Impact of a Step Therapy for Guanfacine Extended-Release on Medication Utilization and Health Care Expenditures Among Individuals Receiving Treatment for ADHD

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ABSTRACT

BACKGROUND: While step therapy (ST) policies are generally effective at reducing cost through the managed utilization of targeted medications, the clinical implications of ST policies are not clear and may vary across therapeutic areas. Guanfacine extended-release (GXR) is approved by the FDA for the treatment of attention-deficit/hyperactivity disorder (ADHD) as both monotherapy and adjunctive to stimulant treatment. At the introduction of GXR to the market, Humana implemented an ST policy on GXR requiring the documentation of previous treatment, intolerance, or contraindication to generic clonidine or guanfacine.

OBJECTIVE: To examine the impact of a GXR ST coverage determination (i.e., approved vs. denied) on medication utilization and health care costs among members of a commercial health plan with an ST policy for GXR.

METHODS: This study was a retrospective cohort study of administrative claims data. Humana commercial members prescribed GXR who had an ST coverage determination review were identified. All members included in this analysis were required to be aged 6-17 years, have a diagnosis of ADHD or be receiving stimulant medication, have an ST coverage determination (index event) between September 1, 2009, and May 30, 2012, and have 6 months of pre- and post-index continuous enrollment. Members were assigned to either the approved or denied group based on the outcome of the ST coverage determination. Medical and pharmacy claims data were used to measure baseline demographic and clinical characteristics and to measure medication utilization and health care costs. Outcomes assessed during follow-up included ADHD medication use, proportion of days covered (PDC) with any ADHD medication treatment, time to first observed post-index ADHD treatment, and all-cause and mental health (MH)-related health care costs. Administrative costs associated with the coverage determination process were also estimated. Bivariate and multivariable adjusted analyses were conducted to compare medication utilization and health care costs between the approved and denied groups.

RESULTS: A total of 642 members were included in the analysis (denied group n = 395 [61.5%], approved group n = 247 [38.5%]). The approved and denied groups were similar in terms of baseline demographics, provider characteristics, and baseline MH diagnoses, with the exception of anxiety disorders being more prevalent in the approved group compared with the denied group (18.2% vs. 10.6%, $P=0.006$). A denied GXR coverage determination was associated with a greater percentage of members receiving no ADHD treatment post-index (13.9% vs. 3.2%, $P<0.001$), greater mean [SD] number of days between index and first observed post-index ADHD medication claim (44.5 [59.6] vs. 17.6 [33.4], $P<0.001$), and lower mean [SD] PDC with any ADHD medication post-index (0.59 [0.33] vs. 0.75 [0.26], $P<0.001$). These findings remained statistically significant in multivariable regression models. Unadjusted pre-index median total health care costs and MH-related costs were greater among the approved group compared with the denied group (total health care: $1,582 vs. $1,465, $P=0.033$; MH-related: $993 vs. $981, $P=0.020$). Likewise, post-index median total health care and MH-related costs were greater among the approved group compared with the denied group (total: $2,056 vs. $1,420, $P<0.001$; MH-related: $1,543 vs. $946, $P<0.001$). After adjustment for potentially confounding covariates including pre-index costs, there were no statistically significant differences between the approved and denied groups in all-cause total health care ($P=0.393$) or MH-related health care costs ($P=0.054$).

CONCLUSIONS: The current study found that GXR coverage denial was associated with lower rate of ADHD medication utilization, greater delay in receiving ADHD medication, and lower PDC with ADHD medication. There were no differences observed between the approved and denied group in terms of all-cause total health care or MH-related total health care costs after controlling for potentially confounding variables. Prior to implementation in the ADHD therapeutic area and others, payers should consider the potentially unintended consequences of ST policies, including delay in treatment and undertreatment.

J Manag Care Spec Pharm. 2015;21(9):793-802

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What is already known about this subject

- Step therapy (ST) policies are generally effective at reducing utilization of the target agent.
- The clinical outcomes associated with ST policies are not clear and may vary across therapeutic areas.

What this study adds

- This study represents a novel analysis of the impact of an ST coverage determination (approval vs. denial) on attention-deficit/hyperactivity disorder (ADHD) medication utilization and health care costs among individuals seeking nonstimulant treatment for ADHD.
- Coverage denial was associated with a lower rate of ADHD treatment, longer time to post-index prescription, and lower proportion of days covered with any ADHD medication during the postreview period.
- After controlling for pre-index costs and other potentially confounding variables, there was no statistically significant difference observed in either all-cause or mental health-related health care costs for members with an approved coverage determination versus members with a denied coverage determination.

Step therapy (ST) is a formulary policy intended to encourage the use of lower-cost medications prior to a member progressing to higher-cost treatment options.[1,2] In a recent insurance benefit design survey conducted by the Pharmacy Benefit Management Institute, 56% of employer-sponsored drug benefit programs utilized ST for 1 or more medication class.[3] While ST interventions have been shown to be generally effective at reducing utilization and medication expenditures for the target drug,[1,2] examination of the broader implications of ST policies on health care costs and treatment patterns has generated mixed results, particularly among psychotropic medications.[4-7] In addition, there has been limited examination of the impact of an ST policy in terms of outcomes for individuals who request a formal coverage determination (i.e., an ST override) and are either approved for or denied the restricted medication. In addition, to our knowledge there has been no published research examining the impact of an ST formulary intervention related to attention-deficit/hyperactivity disorder (ADHD) medications.

Recently, there have been new treatment options and new formulations of existing drugs introduced. Several stimulants in immediate-release (IR) tablets have been reformulated into extended-release tablets. Extended-release formulations may reduce fluctuations in medication blood concentration and extend the duration of effect, thereby eliminating the need for additional doses during the day. Intuniv (guanfacine extended-release [GXR]) has been approved by the U.S. Food and Drug Administration (FDA) and is a once-daily alpha-2 adrenergic agonist formulation for the treatment of ADHD in children and adolescents aged 6-17 years. GXR has been shown to provide sustained therapeutic concentrations over longer periods, with reduced peak-to-trough fluctuations due to its controlled absorption.[8] From an outcomes standpoint, a retrospective analysis of medical and pharmacy claims data found greater medication adherence; lower rates of inpatient and emergency department admissions; and lower rates of treatment discontinuation, switching, and augmentation among patients treated with GXR compared with guanfacine IR (GIR).[9] While patients treated with GXR in that study had greater pharmacy costs, they had lower medical costs compared with patients treated with GIR, and there was no significant difference in total health care costs (medical and pharmacy costs combined) between the 2 treatment groups.[9]

Although not approved by the FDA for the treatment of ADHD, and despite a limited evidence base for IR alpha agonists (clonidine and guanfacine) in the treatment of ADHD, IR alpha agonists have been used off-label as a nonstimulant alternative, combination, or adjunct treatment in patients with ADHD.[10-17] Given the single retrospective comparative study of GXR versus GIR, and the differential cost between the IR alpha agonists and GXR, the use of an ST formulary intervention may be a potentially appropriate technique for controlling utilization. Upon GXR approval for market authorization by the FDA on September 2, 2009, a large managed care health plan (Humana) implemented an ST policy on GXR requiring the documentation of previous treatment, intolerance, or contraindication to generic clonidine IR (CIR) or GIR. The purpose of this study was to examine the impact of a GXR ST formulary intervention on broader ADHD medication utilization and health care costs among commercial health plan members receiving treatment for ADHD.

Methods

Data Sources

In order to identify patients requesting a coverage determination for GXR (either directly or through their physicians), a data file summarizing all ST reviews for GXR between September 1, 2009, and May 30, 2012, was utilized. The ST summary data were linked to medical and pharmacy claims data including diagnoses, service dates, service codes, National Drug Code numbers for prescription drug products, days' supply, refill status, provider information, and plan type. Demographic variables were extracted from member enrollment files and the Knowledge Base Management AmeriLINK dataset. The AmeriLINK dataset contains census and consumer-related variables that were used to provide further covariates to the analyses. The AmeriLINK data are not available for members aged less than 21 years; therefore, household sociodemographic data were attributed to the member in the study based on the primary health plan subscriber.

