b]
Any physical comorbidities,[f] n (%)	208 (27.99)	676 (28.84)	.657
Asthma	53 (7.13)	153 (6.53)	.564
Vision	11 (1.48)	23 (0.98)	.256
Diabetes mellitus	3 (0.40)	5 (0.21)	.374
Iron deficiency anemia	1 (0.13)	5 (0.21)	.671
Accidents and injuries	123 (16.55)	418 (17.83)	.425
Insomnia	8 (1.08)	18 (0.77)	.422
Epilepsy	14 (1.88)	31 (1.32)	.266
Other neurologic disorders	33 (4.44)	132 (5.63)	.209

(Continued)

Table 1. Comparison of Baseline Characteristics *(Continued)*

Baseline Characteristics	GIR Users (n = 743)	GXR Users (n = 2344)	*P*
Any mental comorbidities,[f] n (%)	350 (47.11)	918 (39.16)	<.001[b]
Depression	68 (9.15)	186 (7.94)	.293
Adjustment reaction	74 (9.96)	196 (8.36)	.179
Oppositional defiant disorder	69 (9.29)	168 (7.17)	.059
Obsessive-compulsive disorder	14 (1.88)	45 (1.92)	.951
Conduct disorder	54 (7.27)	130 (5.55)	.084
Substance abuse	10 (1.35)	39 (1.66)	.546
Anxiety disorder	80 (10.77)	229 (9.77)	.430
Bipolar disorder	55 (7.40)	135 (5.76)	.104
Learning disability	36 (4.85)	72 (3.07)	.022[b]
Pervasive developmental disorder	41 (5.52)	81 (3.46)	.012[b]
Autism	28 (3.77)	43 (1.83)	.002[b]
Asperger's disorder	49 (6.59)	93 (3.97)	.003[b]
Tics (excludes Tourette's)	20 (2.69)	36 (1.54)	.040[b]
Tourette's syndrome	22 (2.96)	26 (1.11)	<.001[b]
Total all-cause healthcare costs, mean ± SD, $	4250 ± 7143	3384 ± 5936	.047[b]
Inpatient			
Number of visits per patient, mean ± SD	0.11 ± 0.40	0.06 ± 0.30	<.001[b]
Cost per patient, mean ± SD, $	926 ± 4242	598 ± 4452	<.001[b]
Emergency department			
Number of visits per patient, mean ± SD	0.24 ± 0.67	0.19 ± 0.57	.034[b]
Cost per patient, mean ± SD, $	142 ± 452	131 ± 524	.020[b]
Outpatient			
Number of visits per patient, mean ± SD	9.26 ± 9.48	8.49 ± 7.56	.192
Cost per patient, mean ± SD, $	1899 ± 4648	1323 ± 2212	.071
Drug			
Cost per patient, mean ± SD, $	1283 ± 1796	1333 ± 2362	.167
Total mental health–related costs, mean ± SD, $	2886 ± 5582	2303 ± 4300	.159
Inpatient			
Number of visits per patient, mean ± SD	0.10 ± 0.38	0.06 ± 0.30	<.001[b]
Cost per patient, mean ± SD, $	801 ± 4007	482 ± 3463	<.001[b]
Emergency department			
Number of visits per patient, mean ± SD	0.08 ± 0.41	0.06 ± 0.30	.170
Cost per patient, mean ± SD, $	43 ± 283	35 ± 226	.187
Outpatient			
Number of visits per patient, mean ± SD	6.09 ± 7.54	5.48 ± 5.94	.141
Cost per patient, mean ± SD, $	993 ± 2890	712 ± 1663	.043[b]
Drug			
Cost per patient, mean ± SD, $	1050 ± 1205	1074 ± 1194	.219

ADHD indicates attention-deficit/hyperactivity disorder; GIR, guanfacine immediate release; GXR, guanfacine extended release; SD, standard deviation.
[a]Age was calculated at the index date.
[b]Significant at α <.05.
[c]Combination therapy was defined as the fill of at least 1 nonindex ADHD drug during the preindex period, coupled with a fill of the same nonindex ADHD drug within 30 days after the index date with 30 days or more of overlapping use prior to index drug discontinuation. Monotherapy was defined as not fulfilling the criteria for combination therapy.
[d]As a sensitivity analysis, combination therapy was redefined as the fill of at least 1 nonindex ADHD drug during the preindex period, coupled with a fill of any nonindex ADHD drug within 30 days of the index date with 30 days or more of overlapping use prior to index drug discontinuation. The sensitivity for monotherapy was defined as not fulfilling the criteria for the sensitivity of combination therapy.
[e]Psychotherapy was defined as nonmedication psychotherapies such as behavioral treatment.
[f]Only the specific physical and mental comorbidities listed factored into the overall prevalence of any physical and mental comorbidities.

