Factors Associated With Initiation With Atomoxetine Versus Stimulants in the Treatment of Adults With ADHD: Retrospective Analysis of Administrative Claims Data

DAVID L. VAN BRUNT, PhD; JOSEPH A. JOHNSTON, MD, MSc; WENYU YE, PhD;
GERHARDT M. POHL, PhD; and NINA N. OHARA, PharmD

ABSTRACT

OBJECTIVE: To determine which factors are associated with use of atomoxetine (ATX) relative to stimulant medications (STIMs) for treatment initiation in adults with attention-deficit/hyperactivity disorder (ADHD). A similar exploratory analysis of the use of ATX versus STIMs in children has been published previously.

METHODS: This was an exploratory analysis using a retrospective observational cohort design applied to administrative pharmacy and medical claims from an integrated managed care database. Patients were identified if they had at least 1 administrative claim with a diagnosis for ADHD. Treatment "initiation" was defined as a new prescription for an ADHD medication preceded by 3 months without similar therapy. Two separate analyses were done, one comparing medication starts for ATX with those of any STIM, the other comparing starts of ATX with long-acting stimulants (LA-STIMs). Logistic regression analyses of prior-year administrative claims were used to compare the frequencies of differential predictors of the use of medication.

RESULTS: There were 10,359 patients aged >18 years who initiated ATX or a STIM between April and December of 2003 and had at least 1 claim with a diagnosis for ADHD (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 314.0x). Approximately one third (28 of 82) of the comparisons related to patient demographics, diagnostic history, and previous treatment history was found to be related to the use of ATX versus STIMs and/or LA-STIMs. Patients were more likely to have received ATX than a STIM if they had prior diagnoses of bipolar disorder (odds ratio [OR] 1.47; 95% confidence interval [CI], 1.16-1.87), alcohol dependence (OR 1.80; 95% CI, 1.26-2.58), anxiety (OR 1.21; 95% CI, 1.05-1.40), previous use of antipsychotic medication (OR 1.55; 95% CI, 1.22-1.96), or previous antidepressant use (OR 1.14; 95% CI, 1.01-1.28). Prior use of behavioral services greater than 12 visits was associated with the use of ATX relative to STIMs (OR 1.46; 95% CI, 1.20-1.77) but not for ATX relative to LA-STIMs. Conversely, ATX was used less often than STIMs for initiation in younger adults aged 18 to 24 years (OR 0.66; 95% CI, 0.58-0.74), female patients (OR 0.89, 95% CI, 0.80-0.99), patients with personality disorders (OR 0.53; 95% CI, 0.34-0.82), and those with prior use of STIMs (OR 0.62; 95% CI, 0.56-0.69). The majority of comparisons (54 of 82) related to demographics, diagnostic history, and previous treatment history did not show statistically significant associations.

CONCLUSIONS: During the first year of ATX's market introduction, some differences in the frequency of various clinical factors were found in adults treated with ATX compared with those patients who received STIMs. This association may suggest that STIMs and ATX are used to address different treatment needs in adults with ADHD. Future studies will need to determine the significance of the practice pattern differences inferred here and if they persist after ATX has been on the market longer.

KEYWORDS: Atomoxetine, Stimulants, Administrative claims, Treatment selection, Adult ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is characterized by problems regulating attention and controlling behavior across social settings.¹ Though predominantly viewed as a childhood disorder, there is growing recognition that symptoms often persist into adulthood.² While the etiology of ADHD remains a matter of debate, there is a wealth of literature as to its effects. Persons with ADHD experience academic and occupational underachievement relative to their peers, have impaired social relationships with higher rates of divorce, and have higher rates of traffic violations and accidents resulting in injury.^{3,4} Untreated ADHD in children is also associated with an increased risk for substance abuse problems later in life.⁵

Treatment options for ADHD include both behavioral and pharmacological therapies, with the latter more broadly applied and dominated by the use of psychostimulants.^{6,7} In 2003, a nonstimulant therapy became widely available, offering another pharmacologic alternative to the stimulant (STIM) group. U.S. Food and Drug Administration (FDA) approval for adult use of atomoxetine (ATX, Strattera) was granted after 2 studies of 10 weeks duration, each of which showed improvements on the Conners Adult ADHD Rating Scales.⁷ ATX differs from STIMs both in the mechanism of action and in adverse effects. Like other nonstimulants used for ADHD such as tricyclic antidepressants and bupropion,⁸ ATX can be safely used in patients with comorbid anxiety disorders, does not exacerbate tics, and lacks potential for abuse.⁹

New treatment choices create new challenges. Physicians must balance the risks and benefits of expanding treatment alternatives to optimally care for their patients. In the early days following the approval of a new medication, this task may be

Authors

DAVID L. VAN BRUNT, PhD, is a research scientist; JOSEPH A. JOHNSTON, MD, MSc, is a research physician; WENYU YE, PhD, is an assistant senior statistician; GERHARDT M. POHL, PhD, is a research scientist; and NINA N. OHARA, PharmD, is an outcomes liaison, Health Outcomes, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana.