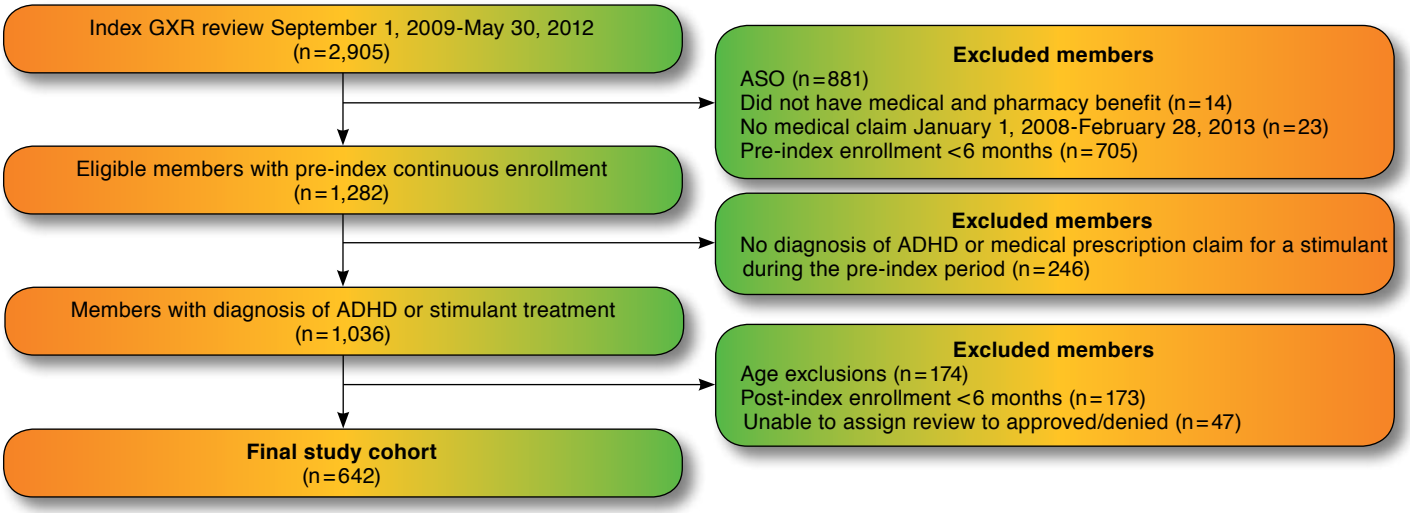
Design and Study Population

This study was a retrospective, claims-based cohort analysis of outcomes among commercial health plan members. Members requesting a coverage determination for GXR were identified, and a corresponding index date was assigned. In the case of multiple reviews during the subject identification period, the first review was considered the index event. In order to be included in the analysis, members were required to have medical and pharmacy coverage, ≥ 6 months of pre- and post-index continuous enrollment, a diagnosis of ADHD or a prescription claim for a stimulant medication during the 6-month pre-index period, and be aged 6-17 years. Health plan members who were enrolled in an administrative services-only plan were not eligible to be included in the study analysis. The study protocol was reviewed and approved prior to study initiation by an independent institutional review board (Schulman Associates IRB, Cincinnati, OH).

Measures

Baseline measures, including member and provider demographic characteristics, medical diagnoses, medication utilization, and health care costs were measured during the 6-month pre-index period. Medication utilization and cost outcomes

FIGURE 1 Attrition Flow Summary



ADHD=attention-deficit/hyperactivity disorder; ASO=administrative services-only plan; GXR=guanfacine extended-release.

were measured during the 6-month post-index observation period. The presence of relevant childhood conditions and mental health (MH) comorbidities were measured based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes observed in any position on 1 or more medical claims during the measurement period (see Appendix A, available in online article).

A medication coverage array was used to evaluate ADHD medication use (amphetamine, methylphenidate, atomoxetine, and alpha agonists). The medication coverage array was populated based on the fill date and associated days' supply for each prescription claim. Based on data contained in the array, medication utilization flags were populated for each member with ≥30 days of medication coverage. Among members utilizing ADHD medication treatment, combination therapy was defined as ≥30 days of overlapping coverage with 2 or more ADHD medication subclasses (with distinction between long- and short-acting formulations). Proportion of days covered (PDC) with any ADHD medication was defined as the sum of days covered with any ADHD treatment divided by the number of days in the observation period. Time to post-index ADHD medication claim was defined as number of days between the index date and the first observed prescription claim for any ADHD medication during the post-index period. Cumulative ADHD treatment gap days were defined as the cumulative number of days during which there was no ADHD medication coverage. Non-ADHD MH medication utilization was identified based on the presence of 1 or more prescription claims.

Direct health care costs were measured based on financial data recorded with adjudicated medical and pharmacy claims (allowed paid amount, including plan- and member-paid shares for paid claims), and all costs were adjusted to 2012 dollars based on the Consumer Price Index. Total health care, medical, and pharmacy costs were calculated. For the medical cost component, ICD-9-CM codes associated with medical claims were used to classify expenditures as MH-related costs (ICD-9-CM codes 290.xx-319.xx in any diagnosis position). For the pharmacy cost component, MH-related pharmacy expenditures were determined for MH medication classes (see Appendix B, available in online article). GXR-related ST administrative costs were determined by health plan staff and were based on estimates of time labor, transaction fees, printing, and postage associated with coverage determination processing; however, administrative cost estimates do not include indirect cost of plan operations, such as associate benefits and overhead, or costs associated with development and maintenance of a formulary policy. GXR ST administrative costs were estimated for each member based on the total number of denied and approved GXR-related reviews for that member multiplied by estimated unit cost for denied and approved reviews. Only GXR reviews were considered in the ST administrative cost estimate.

Statistical Analysis

Study measures are summarized with frequency counts and percentages for categorical data; mean and standard deviation (SD) for noncost continuous measures; and median, first quartile, and third quartile for continuous cost measures. Bivariate statistical tests were used to compare the approved and denied groups on baseline demographic and clinical characteristics, medication utilization, and health care costs. Dichotomous

TABLE 1 Member Demographic and Provider Characteristics for Approved and Denied Groups

Characteristics	Approved (n = 247)		Denied (n = 395)		*P* Value[a]
Age, mean (SD)	11.3	(2.7)	11.4	(2.9)	0.728
Age, n (%)					0.852
6-11 years	147	(59.5)	238	(60.3)	
12-17 years	100	(40.5)	157	(39.7)	
Male, n (%)	191	(77.3)	300	(75.9)	0.689
Plan type, n (%)					0.935
PPO	102	(41.3)	168	(42.5)	
POS	71	(28.7)	118	(29.9)	
HMO	35	(14.2)	51	(12.9)	
Other	39	(15.8)	58	(14.7)	
Geographic region, n (%)					0.319
Northeast	0	(0.0)	0	(0.0)	
Midwest	71	(28.7)	104	(26.3)	
South	154	(62.3)	266	(67.3)	
West	22	(8.9)	25	(6.3)	
Provider degree, n (%)					0.863
MD	209	(84.6)	336	(85.1)	
DO	7	(2.8)	13	(3.3)	
NP/PA	9	(3.6)	9	(2.3)	
Other	1	(0.4)	1	(0.3)	
Missing	21	(8.5)	36	(9.1)	
Provider specialty, n (%)					0.106
Pediatrics	97	(39.3)	175	(44.3)	
Psychiatry	79	(32.0)	89	(22.5)	
Child and adolescent psychiatry	31	(12.6)	50	(12.7)	
Other	27	(10.9)	56	(14.2)	
Missing	13	(5.3)	25	(6.3)	

[a]*P value is from t-test for continuous age variable and from chi-square test for all categorical variables.*

DO = doctor of osteopathic medicine; HMO = health maintenance organization; MD = medical doctor; NP/PA = nurse practitioner/physician assistant; POS = point of service; PPO = preferred provider organization; SD = standard deviation.

and categorical measures were compared between groups using chi-square tests; noncost continuous measures were compared between groups using t-tests; and the Wilcoxon rank-sum test was used to compare health care cost distributions. McNemar's test was used to compare within-group pre- and post-index use of specific non-ADHD MH medication utilization.

A series of a priori prespecified multivariable analyses were conducted to examine the relationship between GXR coverage determination status and study outcomes. GXR coverage determination status was the independent variable of interest in each model. Post-index ADHD medication treatment status (e.g., *any* ADHD treatment vs. no ADHD treatment) was modeled via logistic regression. The 1 relationship between GXR review status and post-index ADHD medication PDC was modeled via linear regression. Time to first observed post-index ADHD prescription claim was modeled using a Cox proportional hazards model. For the logistic, linear, and Cox proportional hazards models, key demographic and clinical variables were forced into the models, and other baseline variables were allowed to enter each model via automated variable selection (Appendix C, available in online article). To test the sensitivity of the findings to selection algorithm, separate models were fit using backward elimination and bidirectional elimination.

Generalized linear models using a log link and a gamma distribution were used to model post-index health care costs while controlling for the influence of potentially confounding baseline characteristics. Total and MH-related health care costs were modeled. Variables included in the cost models were prespecified and were forced into the model (see Appendix C). All analysis was conducted with SAS version 9.3 (SAS Institute, Carey, NC). Alpha level for all analyses was set at 0.05.

Results

Subject Selection and Baseline Characteristics

A total of 642 members who had a diagnosis of ADHD and/or were receiving ADHD medication treatment during the prereview period were identified for the approved (n = 247) or denied (n = 395) groups (see Figure 1). There were no statistically significant differences observed in either member demographics or provider characteristics between the 2 groups

TABLE 2 Baseline Mental Health Conditions and Medication Utilization for Approved and Denied Groups

Characteristics	Approved (n = 247)		Denied (n = 395)		*P* Value[a]
Mental health conditions, n (%)[b]					
ADHD	207	(83.8)	325	(82.3)	0.617
Depression	22	(8.9)	28	(7.1)	0.403
Adjustment reaction	18	(7.3)	25	(6.3)	0.637
ODD	24	(9.7)	35	(8.9)	0.715
OCD	9	(3.6)	7	(1.8)	0.139
Conduct disorder	22	(8.9)	21	(5.3)	0.077
Substance abuse	4	(1.6)	5	(1.3)	0.711
Anxiety disorder	45	(18.2)	42	(10.6)	**0.006**
Bipolar disorder	11	(4.5)	16	(4.1)	0.805
Learning disability	12	(4.9)	18	(4.6)	0.860
Other PDD	10	(4.0)	10	(2.5)	0.282
Autism	6	(2.4)	8	(2.0)	0.733
Asperger's disorder	10	(4.0)	9	(2.3)	0.198
Tics (excluding Tourette's syndrome)	3	(1.2)	13	(3.3)	0.101
Tourette's syndrome	6	(2.4)	3	(0.8)	0.080
Pre-index ADHD medication utilization, n (%)[c]					
No ADHD medication	41	(16.6)	96	(24.3)	**0.020**
Any ADHD medication	206	(83.4)	299	(75.7)	**0.020**
Amphetamine	109	(44.1)	169	(42.8)	0.738
Methylphenidate	92	(37.2)	149	(37.7)	0.904
Alpha agonist	16	(6.5)	4	(1.0)	**<0.001**
Atomoxetine	28	(11.3)	25	(6.3)	**0.025**
Pre-index ADHD treatment pattern, n (%)[d]					
Monotherapy	167	(67.6)	252	(63.8)	0.388
Combination therapy	39	(15.8)	47	(11.9)	0.159
Pre-index PDC with any ADHD medication, mean (SD)	0.53	(0.33)	0.49	(0.34)	0.080

[a]P values for between-group comparisons are from chi-square test. P values in bold represent significance at P < 0.05.