Table 2. Comparison of Treatment Patterns During the 6-Month Study Period

Treatment Pattern	GIR Users (n = 743)	GXR Users (n = 2344)	*P* (Log-Rank Test)	Adjusted Hazard Ratio[a] (95% CI)	*P* (Multivariate Model)
Therapy adjustments[b]					
Discontinuation	73.49%	53.67%	<.001[c]	1.79 (1.61-1.98)	<.001[c]
Switching					
Base definition[d]	31.78%	15.59%	<.001[c]	2.32 (1.89-2.85)	<.001[c]
Sensitivity definition[e]	11.79%	5.70%	<.001[c]	2.17 (1.53-3.08)	<.001[c]
Augmentation					
Base definition[d]	16.13%	11.45%	.003[c]	1.55 (1.16-2.06)	.003[c]
Sensitivity definition[e]	16.27%	9.47%	<.001[c]	1.58 (1.19-2.11)	.002[c]
Medication possession ratio	0.50	0.64	–	–	<.001[c]
Daily average consumption	1.58	1.07	–	–	<.001[c]

ADHD indicates attention-deficit/hyperactivity disorder; CI, confidence interval; GIR, guanfacine immediate release; GXR, guanfacine extended release.
[a]Hazard ratios indicate the relative hazard of the given outcome comparing GIR users with GXR users. A hazard ratio less than 1 indicates that the outcome was more likely for GXR users, whereas a hazard ratio greater than 1 indicates that the outcome was more likely for GIR users.
[b]The reported rates of therapy adjustment were estimated using the Kaplan-Meier survival estimator.
[c]Significant at $\alpha = .05$.
[d]The base definition of switching required the new ADHD medication be taken for 30 days or longer, and the base definition of augmentation required the augmenting drug to have 30 days or more of supply overlap with the index drug. The medications considered for switching/augmentation (base definition) included GIR, GXR, stimulants, atomoxetine, and clonidine extended-release.
[e]The sensitivity definition of switching required the new ADHD medication to be taken for 60 days or more, and the sensitivity definition of augmentation required the augmenting drug to have 60 days or more of supply overlap with the index drug. The medications considered for switching/augmentation (sensitivity definition) included GIR, GXR, stimulants, atomoxetine, clonidine extended release, clonidine immediate release, bupropion, typical and atypical antipsychotics, selective serotonin reuptake inhibitors, and tricyclic antidepressants.

Study Outcomes

Results from the Kaplan-Meier analyses showed that GIR users had significantly higher 6-month rates of discontinuation (73.49% vs 53.67%; *P* <.001), switching (31.78% vs 15.59%; *P* <.001), and augmentation (16.13% vs 11.45%; *P* = .003) than GXR users. After adjusting for baseline characteristics, GIR users remained significantly more likely to discontinue (adjusted hazard ratio [aHR] = 1.79; *P* <.001), switch (aHR = 2.32; *P* <.001), and augment (aHR = 1.55; *P* = .003) treatment. Similar trends were observed when alternative definitions of switching (11.79% vs 5.70%, *P* <.001; aHR = 2.17, *P* <.001) and augmentation (16.27% vs 9.47%, *P* <.001; aHR = 1.58, *P* = .002) were used. In addition, GIR users had a significantly lower average MPR (0.50 vs 0.64; *P* <.001) than GXR users, indicating lower adherence to the index drug. The GIR users also had a significantly higher DACON (1.58 vs 1.07; *P* <.001) than GXR users (**Table 2**).