AUTHOR CORRESPONDENCE: David L. Van Brunt, PhD, Research Scientist, Health Outcomes, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285. Tel: (317) 651-8266; Fax: (317) 277-7444; E-mail: dvb@lilly.com

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particularly daunting. The available evidence upon which clinical decisions for new drugs are based often consists of results from clinical trials evaluating short-term efficacy in highly selected populations. While such trials are critical in establishing a drug's efficacy prior to approval, trial populations and care delivery are often not representative of real-world clinical practice.¹⁰ This creates an information vacuum in the early days following a drug's approval. Later, providers learn from practical clinical experience and additional studies which patients are best suited for the new agent. For instance, an interim open-label study was recently published that enrolled the patients from the initial short-term ATX trials. With a mean treatment length of 40 weeks, longer duration efficacy and safety data were added to the knowledge about ATX.¹¹

Until longer-term clinical trial data for ATX become available, examining emerging patterns of medication use may be informative for care of adult ADHD. Differences in treatment selection reflect not only marketing efforts but perceived medication successes and failures over time. In addition to providing clues as to where the drug may be most useful, managed care decision makers may find information on emerging patterns useful in deciding if use of a new product appears to be meeting previously unmet needs (versus being used interchangeably with existing and usually less costly therapies). From a risk surveillance perspective, understanding which patients are being selected for specific treatments may help provide important context in the event that adverse consequences become apparent. For instance, adverse events may be directly related to drug effects, but they also may be the result of increased baseline risk in the treatment group compared with baseline risk in the group receiving traditional therapy.

Three years after the introduction of ATX, administrative claims data are available to allow study of the early utilization patterns of ATX relative to STIM use for ADHD. We hypothesized that the use of ATX would be preferred in (1) patients with conditions that may be exacerbated by STIMs, such as tics and anxiety; (2) patients for whom present substance abuse is a concern, such as those with a history of alcohol or substance abuse; and (3) difficult-to-treat or treatment-refractory patients, such as those with comorbid psychiatric disorders (e.g., depression, psychosis, or personality disorders) or a recent history of non-pharmacological mental health treatment. In this article, we focus specifically on adults with ADHD. A similar examination in children of ATX versus STIM and long-acting stimulant (LA-STIM) use has been published previously.¹²

Methods

The current analyses were limited to adults (aged >18 years) because treatment priorities, diagnosis, and the importance of certain medication side effects are different for adults and children with ADHD. We focused on the examination of multiple demographic, diagnostic, and treatment factors preceding

TABLE 1 Prescription Stimulants by Duration of Action

Subclass	Agent (Formulations or Brand Names)
Short-acting stimulants (3-5 hour duration of action)	Methylphenidate (generic, Ritalin, Methylin) Dexmethylphenidate (Focalin) Amphetamine mixed salts (generic amphetamines*, Dexedrine, Dextrostat, Dexampex, Biphphetamine) Methamphetamine (Desoxyn) Pemoline (generic, Cylert)† Modafinil (Provigil)‡
Intermediate-acting stimulant (5-8 hour duration of action)	Methylphenidate (generic ER/SR/CR/SA, Ritalin SR, Metadate ER, Methylin ER) Amphetamine mixed salts (generic amphetamines CR*, Adderall, Dexedrine spansules)
Long-acting stimulants (8-12 hour duration of action)	Methylphenidate (Ritalin LA, Metadate CD, Concerta) Amphetamine mixed salts (Adderall XR)

* Includes any combination of amphetamine, dextroamphetamine, or methamphetamine.

† Pemoline is no longer sold in the United States because of liver toxicity.

‡ Modafinil is not FDA-indicated for use in ADHD.