[b]Diagnoses reported were present in any diagnosis position on 1 or more medical claims during observation period. Medical condition categories are not mutually exclusive. Diagnosis of ADHD or a prescription claim for a stimulant medication during the pre-index observation period was a requirement for inclusion in the on-treatment/indication analysis set.

[c]Medication utilization is a status variable that is determined based on coverage with ≥30 days of medication supply during the given observation period. No ADHD medication category is equal to the number of members with no ADHD medication utilization (i.e., <30 coverage days within any class) during pre-index period. Medication utilization categories are not mutually exclusive.

[d]Combination treatment defined as ≥30 days coverage with 2 or more medication subclasses (including long- and short-acting formulations).

ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive compulsive disorder; ODD = oppositional defiant disorder; PDC = proportion of days covered; PDD = pervasive developmental disorder; SD = standard deviation.

(Table 1). There were no baseline differences observed in the prevalence of MH conditions examined, with the exception of anxiety disorders being more frequently observed in the approved group (18.2% vs. 10.6%, $P = 0.006$; Table 2).

Baseline Medication Utilization

No baseline ADHD medication treatment was observed for 16.6% of members in the approved group and 24.3% of members in the denied group ($P = 0.020$; Table 2). Pre-index alpha agonist and atomoxetine use were observed more frequently in the approved group (6.5% vs. 1.0%, $P < 0.001$, and 11.3% vs. 6.3%, $P = 0.025$, respectively). There were no statistically significant between-group differences observed in mean [SD] PDC with any ADHD medication (0.53 [0.33] vs. 0.49 [0.34], $P = 0.080$), frequency of monotherapy (67.6% vs. 63.8%, $P = 0.388$), or frequency of adjunctive therapy (15.8% vs. 11.9%, $P = 0.159$) during the pre-index period.

Non-ADHD MH medication utilization during the baseline period was more common among the approved group (41.3% vs. 28.6%, $P = 0.001$; data not shown in table). Atypical antipsychotic (AAP) utilization was observed more frequently among members in the approved group (22.7% vs. 9.4%, $P < 0.001$), while frequency of antidepressant (23.4% vs. 18.2%, $P = 0.107$), anticonvulsant (7.7% vs. 6.3%, $P = 0.506$), benzodiazepine (2.0% vs. 1.5%, $P = 0.631$), and the other MH medication categories were similar in both groups (data not shown).

Baseline Health Care Costs

Pre-index all-cause total health care, total pharmacy, MH-related total health care, and MH pharmacy cost distributions differed

TABLE 3 Pre-Index All-Cause and Mental Health-Related Health Care Costs (in US$) for Approved and Denied Groups

Costs[a]	Approved (n = 247)			Denied (n = 395)			*P* Value[b]
	Median	Q1	Q3	Median	Q1	Q3	
All-cause costs							
Total health care cost	1,582	953	2,752	1,465	819	2,457	**0.033**
Medical cost	634	290	1,214	510	243	1,243	0.199
Pharmacy cost	828	439	1,421	755	295	1,141	**0.004**
MH-related costs							
Total health care cost	993	651	1,935	981	436	1,607	**0.020**
Medical cost	258	146	591	246	110	581	0.135
Pharmacy cost	681	311	1,131	600	152	1,005	**0.011**

[a]*MH-related costs defined as costs associated with medical claim where ICD-9-CM 290.xx-319.xx was observed in any diagnosis position.*

[b]*P values for between-group comparisons are from Wilcoxon rank-sum test. P values in bold indicate significance at P < 0.05.*

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; MH = mental health; Q1 = first quartile value; Q3 = third quartile value.

significantly between the approved and denied groups (Table 3). In each of these cases, median cost estimates were greater among the approved than the denied group ($P < 0.050$ for all). There were no statistically significant differences in baseline all-cause ($P = 0.199$) or MH-related medical costs ($P = 0.135$).

Post-Index Measures

Members in the denied group displayed longer mean [SD] days to post-index ADHD treatment (44.52 [59.55] vs. 17.62 [33.35], $P < 0.001$), greater cumulative treatment gap days (74.53 [60.09] vs. 45.13 [47.15], $P < 0.001$), and lower PDC with any ADHD medication (0.59 [0.33] vs. 0.75 [0.26], $P < 0.001$; Table 4). No post-index ADHD medication treatment was observed more frequently in the denied than the approved group (13.9% vs. 3.2%, $P < 0.001$). There were no statistically significant differences observed in terms of the frequency of post-index amphetamine, methylphenidate, or atomoxetine use between groups; however, alpha agonist use was lower among the denied group (49.6% vs. 89.9%, $P < 0.001$). GXR utilization was less common among members with a denied GXR coverage determination (14.7% vs. 88.3%, $P < 0.001$), while GIR and CIR utilization was more frequent among the denied group (42.8% vs. 5.3%, P < 0.001, and 6.3% vs. 2.0%, $P = 0.012$, respectively). A higher proportion of members in the approved group were observed to be on adjunctive treatment during the post-index period (44.9% [n = 111] vs. 28.9% [n = 114], $P < 0.001$). In the approved group, most members on adjunctive treatment were receiving a combination of stimulant plus GXR (86.5%, n = 96), while those in the denied group received a stimulant plus GIR (48.2%, n = 55; data not shown).

Similar to baseline, post-index AAP use was more frequent in the approved group (20.6% vs. 10.4%, $P < 0.001$; data not shown). Post-index antidepressant utilization was also greater in the approved group (28.3% vs. 21.5%, $P = 0.049$; data not shown). There were no other differences observed in the non-ADHD MH medication categories examined. An increase in any non-ADHD MH medication use pre- to post-index was observed within the denied group (28.6% vs. 32.2%, $P = 0.048$; data not shown); however, non-ADHD MH medication use did not differ pre- to post-index in the approved group (41.3% vs. 42.5%, $P = 0.622$; data not shown).

Unadjusted post-index health care costs are summarized in Table 5. Median all-cause and MH-related total health care costs were greater for the approved group in the unadjusted analyses (both $P < 0.001$). There were no statistically significant differences between groups in medical costs; however, median all-cause and MH-related pharmacy costs were greater in the approved group (both $P < 0.001$). ST administrative costs were greater in the denied group ($P < 0.001$).

Multivariable Adjusted Analyses

For the linear regression and Cox proportional hazards models, backward elimination and bidirectional elimination resulted in identical models. For the logistic regression model, the 2 variable selection algorithms resulted in inclusion of different variables; however, the results from both models were similar in terms of magnitude and significance (Appendices D-I, available in online article).

After controlling for potentially confounding variables, the odds of observing treatment with any ADHD medication during the post-index period were lower among members with a denied GXR coverage determination compared with those with an approved coverage determination (odds ratio = 0.18, 95% confidence interval [CI] = 0.08-0.42). In the multivariable adjusted model of PDC, GXR coverage approval was associated with a 14 percentage point increase (95% CI = 10-18 percentage points) in the PDC with any ADHD medication during the post-index period (regression coefficient [B] = 0.14, standard error [SE] = 0.02, $P < 0.001$). GXR coverage denial was associated with a lower hazard rate (HR) for observation of a

TABLE 4 Summary of Medication Utilization Outcomes for Approved and Denied Groups

	Approved (n = 247)		Denied (n = 395)		*P* Value[a]
Time to first observed post-index ADHD medical prescription, mean (SD)[b]	17.62	(33.35)	44.52	(59.55)	**< 0.001**
Cumulative treatment gap days, mean (SD)	45.13	(47.15)	74.53	(60.09)	**< 0.001**
Post-index PDC with any ADHD treatment, mean (SD)	0.75	(0.26)	0.59	(0.33)	**< 0.001**
Post-index medication utilization, n (%)[c]					
No ADHD medication	8	(3.2)	55	(13.9)	**< 0.001**
Any ADHD medication	239	(96.8)	340	(86.1)	**< 0.001**
Amphetamine	81	(32.8)	144	(36.5)	0.344
Methylphenidate	78	(31.6)	130	(32.9)	0.726
Alpha agonist	222	(89.9)	196	(49.6)	**< 0.001**
Clonidine immediate-release	5	(2.0)	25	(6.3)	**0.012**
Clonidine extended-release	3	(1.2)	0	(0.0)	**0.028**
Guanfacine immediate-release	13	(5.3)	169	(42.8)	**< 0.001**
Guanfacine extended-release	218	(88.3)	58	(14.7)	**< 0.001**
Atomoxetine	10	(4.0)	24	(6.1)	0.264
Post-index ADHD treatment pattern, n (%)[d]					
Monotherapy	128	(51.8)	226	(57.2)	0.181
Combination therapy	111	(44.9)	114	(28.9)	**< 0.001**

[a]P values for time to event data from log-rank test; P values for comparison of cumulative gap days and PDC from t-test; and P values for medication utilization from chi-square test. P values in bold indicate significance at P < 0.05.