For resource utilizations, GIR users had significantly more frequent all-cause mean inpatient visits per patient (0.09 vs 0.05; *P* = .008), ED visits per patient (0.26 vs 0.16; *P* <.001), and outpatient visits per patient (9.76 vs 7.99; *P* <.001) than GXR users. After adjusting for baseline characteristics, GIR users had significantly more frequent all-cause inpatient visits (adjusted incidence rate ratio [aIRR] = 1.61; *P* = .022) and ED visits (aIRR = 1.31; *P* = .016), but no statistically significant differences were observed in the number of outpatient visits (aIRR = 1.06; *P* = .080). Similar results were observed for MH-related utilizations. The GIR users had significantly more frequent MH-related visits than GXR users (inpatient visits per patient: 0.08 vs 0.04, *P* = .006; ED visits per patient: 0.09 vs 0.04, *P* <.001; outpatient visits per patient: 6.84 vs 5.30, *P* <.001). After adjusting for baseline characteristics, GIR users still had significantly more MH-related inpatient and ED visits than GXR users (inpatient visits: aIRR = 1.72, *P* = .013; ED visits: aIRR = 1.55, *P* = .030), but not more outpatient visits (aIRR = 1.07, *P* = . 104) (**Table 3**).

Consistent with the findings regarding utilization, GIR users had higher all-cause mean medical care costs compared with GXR users (unadjusted costs: $2775 vs $2104; *P* <.001), which were observed across different types of services, with unadjusted cost differences between the 2 groups of $278, $49, and $344 for inpatient, ED, and outpatient visits, respectively. Although GIR users had lower unadjusted all-cause drug costs ($1439 vs $1830; *P* <.001), unadjusted all-cause total healthcare costs were significantly higher ($4214 vs $3934; *P* = .009). After adjusting for baseline characteristics, all-cause medical care costs were still significantly higher among GIR users (adjusted cost difference [aCD] = $331; *P* = .009), and total drug costs remained significantly lower (aCD = –$438; *P*

Table 3. Resource Utilization and Healthcare Costs During the 6-Month Study Period

Type of Utilization or Cost	GIR Users (n = 743) Mean Number of Visits[a]	GXR Users (n = 2344) Mean Number of Visits[a]	Unadjusted Incidence Rate Ratio (95% CI)	*P*	Adjusted Incidence Rate Ratio (95% CI)	*P*
Utilization						
All cause						
Inpatient visits	0.09	0.05	1.79 (1.17-2.74)	.008[b]	1.61 (1.07-2.42)	.022[b]
ED visits	0.26	0.16	1.60 (1.27-2.01)	<.001[b]	1.31 (1.05-1.63)	.016[b]
Outpatient visits	9.76	7.99	1.22 (1.14-1.31)	<.001[b]	1.06 (0.99-1.12)	.080
Mental health–related						
Inpatient visits	0.08	0.04	1.90 (1.21-2.99)	.006[b]	1.72 (1.12-2.64)	.013[b]
ED visits	0.09	0.04	2.23 (1.48-3.37)	<.001[b]	1.55 (1.04-2.31)	.030[b]
Outpatient visits	6.84	5.30	1.29 (1.18-1.41)	<.001[b]	1.07 (0.99-1.15)	.104
Cost	**Mean ± SD, $**	**Mean ± SD, $**	**Unadjusted Difference (GIR − GXR), $**	***P***	**Adjusted Difference (GIR − GXR), $**	***P***
All cause						
Total costs	4214 ± 7972	3934 ± 8497	280	.009[b]	−239	.068
Medical care costs[c]	2775 ± 7373	2104 ± 7918	671	<.001[b]	331	.009[b]
Inpatient visits	978 ± 6191	700 ± 6037	278	.007[b]	−117	.226
ED visits	161 ± 579	112 ± 450	49	.011[b]	12	.212
Outpatient visits	1636 ± 2909	1292 ± 3097	344	<.001[b]	70	.291
Drug costs	1439 ± 1622	1830 ± 2461	−391	<.001[b]	−438	<.001[b]
Mental health–related						
Total costs	3062 ± 6665	2784 ± 4921	278	<.001[b]	−159	.085
Medical care costs[c]	1891 ± 6281	1220 ± 4562	671	<.001[b]	401	.022[b]
Inpatient visits	845 ± 5495	508 ± 3948	338	.003[b]	3	.277
ED visits	45 ± 240	31 ± 222	14	.007[b]	−4	.254
Outpatient visits	1001 ± 2296	681 ± 1692	320	<.001[b]	117	.044[b]
Drug costs	1171 ± 1189	1564 ± 1302	−393	<.001[b]	−440	<.001[b]