ADHD=attention-deficit/hyperactivity disorder; FDA=U.S. Food and Drug Administration.

initiations of ATX and STIMs. Although bupropion and tricyclic antidepressants have been successfully used in adult ADHD and are commonly used as second-line agents,^{13,14} our study design intentionally excluded these drugs from the analysis since they are not approved by the FDA for the treatment of ADHD. Specific STIM medications and their categorizations are shown in Table 1 and are based upon the categorizations described by the Subcommittee on Attention-Deficit/Hyperactivity Disorder of the American Academy of Pediatrics' Committee on Quality Improvement.^{15,16}

Because we were assessing the pattern of treatment in the year of ATX's introduction and because patient care often involves more than one agent over the course of time, we compared treatments based on the most recent treatment initiation for each patient. Since ATX is considered long-acting, we compared recent initiations of ATX with those of STIMs in general and with LA-STIMs specifically. This division into 2 sets of analyses created some replication of findings for STIMs as a class but also allowed for a more direct comparison between treatments of similar cost; the shorter-acting medications are readily available generically, and, thus, findings here may reflect the effect of confounding socioeconomic or other factors. Where findings are repeated across analyses, we have greater confidence that the findings are the result of differences in treatment approach rather than access per se.

Our data were drawn from the proprietary PharMetrics database. At the time of the study, this database consisted of administrative health care claims data from more than 75

managed care organizations covering more than 44.3 million lives. We limited our extraction of data from pharmacy and medical claims to patients with at least 1 filled prescription for ATX or STIMs and at least 1 recorded diagnosis for ADHD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 314.0x). Because diagnoses and medication use in the 1-year period prior to drug initiation were evaluated as predictors of treatment selection, patients with less than 1 year of continuous enrollment prior to the most recent treatment initiation were excluded.

We defined a treatment “initiation” as a new prescription for an ADHD medication preceded by 3 months without similar therapy. The 3-month interval was chosen for consistency with our prior study of children,¹² in which we acknowledged that gaps in treatment may occur during summer months even through college years. ATX was only first widely available in January 2003. To reduce the potential for a systematic bias related to the inclusion of very early adopters, treatment episodes were included with the first date between April 1, 2003, and December 31, 2003. Because “concurrent start” episodes (e.g., a patient’s having a qualifying treatment initiation for methylphenidate and ATX on the same day) could not be clearly assigned to only 1 comparison group, these patients were excluded from our analyses.

Pharmacy claims for ATX and STIMs were examined. STIMs with 8 to 12 hours duration of action were separately examined by comparing initiations of ATX with those of LA-STIMs in separate statistical models. A new treatment initiation was defined as a prescription for a categorized medication preceded by 3 months without that same medication or any other medication within the same treatment category (ATX, STIM, or LA-STIM). For example, a prescription for Concerta (long-acting methylphenidate) would constitute a LA-STIM initiation if, for the 3 months preceding that prescription, the patient was enrolled in the plan but showed no claim for Concerta or any other LA-STIM. This patient could, however, have received a short-acting STIM such as immediate-release (IR) methylphenidate; in that case, the prior short-acting STIM use would appear as a predictor for LA-STIM treatment initiation. In contrast, a STIM episode would be identified by a STIM prescription of any type, preceded by 3 months free of any other STIM. Thus, entry into the STIM category is more restrictive in that it excludes STIM initiations for patients who are moving among various categories of STIM therapies. In the LA-STIM example above, when the patient had taken IR methylphenidate within 3 months prior to starting the LA-STIM, the latter initiation would not be considered their “most recent” initiation of any STIM. For each comparison (ATX with STIMs, and ATX with LA-STIMs), patients were classified according to the most recent treatment initiation between the treatments being compared.

After categorizing patients according to their most recent pharmacological treatment initiation, selected demographic and

historical diagnostic and treatment variables were assessed for the year prior to initiation for each patient (Table 2). These included the presence of common medical and psychiatric disorders (as indicated by ICD-9-CM codes within service claims) and medication use (as indicated by National Drug Code codes on pharmacy claims) within the 1 year prior to treatment initiation. Behavioral health care utilization rates were also assessed by computing the per-patient frequency of claims reflecting services for behavioral or psychological therapies (Current Procedural Terminology codes 90804 through 90831, 90842-90857, 90875-90889, 90901-90910, or 96100), visits to nonprescribing mental health specialists (such as psychologists and social workers), and claims with revenue codes consistent with the provision of nonmedication mental health therapy services as described by the Centers for Medicare and Medicaid Services (revenue codes 914, 915, 916, or 918). Behavioral health care utilization rates were categorized into “never used,” “1-12 visits,” or “>12 visits” in the past year.

Initiators of ATX were compared with STIM and LA-STIM initiators, in turn, on the basis of prior-year demographic and clinical characteristics using multivariate logistic regression. To avoid any collinearity that would result from including both an assessment of psychiatric conditions and the medications used to treat them in the same model, separate models were used to examine the associations between treatment initiation and (1) diagnostic history and (2) treatment history when adjusted for demographics and other diagnoses or treatments. Unadjusted odds ratios were also computed for age and gender. All analyses were conducted using SAS version 8.2 for Unix (Cary, NC). Coverage restrictions such as maximum age limits and formulary status (e.g., copayment tier) of the drugs in this study were not recorded in the database and were not available for evaluation in this research.