[b]Time to first observed post-index medical prescription claim is duration in days between index date and first observed prescription claim for any ADHD medication.

[c]Medication utilization is a status variable that is determined based on coverage with ≥ 30 days of medication supply during the given observation period. No ADHD medication category is equal to the number of members with no ADHD medication utilization (i.e., < 30 coverage days within any class) during pre-index period. Medication utilization categories are not mutually exclusive.

[d]Combination treatment defined as ≥ 30 days coverage with 2 or more medication subclasses (including long- and short-acting formulations).

ADHD = attention-deficit/hyperactivity disorder; PDC = proportion of days covered; SD = standard deviation.

post-index prescription claim for any ADHD medication (B = −0.65, SE = 0.09, HR = 0.52, $P < 0.001$). There was no statistically significant relationship observed between GXR coverage denial and either all-cause total costs (B = −0.07, SE = 0.08, $P = 0.393$) or MH-related total costs (B = −0.15, SE = 0.08, $P = 0.054$) in the multivariable adjusted cost analysis.

Discussion

To our knowledge, this study represents the first analysis of outcomes associated with an ST formulary policy in ADHD, and the first to examine medication utilization and health care costs based on outcome of a coverage determination review.[2,18] Results indicate that a coverage review denial was associated with a lower rate of treatment for ADHD, greater delay in receiving ADHD treatment, and lower PDC with any ADHD treatment. These findings were evident in unadjusted comparisons and analyses that controlled for baseline differences in demographic and clinical characteristics among the study groups.

As expected, GXR utilization during the post-index period was less common among denied than approved members. However, there may have been unintended consequences related to the ADHD treatment, including reduced ADHD medication utilization overall. Approximately 14% of members in the denied group and 3% in the approved group did not receive any ADHD treatment during the postreview period. These findings are generally aligned with previous research in other therapeutic areas, indicating that a substantial portion of patients do not receive prescription medication treatment following ST edit at the point of sale.[19,20] In the context of children and adolescents with ADHD, lack of treatment can have significant consequences, manifesting in school-related difficulties and psychosocial impairment.[21]

Furthermore, only 50% of members who were denied coverage for GXR received any alpha agonist treatment (primarily GIR) during the post-index period, suggesting limited effectiveness in directing members who were requesting GXR to the less expensive CIR or GIR. There was no difference in post-index amphetamine, methylphenidate, or atomoxetine utilization observed between the approved and denied groups, suggesting that there was not an obvious compensatory increase in stimulant treatment among members with a denied coverage determination.

Another potential unintended consequence observed was that members in the approved and denied groups displayed degrees of treatment discontinuity. The PDC with *any* ADHD medication was significantly lower among members in the denied group. Similarly, substantial treatment gap days were observed in both groups, with a greater number of treatment gap days among the denied group. There was also an observed

TABLE 5 Post-Index All-Cause and Mental Health-Related Costs (US$) for Approved and Denied Groups

Costs[a]	Approved (n = 247)			Denied (n = 395)			*P* Value[b]
	Median	Q1	Q3	Median	Q1	Q3	
All-cause costs							
Total health care cost	2,056	1,263	3,325	1,420	775	2,563	**< 0.001**
Medical cost	464	185	1,122	455	191	1,216	0.796
Pharmacy cost	1,283	900	2,037	767	237	1,231	**< 0.001**
ST administrative cost[c]	6	6	6	13	13	13	**< 0.001**
MH-related costs							
Total health care cost	1,543	1,013	2,399	946	443	1,750	**< 0.001**
Medical cost	176	61	479	151	0	538	0.676
Pharmacy cost	1,154	813	1,878	653	178	1,038	**< 0.001**
ST administrative cost[c]	6	6	6	13	13	13	**< 0.001**

[a]MH-related costs defined as costs associated with medical claim where ICD-9-CM 290.xx-319.xx was observed in any diagnosis position.

[b]P values for between-group comparisons are from Wilcoxon rank-sum test. P values in bold indicate significance at P < 0.05.

[c]Only administrative costs related to GXR coverage determination were estimated; therefore MH-related ST administrative costs and all-cause ST administrative costs are equivalent. Adminstrative costs are estimates based on time labor, transaction fees, printing, and postage associated with coverage determination processing; however, administrative cost estimates do not include indirect cost of plan operations, such as associate benefits and overhead.

GXR = guanfacine extended-release; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; MH = mental health; Q1 = first quartile value; Q3 = third quartile value; ST = step therapy.

delay in terms of the time from initiation of the coverage determination review process to receipt of *any* ADHD treatment during the post-index period. The average time to postreview ADHD prescription was more than 2-fold longer in the denied than the approved group. A substantial body of evidence demonstrates that untreated ADHD has a negative impact on long-term outcomes, such as academic performance and psychosocial functioning, and that treatment for ADHD is associated with positive impact on social, academic, and behavioral health outcomes.[22-25] While medication adherence is closely associated with short-term treatment response,[26] the clinical impact of short-term, involuntary delay or discontinuity in treatment is not clear and warrants further research.

ST policies are generally associated with prescription drug savings at the plan level but may be associated with increased medical service utilization and total health care expenditures. In this study, pre- and post-index unadjusted total health care and total pharmacy costs were lower among members in the denied group. The unadjusted health care costs for the approved group may have been higher as a result of greater level of MH-related comorbidity (e.g., anxiety disorders), greater pre-index medication utilization, or other factors. After controlling for potentially confounding baseline characteristics including pre-index health care costs and MH-related comorbidity between groups, no differences were observed in all-cause total health care or MH-related total health care costs.

ST formulary policies directly impact medication utilization by halting adjudication of the prescription claim at the point of service. In response to an ST edit, the provider must be contacted by either the patient or the pharmacist in order to amend the prescription order of the first-line agent or for the provider to request a coverage determination from the health plan. In a survey of health plan members subject to ST for proton pump inhibitors and nonsteroidal anti-inflammatory medications, approximately 20% of members reported that neither they nor their pharmacists contacted the prescribing physicians after a point-of-service ST rejection.[27] The current study focused on treatment patterns and economic outcomes in an insured population for patients who engage with the ST coverage determination process and requested a coverage determination typically through their physicians. This analysis may underestimate the total effect of a ST policy on overall medication utilization patterns and economic outcomes in other populations. For example, ST policies may also impact medication utilization indirectly. Previous research has demonstrated that a formulary policy implemented in 1 market segment (e.g., Medicaid) is associated with a "spillover" effect on prescribing behaviors in other market segments (e.g., commercial health plans).[28] Further research is necessary to address the broader implications of an ST policy in the ADHD therapeutic area and other populations of ADHD (e.g., adults).

Limitations

Several limitations apply to this study. Although the study groups did not appear to be different in observed measures, they may differ on clinical measures, such as symptomatic or functional impairments that are not specified within claims data. In addition, certain factors that may impact the study outcomes may not be possible or practical to operationalize via claims data. For example, time since initial diagnosis of ADHD and time since initial treatment for ADHD were identified as potentially relevant variables during the design of the study;

however, determination of condition onset and time since initial medication treatment was determined to be impractical within the context of the available claims data. Although these specific variables were not included in our study, we attempted to incorporate a broad range of plan, provider, clinical, demographic, and socioeconomic characteristics that could influence study outcomes.

Analysis of medication utilization based on pharmacy claims data is predicated on health plan members using their pharmacy benefits and comprehensive capture of medication utilization via prescription claims. Previous research suggests that, in response to an ST edit, members may obtain prescription medication outside of the pharmacy benefit (e.g., by paying out-of-pocket for medication).[27,29] In addition, shunting of health plan members to these alternative channels may be associated with lower member satisfaction with pharmacy benefits.[29] As is the case with previous claims-based studies examining the impact of an ST policy on medication utilization,[19,20] medication utilization facilitated through channels outside the pharmacy benefit are not assessed in the current study.

We assessed health care costs based on financial data associated with paid medical and pharmacy claims. Medication costs for drugs obtained outside the pharmacy benefit (e.g., by paying out-of-pocket for medication) are not captured in claims data. Costs associated with administration of the coverage determination process are important considerations from the health plan perspective and have not typically been included in previous research.[1] Our analysis included unit cost estimates for approved and denied claims based on time labor, transaction fees, printing, and postage associated with coverage determination processing. Other administrative costs related to development and maintenance of a medication formulary, utilization management policies, and other health plan operations were not included in our administrative cost estimates. Thus, the administrative cost included in this study is an underestimate of the total cost associated with developing, maintaining, and administering a specific formulary policy.

A cause-effect relationship cannot be established based on this study, since it is an observational study based on retrospective claims data. Although multiple regression modeling was used in this analysis to control for potential confounding related to between-group differences in baseline demographic and clinical factors, this approach can only reduce bias caused by appropriately measured covariates that are included in the statistical models. Variables that are not measured or recorded in the administrative claims data may represent a study bias. These results are valid to the health plan and membership examined but may not be generalizable to other populations or plans (e.g., Medicaid).