CI indicates confidence interval; ED, emergency department; GIR, guanfacine immediate release; GXR, guanfacine extended release.
[a]Incidence rate ratios compare the frequency of medical resource utilization by GIR users versus GXR users. An incidence rate ratio greater than 1 indicates that GIR users had more frequent medical visits, whereas an incidence rate ratio less than 1 indicates GIR users had less frequent medical visits.
[b]Significant at $\alpha = .05$.
[c]Medical care consists of inpatient, ED, and outpatient visits.

<.001). The adjusted difference in all-cause total healthcare costs was not significant (aCD = –$239; *P* = .068). Similar patterns were observed for MH-related costs. Without adjustment, GIR users had significantly higher mean MH-related total healthcare costs ($3062 vs $2784; *P* <.001), higher medical care costs ($1891 vs $1220; *P* <.001), and lower drug costs ($1171 vs $1564; *P* <.001). After adjusting for baseline characteristics, GIR users still had significantly higher MH-related medical costs and significantly lower MH-related drug costs (medical care: aCD = $401, *P* <.022; drugs: aCD = –$440, *P* <.001). Mental health–related total healthcare costs were not significantly different between the 2 cohorts (aCD = –$159; *P* = .085) (Table 3).

Using the alternative definition to define combination therapy with the index drug, sensitivity analyses were conducted for all adjusted models. Results for all study outcomes remained robust except for the hazard ratio for augmentation (sensitivity: aHR = 1.32; *P* <.059), which became insignificant between the 2 cohorts.

DISCUSSION

This study examined the real-world differences between GIR and GXR in the treatment of ADHD in children and adolescents using a nationwide claims database. Results showed that GIR users were more likely than GXR users to adjust therapy (discontinue, switch, or augment). In addition, patients treated with GIR had significantly lower adherence to their medication than GXR users. GIR users were also found to have significantly more inpatient and ED visits than GXR users. Even though GIR users incurred significantly lower drug costs compared with GXR users, the difference was offset by significantly higher medical care costs. Thus, the total healthcare costs were comparable between the 2 groups.

The findings from this study were consistent with previous research examining the differences between immediate-release and extended-release neuropsychological medications, in which extended-release formulations were associated with greater adherence, efficacy, and effectiveness than their immediate-release counterparts.[26,27] The higher rates of discontinuation, switching, and augmentation and greater utilization of ED and inpatient visits among GIR users are consistent with the possibility that patients may not have optimal treatment response compared with GXR users.[23,28] Prior research has indicated that immediate-release nonstimulants such as clonidine immediate release and GIR are limited by quick absorption and clearance.[29] Due to the high peak-to-trough fluctuations of GIR relative to the flatter, sustained plasma concentration profile of GXR, patients using GIR may experience lower efficacy (eg, ADHD symptom control), which could potentially lead to more follow-up medical visits in order to better control ADHD symptoms. This might explain the higher medical resource utilization among GIR patients. In addition, this study found better drug adherence among GXR-treated patients, which may be related to GXR's less complicated dosing schedule (GXR once per day vs GIR 2 or 3 times per day, as was shown by the difference in DACON).[15] As better adherence is associated with better clinical responses and less medical care utilization,[30,31] the lower adherence rate with GIR could be another contributor to the observed higher urgent care utilization among its users.

Given that GIR and GXR have the same active moiety, decision makers may assume that GIR and GXR are interchangeable and consider the use of GIR instead of GXR to reduce drug costs. However, clinical evidence supporting GIR use in ADHD has been limited. The current study showed that the lower pharmacy costs associated with GIR use were offset by higher medical costs, resulting in comparable total healthcare costs. Results of this study, combined with prior evidence,[12,15,29] indicate the need for further investigation of health outcomes associated with GIR's off-label use in ADHD relative to GXR to assess this treatment strategy's relative value.