Results

A total of 133,134 patients were identified as receiving medication treatment for ADHD in 2003 and having an ADHD diagnosis anywhere within their administrative claim records. Limiting this group to patients who initiated therapy between April 1, 2003, and December 31, 2003, and who had continuous enrollment for 1 full year preceding a treatment initiation resulted in 46,396 (34.8%) patients. Restricting the sample further to patients aged ≥ 18 years resulted in 10,359 patients (7.8%). The distribution of “most recent initiations” for these patients is shown in Table 3. Note that because the inclusion criteria for initiation requires the nonuse of similar drugs for 3 months preceding a prescription, there are more disqualifications for initiations of STIMs generally than for LA-STIMs specifically. Since each patient is categorized according to his or her most recent therapy initiation, this results in a greater number of ATX initiators for the analyses comparing ATX with STIM use than for those comparing ATX with LA-STIM use.

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TABLE 2 Demographics and Past-Year Diagnostic and Treatment History
for Initiations of Atomoxetine and Stimulant Therapies

	ATX Versus STIM		ATX Versus LA-STIM			ATX Versus STIM		ATX Versus LA-STIM	
	No. (%) ATX (n = 2,036)*	No. (%) STIM (n = 6,814)	No. (%) ATX (n = 1,956)*	No. (%) LA-STIM (n = 3,567)		No. (%) ATX (n = 2,036)*	No. (%) STIM (n = 6,814)	No. (%) ATX (n = 1,956)*	No. (%) LA-STIM (n = 3,567)
Age group (years)					Explosive PD	1 (0.1)	4 (0.1)	1 (0.1)	3 (0.1)
Age 18-24	829 (40.7)	3,485 (51.1)	796 (40.7)	1,795 (50.3)	Passive aggressive PD	0	1 (0.0)	0	1 (0.0)
Age 25-44	726 (35.7)	1,963 (28.8)	697 (35.6)	1,115 (31.3)	Alcohol dependence (303.xx)	72 (3.5)	84 (1.2)	70 (3.6)	54 (1.5)
Age 45+†	481 (23.6)	1,366 (20.1)	463 (23.7)	657 (18.4)	Drug dependence (304.xx)	76 (3.7)	99 (1.5)	74 (3.8)	66 (1.9)
Gender					Nondependent drug abuse (305.xx)	171 (8.4)	361 (5.3)	165 (8.4)	213 (6.0)
Male	1,177 (57.8)	3,875 (56.9)	1,139 (58.2)	2,028 (56.9)	Tics (307.2x)	10 (0.5)	16 (0.2)	10 (0.5)	9 (0.3)
Female	859 (42.2)	2,939 (43.1)	817 (41.8)	1,539 (43.2)	Sleep disorders				
Past year medication use					of sleep loss (307.41-42, 307.45-49, 780.5x excluding 780.53-780.54)	142 (7.0)	358 (5.3)	136 (7.0)	199 (5.6)
Stimulant	1,013 (49.8)	4,246 (62.3)	933 (47.7)	2,293 (64.3)	of hypersomnolence (307.43-44, 780.53, 780.54, 347)	42 (2.1)	139 (2.0)	41 (2.1)	67 (1.9)