Conclusions

GXR coverage determination denial, compared with approval, was associated with a lower rate of ADHD medication utilization as measured by pharmacy claims, greater delay in receiving ADHD treatment, and lower PDC with ADHD treatment. No differences were observed between the approved and denied groups in terms of all-cause total health care or MH-related total health care costs after controlling for relevant variables including pre-index costs. Payers should consider the potentially unintended consequences of ST policies, in particular treatment discontinuity and under treatment, when developing and implementing policies in the ADHD therapeutic area.

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DISCLOSURES

Funding for this research was provided by Shire Development. Shire Pharmaceuticals is the parent company of Shire Development, which is a research and development organization. Sikirica was an employee of Shire at the time of this work and owns stock in Shire. Suehs, Mudumby, Dufour, and Patel are employees of Comprehensive Health Insights, a subsidiary of Humana, which received funding from Shire Development for this study. Suehs, Mudumby, Dufour, and Patel own stock in Humana.

Study concept and design were contributed by Suehs, Sikirica, Dufour, Patel, and Mudumby. Mudumby, Dufour, Patel, and Suehs were responsible for data collection, and data interpretation was contributed by Suehs, Sikirica, Mudumby, Patel, and Dufour. The manuscript was written and revised by Suehs, Sikirica, Dufour, Patel, and Mudumby.

ACKNOWLEDGMENTS

The authors thank Anthony DeLeon, PharmD, MS, for his contributions to the development of the study concept and Moshe Fridman, PhD, for his contributions to the study statistical analysis, both of which were funded by Shire Pharmaceuticals. The authors also acknowledge Caudex (supported by Shire International GmbH, Switzerland) for editorial assistance and Antonia Panayi of Shire for helpful comments.

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APPENDIX A Comorbidities and Associated ICD-9-CM Diagnostic Codes

Medical Condition	ICD-9-CM Codes
Mental health comorbidities	
Depression	296.2x, 296.3x, 311.xx, 300.4x
Adjustment reaction	309.xx
Oppositional defiant disorder	313.81
Obsessive compulsive disorder	300.3x
Conduct disorder	312.xx
Substance abuse	291.xx, 292.xx, 303.xx, 304.xx, 305.xx
Anxiety disorder	293.84, 300.0x, 300.2x, 313.0x
Bipolar disorder	296.0x–296.1x, 296.4x–296.8x
Learning disability	315.xx
Other pervasive developmental disorder	299.1x, 299.9x
Autism	299.0x
Asperger's disorder	299.8x
Tics (excluding Tourette's syndrome)	307.2x (excluding 307.23)
Tourette's syndrome	307.23

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B Mental Health Medication Classes and Associated Generic Product Identifier Codes

Class	Identifier
Atypical antipsychotics	
Clozapine	5915202000
Risperidone	5907007000
Olanzapine	5915706000
Quetiapine	5915307010
Ziprasidone	5940008510
Asenapine	5915501510
Paliperidone	5907005000
Iloperidone	5907003500
Aripiprazole	5925001500
Lurasidone	5940002310
Long-acting atypical antipsychotics	
Paliperidone palmitate	5907005010
Olanzapine pamoate	5915706010
Risperidone microspheres	5907007010
Conventional antipsychotics	
Chlorpromazine HCl	5920001510
Fluphenazine HCl	5920002510
Haloperidol	5910001010
Loxapine HCl	5915402010
Loxapine succinate	5915402020
Mesoridazine	5920003010
Molindone HCl	5916005010 & 5940001010
Perphenazine	5920004500
Prochlorperazine	5920005510
Thioridazine	5920008010
Thiothixene	5930002010
Thiothixene HCl	5930002020
Trifluoperazine	5920008510
Long-acting conventional antipsychotics	
Fluphenazine decanoate	5920002530
Haloperidol decanoate	5910001030
Antidepressants	
Tricyclic antidepressants	
Amitriptyline	5820001010
Amoxapine	5820002000
Clomipramine	5820002510
Desipramine	5820003010
Doxepin	5820004010
Imipramine HCl	5820005010
Imipramine pamoate	5820005020
Nortriptyline	5820006010
Protriptyline	5820007010
Trimipramine	5820008010
Selective serotonin reuptake inhibitors	
Citalopram	5816002010
Escitalopram	5816003410
Fluoxetine	5816004000
Fluvoxamine	5816004510
Paroxetine HCl	5816006000
Paroxetine mesylate	5816006030
Sertraline	5816007010
Serotonin norepinephrine reuptake inhibitors	
Desvenlafaxine	5818002020
Duloxetine	5818002510
Venlafaxine	5818009010
Atypical antidepressants	
Bupropion HCl	5830004010
Bupropion HBr	5830004020
Maprotiline	5830001010
Mirtazapine	5803005000
Nefazodone	5812005010
Trazodone	5812008010
Monoamine oxidase inhibitors	
Selegiline transdermal system	5810002700
Tranylcypromine	5810003010
Phenelzine	5810002010
Isocarboxazid	5810001000
Benzodiazepines	
Alprazolam	5710001000
Chlordiazepoxide	5710002010
Clonazepam	7210001000
Clorazepate	5710003010
Diazepam	5710004000
Estazolam	6020100500
Flurazepam	6020101010
Lorazepam	5710006000
Oxazepam	5710007000
Quazepam	6020102800
Temazepam	6020103000
Triazolam	6020104000
Sedative hypnotics, non-benzodiazepine	
Chloral hydrate	6020002000
Butabarbital	6010002510
Amobarbital and secobarbital	6099000210
Phenobarbital	6010006000
Eszopiclone	6020403500
Mephobarbital	6010004000
Pentobarbital	6010005510
Ramelteon	6025006000
Secobarbital	6099000210
Zaleplon	6020407000
Zolpidem	6020408010
Anxiolytics, non-benzodiazepine	
Buspirone	5720005000
Hydroxyzine HCl	5720004010
Hydroxyzine pamoate	5720004020
Lithium	
Lithium carbonate	5950001010
Lithium citrate	5950001020
Anticonvulsants	
Mood-stabilizing anticonvulsants	
Carbamazepine	7260002000
Carbamezepine	5940001500
Divalproex	7250001010
Lamotrigine	7260004000
Oxcarbazepine	7260004600
Valproate sodium	7250002010
Valproic acid	7250003000
Other anticonvulsants	
Ethosuximide	7240001000
Ethotoin	7220001000
Felbamate	7212002000
Gabapentin	7260003000
Lacosamide	7260003600
Levetiracetam	7260004300
Methsuximide	7240002000
Phenytoin	7220003020
Phenytoin sodium	7220003000
Phenytoin sodium	7220003010
Pregabalin	7260005700
Primidone	7260006000
Rufinamide	7260006500
Tiagabine	7217007010
Topiramate	7260007500
Trimethadione	7230002000
Vigabatrin	7217008500
Zonisamide	7260009000
Anti-Parkinsonism agents	
Amantadine	7320001010
Benztropine	7310001010
Biperiden	7310002010
Trihexyphenidyl	7310007010

APPENDIX C Summary of Multivariable Model Variables

Independent Variables	Variable Type	Any ADHD Tx	PDC	Time to ADHD Claim	Total HC Cost	MH-Related HC Cost
GXR review disposition	Dichotomous	F	F	F	F	F
Member age	Continuous	F	F	F	F	F
Member female sex	Dichotomous	F	F	F	F	F
Plan type: POS	Indicator ref: PPO	AS	AS	AS	F	F
Plan type: HMO	Indicator ref: PPO	AS	AS	AS	F	F
Plan type: other	Indicator ref: PPO	AS	AS	AS	F	F
Member GR: Midwest	Indicator ref: South	AS	AS	AS	N/A	N/A
Member GR: West	Indicator ref: South	AS	AS	AS	N/A	N/A
Member dwelling type: dwelling other/missing	Ref: Single family	AS	AS	AS	N/A	N/A
HH education: HS/<12/missing	Indicator ref: some college	AS	AS	AS	F	F
HH education: associate degree	Indicator ref: some college	AS	AS	AS	F	F
HH education: bachelor or master	Indicator ref: some college	AS	AS	AS	F	F
HH income: 40-100k (US$)	Indicator ref: <40k or missing	F	F	F	F	F
HH income: 100-200k (US$)	Indicator ref: <40k or missing	F	F	F	F	F
HH income: >200k (US$)	Indicator ref: <40k or missing	F	F	F	F	F
Number of persons in HH	Continuous	AS	AS	AS	N/A	N/A
Provider specialty: pediatrics	Indicator ref: FP/GP/other/missing	F	F	F	N/A	N/A
Provider specialty: psychiatry	Indicator ref: FP/GP/other/missing	F	F	F	N/A	N/A
Provider specialty: CAP	Indicator ref: FP/GP/other/missing	F	F	F	F	F
Provider GR: Midwest	Indicator ref: South	AS	AS	AS	F	F
Provider GR: other/Northeast/West	Indicator ref: South	AS	AS	AS	F	F
Provider sex	Dichotomous	AS	AS	AS	N/A	N/A
Provider type: DO	Indicator ref: MD	AS	AS	AS	N/A	N/A
Provider type: NP/PA	Indicator ref: MD	AS	AS	AS	N/A	N/A
Provider type: other/missing	Indicator ref: MD	AS	AS	AS	N/A	N/A
Review time frame: nonsummer	Indicator ref: summer	F	F	F	F	F
Sequential quarter count	Continuous	F	F	F	F	F
Pre-index diagnosis: ADHD	Dichotomous	F	F	F	F	F
Pre-index diagnosis: depression	Dichotomous	F	F	F	F	F
Pre-index diagnosis: anxiety disorder	Dichotomous	F	F	F	F	F
Pre-index diagnosis: bipolar disorder	Dichotomous	F	F	F	F	F
Pre-index diagnosis: substance abuse	Dichotomous	F	F	F	F	F
Pre-index diagnosis: adjustment reaction	Dichotomous	F	F	F	F	F
Pre-index diagnosis: ODD/CD	Dichotomous	F	F	F	F	F
Pre-index diagnosis: PDD	Dichotomous	F	F	F	F	F
Pre-index diagnosis: tics or Tourette's syndrome	Dichotomous	F	F	F	F	F
Any treatment days 91-180 pre-index	Dichotomous	AS	AS	AS	F	F
Any treatment within 90 days pre-index	Dichotomous	AS	AS	AS	F	F
Pre-index amphetamine	Dichotomous	F	F	F	F	F
Pre-index methylphenidate	Dichotomous	F	F	F	F	F
Pre-index alpha agonist	Dichotomous	F	F	F	F	F
Pre-index atomoxetine	Dichotomous	F	F	F	F	F
No pre-index treatment	Indicator ref: monotherapy	F	F	F	F	F
Adjunctive treatment pre-index	Indicator ref: monotherapy	F	F	F	F	F
Pre-index PDC	Continuous	AS	AS	AS	F	F
Pre-index MH-related medical costs	Continuous	AS	AS	AS	N/A	F
Pre-index MH-related pharmacy costs	Continuous	AS	AS	AS	N/A	F
Pre-index number MH-related OP encounters	Continuous	AS	AS	AS	N/A	F
Pre-index all-cause medical costs	Continuous	N/A	N/A	N/A	F	N/A
Pre-index all-cause pharmacy costs	Continuous	N/A	N/A	N/A	F	N/A
Pre-index number all-cause outpatient encounters	Continuous	N/A	N/A	N/A	F	N/A