This study is subject to several limitations. First, although the study uses multiple regressions to control for the observed baseline characteristics, unobserved confounding, which is a common limitation in observational studies, might still impact the analysis. At baseline, it appeared that patients in the GIR cohort might have been more severely ill because they generally had a higher prevalence of comorbidities and utilized more resources than the GXR cohort. Adjusting for differences in observed baseline characteristics, including comorbidities, and the corresponding resource utilization and costs, might control for the difference in disease severity to a certain extent. However, the difference in clinical severity was unobserved. If this difference remained after controlling for the baseline variables in the model, the results could be biased. More information on clinical severity or symptoms might help improve the study, but only randomized, controlled studies can validly address the unobserved confounding issue. Second, because this study only examined data collected from commercial health plans, caution should be exercised in generalizing this study's results to other populations. Lastly, only the first 6 months following treatment initiation were analyzed due to the recent entry of GXR. Further research with a longer time horizon in which treatment outcomes can be assessed is warranted to better compare the long-term impacts of GIR and GXR use.

CONCLUSION

After adjustment for observed baseline differences, this retrospective claims analysis found that GXR use by children and adolescents was associated with lower rates of therapy adjustment and fewer inpatient and ED visits compared with GIR use. Medical costs were higher among GIR users than GXR users, which offset the lower drug costs associated with GIR use and led to comparable total healthcare costs between the 2 groups. These findings could inform decision and policy makers by highlighting the tradeoffs associated with the use of GIR and GXR.

Acknowledgment

Preliminary results of this research were presented as a poster at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 17th Annual International Meeting; June 2-6, 2012; Washington, DC. Julia DiBello, a previous employee of Shire Development LLC, provided research support in the early stages of research design.

Author Affiliations: From Analysis Group, Inc (JX, TLH, HY, TS, EQW), Boston, MA; Shire Development LLC (VS, MHE, PH), Wayne, PA.

Funding Source: This research was funded by Shire Development LLC.

Author Disclosures: Drs Sikirica, Erder, and Hodgkins report employment with Shire Development LLC, as well as stock ownership in the company. Drs Xie, Yang, and Wu, Mr He, and Mr Samuelson report employment with the Analysis Group, Inc, which received funding from Shire Development Inc for the preparation of this manuscript.

Authorship Information: Concept and design (VS, JX, TL, MHE, TS, EQW); acquisition of data (VS, JX, TL, TS); analysis and interpretation of data (VS, JX, TL, PH, HY, TS, EQW); drafting of the manuscript (VS, TL, PH, TS); critical revision of the manuscript for important intellectual content (VS, JX, TL, MHE, PH, HY, TS, EQW); statistical analysis (TL, HY, TS); obtaining funding (VS, JX, EQW); administrative, technical, or logistic support (VS, JX, TL, MHE, PH, HY, TS, EQW); and supervision (VS, JX, MHE, PH, HY, EQW).

Address correspondence to: Vanja Sikirica, PharmD, MPH, Shire, 725 Chesterbrook Blvd, Wayne, PA 19087. E-mail: vsikirica@shire.com.

REFERENCES

1. Centers for Disease Control and Prevention. Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children—United States, 2003 and 2007. *MMWR.* 2010;59(44):1439-1443.

2. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *J Pediatr Psychol.* 2007;32(6): 631-642.

3. Goksøyr PK, Nøttestad JA. The burden of untreated ADHD among adults: the role of stimulant medication. *Addict Behav.* 2008;33(2):342-346.

4. Adler LA. Epidemiology, impairments, and differential diagnosis in adult ADHD: introduction. *CNS Spectr.* 2008;13(8)(suppl 12):4-5.

5. Biederman J, Petty CR, Evans M, Small J, Faraone SV. How persistent is ADHD? a controlled 10-year follow-up study of boys with ADHD. *Psychiatry Res.* 2010; 177(3):299-304.

6. Doshi JA, Hodgkins P, Kale J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry.* 2012;51(10):990-1002.

7. Birnbaum HG, Kessler RC, Lowe SW, et al. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Curr Med Res Opin.* 2005;21(2):195-206.

8. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics.* 2011;128(5):1007-1022.