Nonstimulant (bupropion)	379 (18.6)	850 (12.5)	359 (18.4)	494 (13.9)	Mental retardation or developmental disorders (317-319, 299.x, 314.1, 315.xx)	44 (2.2)	114 (1.7)	42 (2.2)	71 (2.0)
Antidepressants	832 (40.9)	2,288 (33.6)	802 (41.0)	1,265 (35.5)	Accidents/injuries (800-959)	580 (28.5)	1,889 (27.7)	553 (28.3)	1,028 (28.8)
TACs	77 (3.8)	270 (4.0)	74 (3.8)	146 (4.1)	COPD (490.x-492.x, 493.2, 496.x)	90 (4.4)	256 (3.8)	89 (4.6)	123 (3.5)
SSRIs	622 (30.6)	1,712 (25.1)	598 (30.6)	946 (26.5)	Asthma (493.[0-1,9]x)	133 (6.5)	433 (6.4)	127 (6.5)	230 (6.5)
Other‡	335 (16.5)	812 (11.9)	323 (16.5)	473 (13.3)	Diabetes (250x)	53 (2.6)	147 (2.2)	51 (2.6)	83 (2.3)
Antipsychotics	137 (6.7)	236 (3.5)	132 (6.8)	150 (4.2)	Hepatitis or cirrhosis (070x, 571.xx, 573.1-3)	20 (1.0)	40 (0.6)	19 (1.0)	24 (0.7)
Typical/first generation	10 (0.5)	14 (0.2)	9 (0.5)	9 (0.3)	Cardiac dysrhythmias (427.x)	35 (1.8)	121 (1.78)	35 (1.79)	61 (1.71)
Atypical/second generation	133 (6.5)	231 (3.4)	128 (6.5)	147 (4.1)	Hypertension (401.x)	185 (9.1)	449 (6.6)	179 (9.2)	250 (7.0)
Antimanics	158 (7.8)	331 (4.9)	151 (7.7)	202 (5.7)	Alzheimers or other dementia (290.x, 331.x)	6 (0.3)	6 (0.1)	6 (0.3)	5 (0.1)
Anxiolytics	401 (19.7)	1,033 (15.2)	382 (19.5)	569 (16.0)	Sexually transmitted diseases and HIV (genital herpes, [051.1x], syphilis [090-099] human papillomavirus [079.4], HIV or AIDS [042, V08, 079.53])	8 (0.4)	37 (0.5)	8 (0.4)	23 (0.6)
Previous BHP§ services					Poisoning/ingestion (960-989)	42 (2.1)	71 (1.0)	42 (2.2)	39 (1.1)
Never used	1,255 (61.6)	4,835 (71.0)	1,216 (62.2)	2,365 (66.3)	Obesity (278, 2780, 27800, 27801)	58 (2.9)	179 (2.6)	55 (2.8)	119 (3.3)
1-12 visits	583 (28.6)	1,573 (23.1)	552 (28.2)	936 (26.2)	Epilepsy (345.xx)	9 (0.4)	47 (0.7)	9 (0.5)	26 (0.7)
>12 visits	198 (9.7)	406 (6.0)	188 (9.6)	266 (7.5)					
Previous diagnosis									
ADHD (314.x)	1,443 (70.9)	4,453 (65.4)	1,384 (70.8)	2,470 (69.3)					
ADHD inattentive (314.00)	683 (33.6)	2,378 (34.9)	666 (34.1)	1,259 (35.3)					
ADHD hyperactive (314.01 or 314.00 +314.01)	742 (36.4)	2,034 (29.9)	701 (35.8)	1,195 (33.5)					
Schizophrenia (295.xx)	14 (0.7)	22 (0.3)	14 (0.7)	10 (0.3)					
Bipolar/mania (296.0x-296.8x, 301.13)	128 (6.3)	237 (3.5)	125 (6.4)	140 (3.9)					
Psychosis (297, 298)	28 (1.4)	33 (0.5)	27 (1.4)	22 (0.6)					
Depression (296.2x- 296.3x, 300.4, 311)	716 (35.2)	1,932 (28.4)	689 (35.2)	1,107 (31.0)					
Anxiety states (300.xx, 313.0)	396 (19.5)	944 (13.9)	375 (19.2)	567 (15.9)					
Personality disorder (PD) (301.xx)	30 (1.5)	100 (1.5)	30 (1.5)	63 (1.8)					
Antisocial PD	1 (0.1)	5 (0.1)	1 (0.1)	4 (0.1)					
Borderline PD	6 (0.3)	26 (0.4)	6 (0.3)	16 (0.5)					