ADHD = attention-deficit/hyperactivity disorder; AS = automated selection; CAP = child and adolescent psychiatry; DO = doctor of osteopathy; F = forced; FP = family practioner; GP = general practioner; GR = geographic region; GXR = guanfacine extended-release; HC = health care; HH = household; HMO = health maintenance organization; HS = high school; MD = medical doctor; MH = mental health; N/A = not applicable; NP/PA = nurse practitioner/physician assistant; ODD/CD = oppositional defiant disorder/conduct disorder; OP = outpatient; PDC = proportion of days covered; PDD = pervasive developmental disorder; POS = point of service; ref = reference; Tx = treatment.

APPENDIX D Logistic Regression Model for Post-Index ADHD Treatment Status, Backward Elimination Variable Selection Process

Parameter	Estimate	SE	Chi-square	*P* Value[a]	OR	95% CI	
Intercept	15.20	513.90	0.00	0.976			
Index review denied	**–0.85**	**0.21**	**16.02**	***<0.0001***	**0.18**	**0.08**	**0.42** [b]
Age (years)	–0.07	0.05	1.95	0.163	0.93	0.84	1.03 [b]
Member female sex	0.00	0.18	0.00	0.980	1.01	0.50	2.03 [b]
HH income: 40-100k (US$)	–0.10	0.25	0.17	0.537	1.35	0.63	2.86 [b]
HH income: 100-200k (US$)	–0.19	0.31	0.38	0.683	1.23	0.51	3.01 [b]
HH income: >200k (US$)	0.69	0.36	3.78	0.052	2.99	1.07	8.32 [b]
Provider specialty: child and adolescent psychiatry	0.43	0.37	1.40	0.238	1.86	0.62	5.58 [b]
Provider specialty: pediatrics	–0.08	0.25	0.09	0.758	1.12	0.51	2.46 [b]
Provider specialty: psychiatry	–0.17	0.32	0.29	0.592	1.01	0.38	2.70 [b]
Nonsummer vs. summer	0.35	0.20	3.15	0.076	2.01	0.93	4.34 [b]
Sequential quarter count	0.06	0.06	1.24	0.266	1.07	0.95	1.19 [b]
ADHD diagnosis	–0.17	0.26	0.45	0.501	0.71	0.26	1.93 [b]
Depression diagnosis	0.48	0.43	1.29	0.257	2.63	0.50	14.01 [b]
Anxiety disorder	0.12	0.27	0.19	0.660	1.27	0.45	3.60 [b]
Bipolar disorder	0.63	0.58	1.20	0.274	3.55	0.37	34.25 [b]
Substance abuse	7.14	394.50	0.00	0.986	NE	NE	NE [b]
Adjustment or reaction disorder	–0.31	0.28	1.15	0.283	0.54	0.18	1.66 [b]
ODD/CD	0.24	0.25	0.89	0.345	1.62	0.60	4.37 [b]
PDD	–0.34	0.37	0.84	0.359	0.51	0.12	2.17 [b]
Tics or Tourette's syndrome	0.33	0.44	0.55	0.459	1.93	0.34	10.98 [b]
Amphetamine use pre-index	0.19	0.38	0.26	0.608	1.47	0.34	6.42 [b]
Methylphenidate use pre-index	–0.02	0.39	0.00	0.962	0.96	0.21	4.37 [b]
Alpha agonist use pre-index	6.27	329.30	0.00	0.985	NE	NE	NE [b]
Atomoxetine use pre-index	–0.74	0.37	4.08	0.043	0.23	0.05	0.96 [b]
No pre-index treatment	0.56	0.72	0.61	0.435	1.83	0.31	10.74 [b]
Adjunctive treatment pre-index	–0.52	0.66	0.61	0.434	0.62	0.14	2.77 [b]
Plan type: HMO	0.42	0.38	1.22	0.269	1.11	0.40	3.14
Plan type: Other	–0.77	0.30	6.60	*0.010*	0.34	0.15	0.77
Plan type: POS	0.04	0.28	0.02	0.881	0.77	0.35	1.68
Pre-index PDC (any ADHD medication)	0.49	0.10	22.32	*<0.0001*	1.63	1.33	1.99

Note: N = 642, df = 30, LR = 119.03, P < 0.001, AIC = 414.11, c = 0.873.

Outcome modeled = post-index ADHD treatment status (1, ADHD medication observed; 0, no ADHD treatment observed).

Reference variables: HH income (US$): <40k or missing; member sex: male; nonsummer: summer; plan type: preferred provider organization; provider geographic region: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing.

Pre-index PDC is scaled to range of values = 0-10.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

[b]*Variable forced into the model.*

ADHD = attention-deficit/hyperactivity disorder; AIC = Akaike's information criterion; c = c-statistic; CI = confidence interval; df = degrees of freedom; HH = household; HMO = health maintenance organization; LR = likelihood ratio; NE = not estimable; ODD/CD = oppositional defiant disorder/conduct disorder; OR = odds ratio; PDC = proportion of days covered; PDD = pervasive developmental disorder; POS = point of service; SE = standard error.

APPENDIX E Logistic Regression Model for Post-Index ADHD Treatment Status, Stepwise Variable Selection Process

Parameter	Estimate	SE	Chi-square	*P* Value[a]	OR	95% CI	
Intercept	15.08	522.10	0.00	0.977			
Index review denied	**–0.86**	**0.21**	**16.22**	***<0.0001***	**0.18**	**0.08**	**0.41** [b]
Age (years)	–0.07	0.05	1.59	0.207	0.93	0.84	1.04 [b]
Member female sex	0.08	0.19	0.20	0.653	1.18	0.57	2.44 [b]
HH income: 40-100k (US$)	–0.13	0.26	0.26	0.750	1.38	0.65	2.93 [b]
HH income: 100-200k (US$)	–0.10	0.32	0.10	0.609	1.42	0.57	3.53 [b]
HH income: >200k (US$)	0.68	0.36	3.59	0.058	3.10	1.11	8.68 [b]
Provider specialty: child and adolescent psychiatry	0.60	0.38	2.51	0.113	2.76	0.87	8.74 [b]
Provider specialty: pediatrics	–0.03	0.25	0.02	0.898	1.47	0.64	3.38 [b]
Provider specialty: psychiatry	–0.15	0.32	0.21	0.650	1.31	0.48	3.58 [b]
Nonsummer vs. summer	0.35	0.20	3.02	0.082	2.00	0.92	4.39 [b]
Sequential quarter count	0.08	0.06	1.78	0.182	1.08	0.96	1.21 [b]
ADHD diagnosis	–0.22	0.26	0.72	0.397	0.64	0.23	1.80 [b]
Depression diagnosis	0.42	0.42	1.00	0.317	2.32	0.45	11.98 [b]
Anxiety disorder	0.01	0.27	0.00	0.961	1.03	0.36	2.96 [b]
Bipolar disorder	0.62	0.58	1.14	0.286	3.48	0.35	34.46 [b]
Substance abuse	7.17	402.10	0.00	0.986	NE	NE	NE [b]
Adjustment or reaction disorder	–0.31	0.29	1.15	0.285	0.54	0.17	1.68 [b]
ODD/CD	0.25	0.26	0.95	0.329	1.65	0.60	4.51 [b]
PDD	–0.38	0.38	1.02	0.312	0.47	0.11	2.04 [b]
Tics or Tourette's syndrome	0.28	0.44	0.40	0.526	1.76	0.31	9.98 [b]
Amphetamine use pre-index	0.19	0.39	0.24	0.627	1.45	0.32	6.58 [b]
Methylphenidate use pre-index	0.01	0.39	0.00	0.989	1.01	0.22	4.71 [b]
Alpha agonist use pre-index	6.13	333.10	0.00	0.985	NE	NE	NE [b]
Atomoxetine use pre-index	–0.78	0.37	4.38	0.036	0.21	0.05	0.91 [b]
No pre-index treatment	0.54	0.74	0.53	0.467	1.78	0.29	10.80 [b]
Adjunctive treatment pre-index	–0.49	0.68	0.53	0.466	0.64	0.14	2.90 [b]
Plan type: HMO	0.53	0.39	1.90	0.168	1.27	0.44	3.68
Plan type: Other	–0.83	0.30	7.46	*0.006*	0.32	0.14	0.75
Plan type: POS	0.00	0.28	0.00	0.991	0.74	0.33	1.64
Provider GR: Midwest	–0.11	0.30	0.13	0.722	1.56	0.71	3.43
Provider GR: West/Northeast/missing	0.65	0.38	2.99	0.084	3.32	1.08	10.21
Pre-index PDC (any ADHD medication)	0.49	0.10	22.13	*<0.0001*	1.64	1.33	2.01

Note: N = 642, df = 32, LR = 124.43, P < 0.001, AIC = 414.11, c = 0.877.