9. Banaschewski T, Roessner V, Dittmann RW, et al. Non-stimulant medications in the treatment of ADHD. *Eur Child Adolesc Psychiatry.* 2004;13(suppl 1):102-116.

10. Duong S, Chung K, Wigal SB. Metabolic, toxicological, and safety considerations for drugs used to treat ADHD. *Expert Opin Drug Metab Toxicol.* 2012;8(5): 543-552.

11. Arnsten AF, Jin LE. Guanfacine for the treatment of cognitive disorders: a century of discoveries at Yale. *Yale J Biol Med.* 2012;85(1):45-58.

12. Childress AC. Guanfacine extended release as adjunctive therapy to psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Adv Ther.* 2012;29(5):385-400.

13. Signorovitch J, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health.* 2012;15(6):940-947.

14. Signorovitch J, Erder MH, Xie J, et al. Comparative effectiveness research using matching-adjusted indirect comparison: an application to treatment with guanfacine extended release or atomoxetine in children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *Pharmacoepidemiol Drug Saf.* 2012;21(suppl 2):130-137.

15. Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. *Neuropsychiatr Dis Treat.* 2008;4(3):499-506.

16. Posey DJ, McDougle CJ. Guanfacine and guanfacine extended release: treatment for ADHD and related disorders. *CNS Drug Rev.* 2007;13(4):465-474.

17. Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry.* 2001;158(7):1067-1074.

18. Boellner SW, Pennick M, Fiske K, Lyne A, Shojaei A. Pharmacokinetics of a guanfacine extended-release formulation in children and adolescents with attention-deficit-hyperactivity disorder. *Pharmacotherapy.* 2007;27(9):1253-1262.

19. Vivek K, Fanda AK, Varshney S, et al. Extended release pharmaceutical compositions of guanfacine hydrochloride. US Patent Application 20110217373. September 8, 2011.

20. Humana Inc. Provider drug search results. http://apps.humana.com/prescription_benefits_and_services/execreq.asp?processcode=3&srcsite=physician&productid=4&ndc=54092051902&view=c. Accessed September 25, 2012.

21. Aetna, Inc. Pharmacy clinical policy bulletins—Aetna non-Medicare prescription drug plan—attention deficit hyperactivity disorder (ADHD) agents. http://www.aetna.com/products/rxnonmedicare/data/2012/CNS2012/adhd_2012.html. Accessed September 25, 2012.

22. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008;11(1):44-47.

23. Erder MH, Signorovitch JE, Setyawan J, et al. Identifying patient subgroups who benefit most from a treatment: using administrative claims data to uncover treatment heterogeneity. *J Med Econ.* 2012;15(6):1078-1087.

24. Rubino M, Summers KH, Puenpatom A, Fu C, Ohsfeldt RL, Ben-Joseph RH. A comparison of daily average consumption (DACON) of oxycodone and oxymorphone long-acting oral tablets. *J Manag Care Pharm.* 2011;17(5):367-376.

25. Bureau of Labor Statistics, US Department of Labor. Measuring the price change for medical care in the CPI. http://www.bls.gov/cpi/cpifact4.htm. Accessed September 10, 2012.

26. Döpfner M, Gerber WD, Banaschewski T, et al. Comparative efficacy of once-a-day extended-release methylphenidate, two-times-daily immediate-release methylphenidate, and placebo in a laboratory school setting. *Eur Child Adolesc Psychiatry.* 2004;13(suppl 1):I93-I101.

27. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry.* 2006;45(4):408-414.

28. Christensen L, Sasané R, Hodgkins P, Harley C, Tetali S. Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population. *Curr Med Res Opin.* 2010;26(4):977-989.

29. Sallee FR. The role of alpha2-adrenergic agonists in attention-deficit/hyperactivity disorder. *Postgrad Med.* 2010;122(5):78-87.

30. Al-Zakwani IS, Barron JJ, Bullano MF, Arcona S, Drury CJ, Cockerham TR. Analysis of healthcare utilization patterns and adherence in patients receiving typical and atypical antipsychotic medications. *Curr Med Res Opin.* 2003;19(7): 619-626.

31. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care.* 2006;44(4):300-303. ajpb