* N of ATX is higher in STIM comparison due to stricter exclusions in defining STIM initiations (see Table 3).

† Only 9 patients for ATX therapy and 227 patients for STIM therapy were aged 65 years.

‡ "Other" includes MAOIs, SNRIs, mirtazapine, nefazodone, and trazodone.

§ Behavioral health/psychology (BHP) services represent therapeutic interventions other than pharmaceutical treatment.

|| Though all patients were required to have an ADHD claim on record to be included for analysis, this table reflects claims within the one year prior to the initiation.

ADHD=attention-deficit/hyperactivity disorder; AIDS=acquired immune deficiency syndrome; ATX=atomoxetine; COPD=chronic obstructive pulmonary disease;

HIV=human immunodeficiency virus; LA-STIM=long-acting stimulants; MAOI=monoamine oxidase inhibitor; SNRI=serotonin and norepinephrine reuptake inhibitor;

SSRI=selective serotonin reuptake inhibitor; STIM=any stimulant; TCA=tricyclic antidepressant.

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TABLE 3 Sample Selection

	For Comparing Initiations of ATX to STIM:		For Comparing Initiations of ATX to LA-STIM:	
Source patients Those using ADHD medication in 2003 and having one or more claims with ADHD diagnosis in claims records	133,134		133,134	
	n (%)	n (%) Remaining	n (%)	n (%) Remaining
Excluding patients with no initiations between April 1, 2003, and December 31, 2003, or without one full year of continuous enrollment	86,738 (65.2% of source)	46,396 (34.9% of source)	86,738 (65.2% of source)	46,396 (34.9% of source)
Excluding children (patients aged <18 years)	36,037 (27.1% of source)	10,359 (7.8% of source)	36,037 (27.1% of source)	10,359 (7.8% of source)
Cohort of qualified adult patients	10,359		10,359	
Excluding patients with no qualifying treatment initiations* for either ATX or analysis-specific comparator	1,481 (14.3% of cohort)	8,877 (85.7% of cohort)	4,529† (43.7% of cohort)	5,830 (56.3% of cohort)
Excluding patients with ambiguous initiation (i.e., with most-recent qualifying initiations of ATX and analysis-specific comparator on the same day)	28 (0.3% of cohort)	8,850 (85.4% of cohort)	307 (3.0% of cohort)	5,523 (53.3% of cohort)
Initiations compared Unique patients assigned by most recent qualifying initiation, relative to analysis-specific comparator	8,850		5,523	
ATX	2,036 (23.0% of initiations)		1,956 (35.4% of initiations)	
STIM	6,814 (77.0% of initiations)		—	
LA-STIM	—		3,567 (64.6% of initiations)	

* "Qualifying initiations" are pharmacy claims preceded by a 90-day period free of a pharmacy claim for the same or similar drug. See "Methods" for details and example.

† The ATX to LA-STIM analysis excludes patients treated primarily with medications other than ATX or LA-STIM, resulting in greater overall exclusion than for the ATX to STIM analysis.

ADHD=attention-deficit/hyperactivity disorder; ATX=atomoxetine; LA-STIM=long-acting stimulant; STIM=stimulant.

TABLE 4 Unadjusted Association Between
Patient Demographics and
Atomoxetine Treatment Selection

	Medication Episodes			
	ATX Versus Stimulant		ATX Versus LA-STIM	
	OR	95% Confidence Limits	OR	95% Confidence Limits
Age group (years)				
18-24 (versus 25-44)	0.64	[0.57, 0.72]	0.71	[0.63, 0.81]
45+ (versus 25-44)	0.95	[0.83, 1.09]	1.13	[0.97, 1.31]
Gender				
Female (versus male)	0.96	[0.87, 1.06]	0.95	[0.85, 1.06]

ATX=atomoxetine; LA-STIM=long-acting stimulants; OR=odds ratio.

Table 2 shows the frequency distributions for demographic factors and past-year diagnostic and treatment history for ATX compared with STIM and LA-STIM initiations. Specific testing of these relationships was done within the adjusted logistic regression models. Compared with our predefined arbitrary referent category of patients aged 25 to 44 years, younger adults (18-24 years) showed a decreased likelihood of receiving ATX relative to both STIMs and LA-STIMs whereas no significant

difference was noted for older (45+ years) adults. While no significant gender differences were observed in unadjusted analyses (Table 4), females were less likely to receive ATX than STIMs and LA-STIMs in adjusted models.

Diagnostic history was informative in treatment selection. Figure 1 depicts the diagnoses assessed within claims along with the corresponding adjusted odds ratios for ATX initiation and associated 95% confidence intervals. For the broader comparison of ATX with STIMs, but not always when comparing ATX with LA-STIMs, patients with past-year claims for alcohol and drug dependence, psychosis, bipolar disorder, and anxiety disorders were more likely to initiate treatment with ATX, whereas patients with past-year claims for personality disorder were more likely to initiate treatment with STIMs or LA-STIMs. Though the rate of tics or Tourette's was nearly 3 times higher for ATX initiators than STIM initiators, the overall past-year prevalence of this condition (<1%) was too low for this difference to reach significance in the adjusted models.

The direction of effect for all diagnostic predictors of ATX versus LA-STIM initiation was the same as for the comparison with STIM. However, drug dependence, psychosis, and anxiety disorders—all significant positive predictors of ATX versus STIM initiation—were not significantly associated with ATX

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initiation compared with LA-STIM initiation.

The findings for historical medication use (Figure 2) only partly replicated the diagnostic history results. For example, antipsychotic use, like a historical diagnosis of a psychotic disorder, was significantly associated with an increased likelihood of initiating ATX as opposed to STIMs. However, while antidepressant use in the treatment model was significantly associated with ATX initiation compared with both STIM and LA-STIM initiation, this relationship was not evident for depression in the diagnosis models. Use of bupropion, indicated for major depression but commonly used off-label for treatment of adults with ADHD, was similarly associated with an increased likelihood of initiating ATX. This trend is similar to—and may, in fact, be simply a reiteration of—the trends for other antidepressants. Conversely, prior antimanic medication use was not associated with treatment selection, whereas a bipolar/mania diagnosis was. A past-year STIM prescription was associated with an increased likelihood of resuming STIMs; this was true for both STIMs and for LA-STIMs specifically.