Outcome modeled = post-index ADHD treatment status.

Reference variables: HH income: <40k or missing; member sex: male; nonsummer: summer; plan type: preferred provider organization; provider GR: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing.

Pre-index PDC is scaled to range of values = 0-10.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

[b]*Variable forced into the model.*

ADHD = attention-deficit/hyperactivity disorder; AIC = Akaike's information criterion; c=c-statistic; CI = confidence interval; df = degrees of freedom; GR = geographic region; HH = household; HMO = health maintenance organization; LR = likelihood ratio; NE = not estimable; ODD/CD = oppositional defiant disorder/conduct disorder; OR = odds ratio; PDC = proportion of days covered; PDD = pervasive developmental disorder; POS = point of service; SE = standard error.

APPENDIX F Linear Regression Model of Post-Index PDC (any ADHD)

Parameter	Estimate	SE	T3SS	F	*P* Value[a]
Intercept	0.49	0.09	2.06	29.97	*<0.001*
Index review approved	**0.14**	**0.02**	**2.82**	**41.12**	***<0.001*** [b]
Age (years)	−0.01	0.00	0.92	13.42	*<0.001* [b]
Member female sex	−0.02	0.03	0.06	0.89	0.346 [b]
HH income: 40-100k vs. <40k or missing (US$)	0.05	0.03	0.19	2.82	0.093 [b]
HH income: 100-200k vs. <40k or missing (US$)	0.03	0.03	0.06	0.83	0.364 [b]
HH income: >200k vs. <40k or missing (US$)	0.09	0.04	0.37	5.46	*0.020* [b]
Provider specialty: child and adolescent psychiatry	0.08	0.04	0.26	3.77	0.053 [b]
Provider specialty: pediatrics	0.05	0.03	0.21	3.06	0.082 [b]
Provider specialty: psychiatry	0.09	0.03	0.47	6.84	*0.009* [b]
Nonsummer vs. summer	−0.01	0.03	0.01	0.21	0.650 [b]
Sequential quarter count	0.00	0.00	0.00	0.00	0.960 [b]
ADHD diagnosis	−0.01	0.03	0.01	0.08	0.775 [b]
Depression diagnosis	0.00	0.04	0.00	0.00	0.996 [b]
Anxiety disorder	−0.07	0.03	0.34	4.98	*0.026* [b]
Bipolar disorder	0.05	0.06	0.07	0.96	0.328 [b]
Substance abuse	0.10	0.09	0.08	1.23	0.267 [b]
Adjustment or reaction disorder	0.03	0.04	0.04	0.62	0.431 [b]
ODD/CD	0.02	0.03	0.02	0.31	0.576 [b]
PDD	−0.09	0.05	0.21	3.05	0.081 [b]
Tics or Tourette's syndrome	−0.03	0.06	0.02	0.35	0.552 [b]
Amphetamine use pre-index	−0.05	0.04	0.11	1.56	0.212 [b]
Methylphenidate use pre-index	−0.02	0.04	0.02	0.25	0.617 [b]
Alpha agonist use pre-index	0.00	0.07	0.00	0.00	0.956 [b]
Atomoxetine use pre-index	−0.13	0.04	0.57	8.33	*0.004* [b]
No pre-index treatment	0.03	0.06	0.02	0.26	0.612 [b]
Adjunctive treatment pre-index	0.05	0.04	0.14	2.06	0.152 [b]
HH education: bachelor/master	−0.06	0.03	0.21	3.03	0.083
Provider GR: West/Northeast/missing	0.10	0.03	0.56	8.20	*0.004*
Any ADHD medication days 91-180 pre-index	−0.09	0.04	0.34	4.93	*0.027*
Pre-index PDC (any ADHD medication)	0.05	0.01	5.20	75.82	*<0.001*
Pre-index MH encounter count	0.00	0.00	0.19	2.78	0.096

Note: N = 642, df = 31, F = 10.83, P < 0.001, R-squared = 0.3549.

Outcome modeled = post-index PDC (any ADHD medication).

Reference variables: HH income: <40k or missing; member sex: male; nonsummer: summer; plan type: preferred provider organization; provider GR: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing; HH education: some college.

Pre-index PDC is scaled to range of values = 0-10.

Both backward elimination and stepwise variable selection processes result in identical selection of variables in the model.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

[b]*Variable forced into the model by the INCLUDE option.*

ADHD = attention-deficit/hyperactivity disorder; df = degrees of freedom; F = F statistic; GR = geographic region; HH = household; MH = mental health; ODD/CD = oppositional defiant disorder/conduct disorder; PDC = proportion of days covered; PDD = pervasive developmental disorder; SE = standard error; T3SS: Type III Sum of Squares.

APPENDIX G Results of Cox Proportional Hazards Model of Time to Post-Index ADHD Medication Prescription Claim

Parameter	Estimate	SE	Chi-square	*P* Value[a]	HR
Index review denied	**−0.65**	**0.09**	**50.87**	***<0.001***	**0.52** [b]
Age (years)	−0.02	0.02	0.97	0.325	0.98 [b]
Member female sex	0.13	0.10	1.54	0.215	1.14 [b]
HH income: 40-100k (US$)	0.07	0.11	0.42	0.492	1.09 [b]
HH income: 100-200k (US$)	0.09	0.13	0.47	0.518	1.08 [b]
HH income: >200k (US$)	0.15	0.13	1.37	0.242	1.17 [b]
Provider specialty: child and adolescent psychiatry	0.31	0.16	3.75	0.053	1.36 [b]
Provider specialty: pediatrics	0.19	0.13	2.21	0.137	1.21 [b]
Provider specialty: psychiatry	0.08	0.14	0.31	0.579	1.08 [b]
Nonsummer vs. summer	0.15	0.12	1.69	0.194	1.17 [b]
Sequential quarter count	0.03	0.01	3.84	*0.050*	1.03 [b]
ADHD diagnosis	−0.24	0.12	3.69	0.055	0.79 [b]
Depression diagnosis	0.24	0.17	2.15	0.142	1.28 [b]
Anxiety disorder	−0.34	0.14	6.45	*0.011*	0.71 [b]
Bipolar disorder	0.30	0.22	1.82	0.178	1.35 [b]
Substance abuse	−0.13	0.36	0.14	0.709	0.87 [b]
Adjustment or reaction disorder	−0.05	0.18	0.08	0.783	0.95 [b]
ODD/CD	0.22	0.13	2.69	0.101	1.24 [b]
PDD	−0.22	0.21	1.04	0.308	0.81 [b]
Tics or Tourette's syndrome	0.09	0.23	0.14	0.710	1.09 [b]
Amphetamine use pre-index	−0.07	0.16	0.22	0.641	0.93 [b]
Methylphenidate use pre-index	−0.09	0.16	0.33	0.565	0.91 [b]
Alpha agonist use pre-index	0.02	0.26	0.01	0.931	1.02 [b]
Atomoxetine use pre-index	−0.25	0.18	1.86	0.173	0.78 [b]
No pre-index treatment	0.00	0.23	0.00	0.995	1.00 [b]
Adjunctive treatment pre-index	−0.13	0.14	0.85	0.356	0.88 [b]
Provider GR: Midwest	0.03	0.10	0.10	0.754	1.03
Provider GR: West/Northeast/missing	0.36	0.14	6.65	*0.010*	1.43
Pre-index PDC (any ADHD medication)	0.12	0.02	30.38	*<0.001*	1.13
Pre-index MH encounter count	0.02	0.01	3.67	0.055	1.02

Note: N = 642, df = 30, LR = 150.79, P < 0.001.

Modeled outcome=time to first observed post-index ADHD medication claim.

Reference variables: HH income: <40k or missing; member sex: male; nonsummer: summer; plan type: preferred provider organization: provider GR: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing.

Pre-index PDC is scaled to range of values = 0-10.

Both backward elimination and stepwise variable selection processes result in identical selection of variables in the model.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

[b]*Variable forced into the model.*

ADHD = attention-deficit/hyperactivity disorder; df = degrees of freedom; GR = geographic region; HH = household; HR = hazard ratio; LR = likelihood ratio; MH = mental health; ODD/CD = oppositional defiant disorder/conduct disorder; PDC = proportion of days covered; PDD = pervasive developmental disorder; SE = standard error.