Using “no prior-year visits” as a reference category, prior use of behavioral services up to a once-monthly average rate was associated with significantly higher odds of initiating ATX as opposed to STIMs. Behavioral service utilization, however, did not predict treatment selection between ATX and LA-STIMs.

Discussion

Our findings demonstrate that in adults with ADHD, a statistically significant association was found between some demographic characteristics and clinical history, and the initiation of treatment with a STIM versus ATX.

Our first hypothesis, that ATX would be used more often in patients with conditions potentially exacerbated by STIMs, was partially supported. ATX use was more common than STIM use in patients with anxiety, but it was not more common than LA-STIM use. ATX was also not associated with preferred use in patients with tic disorders. The second hypothesis, that patients at risk for substance abuse would be less likely to initiate STIMs, likewise received partial support. ATX was preferred over STIMs and LA-STIMs in patients with histories of alcohol dependence but not in patients with histories of nondependent drug abuse. Drug-dependent patients were more likely to initiate ATX over STIMs, but there was no difference between ATX and LA-STIM use.

The third hypothesis, that difficult-to-treat patients with psychiatric comorbidities or recent counseling would more frequently initiate ATX, was also only partially supported. ATX use was more likely in patients with psychosis, bipolar disorder, or anxiety (though in the latter 2 instances the effect was present only for STIMs, not for LA-STIMs), while STIMs were associated with increased preference in patients with personality disorder. Patients who have recent prescriptions for antidepressants or antipsychotics were slightly more likely to initiate ATX. ATX

FIGURE 1 Adjusted Odds Ratios for Atomoxetine Initiation Based on Diagnostic History and Demographics

ATX=atomoxetine; CI=confidence interval; COPD=chronic obstructive pulmonary disease; HIV=human immunodeficiency virus; LA-STIM=long-acting stimulant; STIM=stimulant.

was not initiated more frequently in patients with prior depression or in those patients currently taking antimanic or anxiolytic medication. With respect to recent counseling, the use of behavioral services was positively associated with increased likelihood for ATX initiation relative to STIMs in general, but this distinction was not found for ATX use relative to LA-STIM use specifically.

While the above is somewhat consistent with our expectations, some patient factors associated with STIM initiation are more

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FIGURE 2 Adjusted Odds Ratios for Atomoxetine Initiation Based on Treatment History and Demographics

ATX=atomoxetine; BHP=behavioral health/psychological; CI=confidence interval; LA-STIM=long-acting stimulant; STIM=stimulant.

difficult to understand. Female gender (in the adjusted models), young adulthood (18-24 years), and personality disorders were all associated with increased odds of receiving STIMs. If we make the assumption that women are more likely than men to be interested in weight loss, the finding with regard to gender may reflect a preference for STIM treatment among women (without a formal diagnosis of obesity) inclined to view the anorexic effects of STIMs as an added benefit of treatment.

We can imagine 2 possible reasons that younger adults with ADHD would be more likely to prefer STIMs over ATX than older adults with ADHD. The first is the increasing acceptance of ADHD in adults as a treatment focus in recent years.¹⁷ As medication treatment rates have increased along with recognition of the persistence of ADHD into adulthood, the predominance of STIM use in this age group may reflect an extension of the dominance of STIM use prior to the introduction of nonstimulant alternatives.¹⁸ This might also reflect an extension of prior patient experiences, to the extent that patients who had used STIMs successfully during childhood might be more inclined to reinstate therapies previously found to be beneficial. The significant extent to which we observed that past-year STIM use could predict new initiations is certainly consistent with that idea. Older adults initiating treatment may not have as much personal history with ADHD treatment and thus come into the treatment decision with a “cleaner slate.”

A more pessimistic interpretation of this finding might be that this relationship is a reflection of the desire to divert STIM medications for abuse within the young adult population.^{19,20} Although diverted STIMs must ultimately have come from

someone, the current data do not assess whether the patients who filled their prescriptions are the same people who are using or selling their medication. Future research would be needed to examine the supply side of diversion to understand to what degree prescriptions that are intended for insured persons in this age group end up in the hands of others.

With concerns over the diversion of prescription STIMs,²¹⁻²³ we expected patients with substance-abuse histories to be directed away from STIMs, given their potential for abuse.²⁴ We were, therefore, somewhat surprised to see that an overt history of nondependent drug abuse was not associated with medication selection. The more severe diagnoses of drug and alcohol dependence, however, did show a relationship in the expected direction (though the difference was not statistically significant in favor of ATX versus LA-STIMs for drug dependence).