APPENDIX H Generalized Linear Regression Model of All-Cause Total Health Care Costs (Log Link, Gamma Variance Function)

Parameter	Estimate	SE	95% CI		Wald Chi-square	*P* Value[a]
Intercept	8.15	0.97	6.26	10.05	71.05	*<0.001*
Index review denied	**–0.07**	**0.08**	**–0.22**	**0.09**	**0.73**	**0.393**
Age (years)	0.02	0.01	–0.01	0.05	2.01	0.156
Member female sex	–0.20	0.09	–0.37	–0.03	5.10	*0.024*
Plan type: HMO	0.16	0.12	–0.06	0.39	1.98	0.160
Plan type: Other	–0.36	0.11	–0.58	–0.14	10.54	*0.001*
Plan type: POS	0.19	0.09	0.01	0.37	4.35	*0.037*
HH education: associates degree	0.35	0.13	0.09	0.61	6.84	*0.009*
HH education: bachelor/master	–0.02	0.12	–0.26	0.23	0.02	0.895
HH education: high school/missing	0.04	0.14	–0.22	0.31	0.10	0.751
HH income: 40-100k (US$)	–0.09	0.15	–0.38	0.20	0.34	0.733
HH income: 100-200k (US$)	–0.05	0.14	–0.31	0.22	0.12	0.558
HH income: >200k (US$)	0.15	0.18	–0.21	0.50	0.65	0.419
Provider specialty: child and adolescent psychiatry	–0.11	0.14	–0.39	0.16	0.63	0.426
Provider specialty: pediatrics	–0.10	0.11	–0.32	0.12	0.75	0.386
Provider specialty: psychiatry	0.18	0.12	–0.05	0.42	2.31	0.128
Provider GR: Midwest	0.14	0.09	–0.03	0.31	2.63	0.105
Provider GR: West/Northeast/missing	0.34	0.12	0.09	0.58	7.45	*0.006*
Nonsummer	0.17	0.10	–0.03	0.36	2.90	0.088
Sequential quarter count	0.02	0.01	–0.01	0.04	2.17	0.141
ADHD diagnosis	–0.53	0.10	–0.74	–0.33	25.89	*<0.001*
Depression diagnosis	0.33	0.14	0.05	0.61	5.21	*0.023*
Anxiety disorder	–0.13	0.12	–0.35	0.10	1.19	0.275
Bipolar disorder	0.26	0.19	–0.12	0.64	1.85	0.174
Substance abuse	–0.12	0.33	–0.76	0.52	0.14	0.713
Adjustment or reaction disorder	0.32	0.16	0.01	0.63	4.22	*0.040*
ODD/CD	0.04	0.11	–0.17	0.25	0.12	0.724
PDD	0.41	0.18	0.05	0.76	5.07	*0.024*
Tics or Tourette's syndrome	0.14	0.20	–0.24	0.53	0.54	0.463
Any ADHD medication days 91-180 pre-index	–1.18	0.92	–2.97	0.62	1.65	0.199
Any ADHD medication within 90 days pre-index	–1.09	0.91	–2.87	0.69	1.44	0.230
Amphetamine use pre-index	–0.22	0.13	–0.47	0.02	3.20	0.074
Methylphenidate use pre-index	–0.01	0.12	–0.25	0.23	0.00	0.953
Alpha agonist use pre-index	–0.34	0.23	–0.78	0.11	2.23	0.135
Atomoxetine use pre-index	–0.06	0.16	–0.36	0.25	0.14	0.707
No pre-index treatment	–0.77	0.91	–2.55	1.01	0.71	0.398
Adjunctive treatment pre-index	0.13	0.12	–0.11	0.36	1.07	0.302
Pre-index PDC (any ADHD medication)	0.07	0.02	0.03	0.11	12.32	*<0.001*
Pre-index total medical cost	0.04	0.02	0.01	0.08	4.95	*0.026*
Pre-index total prescription cost	0.10	0.02	0.06	0.13	23.95	*<0.001*
Pre-index MH encounter count	0.03	0.01	0.01	0.04	11.46	*<0.001*
Scale	1.30	0.07	1.18	1.43		

Note: All variables forced into model; N = 642.

Modeled outcome = total all-cause health care costs.

Reference variables: HH income: <40k or missing; member sex: male; nonsummer: summer; plan type: preferred provider organization; provider GR: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing; HH education: some college.

Pre-index costs are standardized by dividing member cost by the overall standard deviation of the cost component.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; GR = geographic region; HH = household; HMO = health maintenance organization; MH = mental health; ODD/CD = oppositional defiant disorder/conduct disorder; PDC = proportion of days covered; PDD = pervasive developmental disorder; POS = point of service; SE = standard error.

APPENDIX I Generalized Linear Regression Model of Mental Health-Related Total Health Care Costs (Log Link, Gamma Variance Function)

Parameter	Estimate	SE	95% CI		Wald Chi-square	*P* Value[a]
Intercept	7.45	0.98	5.53	9.37	57.99	*<0.001*
Index review denied	**–0.15**	**0.08**	**–0.31**	**0.00**	**3.73**	**0.054**
Age (years)	0.02	0.01	–0.01	0.04	1.43	0.233
Member female sex	–0.12	0.09	–0.30	0.05	1.90	0.169
Plan type: HMO	0.14	0.12	–0.09	0.37	1.43	0.232
Plan type: other	–0.35	0.11	–0.56	–0.13	9.61	*0.003*
Plan type: POS	0.05	0.09	–0.12	0.23	0.35	0.554
HH education: associates degree	0.43	0.14	0.16	0.70	9.54	*0.002*
HH education: bachelor/master	0.07	0.12	–0.18	0.31	0.29	0.588
HH education: high school/missing	0.11	0.13	–0.14	0.37	0.75	0.388
HH income: 40-100k (US$)	–0.10	0.14	–0.38	0.18	0.47	0.715
HH income: 100-200k (US$)	–0.05	0.13	–0.31	0.21	0.13	0.494
HH income: >200k (US$)	0.19	0.17	–0.15	0.53	1.18	0.278
Provider specialty: child and adolescent psychiatry	–0.20	0.14	–0.48	0.08	2.04	0.153
Provider specialty: pediatrics	–0.12	0.12	–0.35	0.10	1.11	0.292
Provider specialty: psychiatry	0.18	0.13	–0.07	0.42	2.07	0.152
Provider GR: Midwest	–0.08	0.09	–0.25	0.10	0.78	0.376
Provider GR: West/Northeast/missing	0.31	0.12	0.07	0.55	6.20	*0.013*
Nonsummer	0.05	0.10	–0.15	0.25	0.25	0.618
Sequential quarter count	0.02	0.01	0.00	0.05	3.11	0.078
ADHD diagnosis	–0.49	0.11	–0.70	-0.28	20.39	*<0.001*
Depression diagnosis	0.39	0.15	0.09	0.69	6.34	*0.012*
Anxiety disorder	–0.07	0.12	–0.30	0.17	0.32	0.572
Bipolar disorder	0.10	0.20	–0.29	0.49	0.27	0.606
Substance abuse	–0.28	0.32	–0.92	0.35	0.76	0.385
Adjustment or reaction disorder	0.33	0.16	0.01	0.64	4.21	*0.040*
ODD/CD	0.29	0.11	0.08	0.51	7.03	*0.008*
PDD	0.50	0.19	0.13	0.88	7.03	*0.008*
Tics or Tourette's syndrome	0.05	0.20	–0.35	0.44	0.05	0.823
Any ADHD medication days 91-180 pre-index	–0.73	0.93	–2.55	1.10	0.61	0.434
Any ADHD medication within 90 days pre-index	–0.85	0.92	–2.65	0.96	0.85	0.357
Amphetamine use pre-index	–0.21	0.13	–0.46	0.05	2.48	0.115
Methylphenidate use pre-index	0.00	0.13	–0.26	0.26	0.00	0.994
Alpha agonist use pre-index	–0.30	0.23	–0.75	0.15	1.74	0.187
Atomoxetine use pre-index	–0.28	0.16	–0.60	0.03	3.13	0.077
No pre-index treatment	–0.56	0.93	–2.38	1.25	0.37	0.543
Adjunctive treatment pre-index	0.15	0.13	–0.10	0.39	1.42	0.233
Pre-index PDC (any ADHD medication)	0.07	0.02	0.03	0.11	12.06	*<0.001*
Pre-index MH-related medical cost	0.06	0.02	0.03	0.09	15.93	*<0.0001*
Pre-index MH-related Rx cost	0.24	0.04	0.16	0.32	31.56	*<0.0001*
Pre-index MH encounter count	0.02	0.01	0.00	0.04	3.24	0.0721
Scale	1.26	0.06	1.14	1.39		

Note: All variables forced into model; N = 642.

Modeled outcome = total MH-related health care costs.

Reference variables: HH income: <40k or missing; member gender: male; nonsummer: summer; plan type: preferred provider organization; provider GR: South; no pre-index treatment: monotherapy pre-index; adjunctive treatment pre-index: monotherapy pre-index; provider specialty: family practice/general practitioner/other/missing; HH education: some college.

Pre-index costs are standardized by dividing member cost by the overall standard deviation of the cost component.

[a]*Italic P values indicate statistical significance at an alpha level of 0.05.*

ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; GR = geographic region; HH = household; HMO = health maintenance organization; MH = mental health; ODD/CD = oppositional defiant disorder/conduct disorder; PDC = proportion of days covered; PDD = pervasive developmental disorder; POS = point of service; Rx = medical prescription; SE = standard error.