The preference for STIM therapy in patients with personality disorders is more obscure, insofar as there is no obvious clinical reason that such patients should preferentially receive either therapy. It is possible that certain providers (e.g., psychiatrists) are both more likely to diagnose and/or code for personality disorders than other providers (e.g., primary care physicians) and more likely to use STIMs.²¹ If so, the observed treatment difference for patients with personality disorders could simply reflect unmeasured practice variation.

Patients who were prior users of psychological or behavioral health care services showed mixed results. They were more likely to be treated with ATX than general STIMs, but no preference was seen for ATX over LA-STIMs specifically.

Limitations

Our methods of patient selection may have resulted in the inclusion of some patients without ADHD since coding errors would go unnoticed in the absence of thorough medical record reviews. Such coding errors, if present, may also result in the exclusion of true ADHD patients. Although we did not measure the rate of recording errors in our database, the large sample size leads us to believe that such unrecorded errors did not introduce any systematic bias when comparing the treatments of interest. We therefore believe that our analysis provides a reasonable characterization of the differences in how these medications are being prescribed in managed care settings. While the current methodology cannot prove cause and effect and does not address the relative effectiveness of the treatment alternatives studied, it does highlight the relative associations between clinical factors and medication choices that have emerged during the first year of ATX's availability.

A further limitation is the availability of data on systemic factors that may affect care—for example, the rate of dispensation through mail-service pharmacies, plan limits such as noncoverage of STIMs in adults, or the formulary tier status of the drugs under study. Because our database contained information from many diverse health plans, a broad range of these and other systemic

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factors was likely represented. Whether or not these systemic factors directly impact utilization or drug choice by providers is an important policy-related question and merits future study.

Similarly, the effect of provider specialty was unmeasured because of limitations in our ability to confidently determine provider specialty from claims. Often, the “provider” was not an individual specialist but a clinic that may have contained providers of diverse specialties. In addition, where specialty could not be clearly identified, the PharMetrics database imputed this based on practice patterns; as a result, the “psychiatric” specialty may in fact represent psychiatrists, psychologists, and social workers. To avoid statistical confounding with our “behavioral care” variable, we chose to omit provider specialty as an independent variable for this study.

Besides limited information on systemic factors affecting care, the exclusion of bupropion and tricyclic antidepressants leaves unexamined the utilization patterns of these commonly used agents for adult ADHD. As with other nonstimulants (with evidence supporting off-label use in adult ADHD), further research is merited.

Our study shares the limitations of all research conducted using administrative claims. As administrative rather than research tools, claims cannot be considered as accurate or reliable as the data derived from cohort clinical trials that follow patients over time; our data are observational and cannot provide insights into cause and effect.

Conclusions

To our knowledge, this is the first examination of emerging patterns of treatment with ATX and STIMs for adults with ADHD; previously published research examined initiation of ATX and STIMs in children and adolescents with ADHD. The significance of patient demographics, clinical histories, and prior behavioral service use suggest that ATX and STIMs may be used for different purposes in the treatment of adults with ADHD. Future research into health service utilization patterns and outcomes, including relative effectiveness over time for ATX versus STIMs, should consider potential differences between patients receiving these treatment alternatives.

DISCLOSURES

Funding for this research was provided by Eli Lilly and Company and was obtained by author David L. Van Brunt. Van Brunt and authors Joseph A. Johnston, Wenyu Ye, Gerhardt M. Pohl, and Nina N. Ohara, are employed by Eli Lilly and Company and disclose that they receive company stock within employee 401(k) plans. They state that their employer reviews their work prior to disclosure to ensure that they have not violated any federal regulations or privacy laws or disclosed any trade secrets, and that the information being disclosed is scientifically accurate. However, the authors attest to the fact that the scientific content is their own and that company policy encourages the disclosure of findings from all research, regardless of whether or not the outcome of that research is favorable to the company's products (which include ATX). Similar research of administrative claims data for children with ADHD was published in November 2005 in *Pharmacotherapy* (Van Brunt DL, Johnston JA, Pohl G, et al. Predictors of pharmaceutical treatment selection

for children with ADHD following the introduction of ATX. *Pharmacotherapy*. 2005;25(11):1541-49.)

Van Brunt served as principal author of the study. Study concept and design were contributed by Van Brunt, Johnston, and Pohl, with input from Ye and Ohara. Data collection was the work of Ye and Van Brunt, with input from Johnston and Pohl; data interpretation was primarily the work of Ye, Van Brunt, and Johnston, with input from Pohl and Ohara. Drafting of the manuscript and its revision were primarily the work of Van Brunt, with input from Johnston and the other coauthors.

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