Evidence of Low Adherence to Stimulant Medication Among Children and Youths With ADHD: An Electronic Health Records Study

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Objective: The objective of this study was to evaluate rates and correlates of stimulant medication adherence in a sample of pediatric patients using data derived from electronic medical records (EMRs) from a large health care organization in a large metropolitan area. The study relied on a novel definition of medication adherence as a timely renewal of an index prescription determined using the electronically recorded issuance of a stimulant prescription in the EMR ("refill").

Methods: Prescription and sociodemographic data were extracted from the Partners HealthCare Research Patient Data Registry to calculate adherence to stimulant medication treatment.

Results: In the EMR, 2,206 patients with prescriptions for central nervous system stimulant medication were identified. Results showed that 46% of the index prescriptions were refilled within the timeframe necessary for the patient to be considered consistently medicated. A multivariable logistic regression model predicting medication adherence from patient demographic and treatment characteristics yielded an area-under-the-curve statistic of 0.57, indicating that these characteristics predicted adherence only modestly better than chance.

Conclusions: EMR data from a large health care organization showed that 46% of pediatric patients were adherent to treatment with stimulants. Rates of medication adherence were worse among patients receiving care from a primary care provider than among those receiving care from a psychiatrist, in older patients, and in female patients and did not appear to be influenced by racial-ethnic group, economic class, stimulant type, or medication formulation (short or long acting). These findings, which show low rates of medication adherence among children and adolescents with ADHD, suggest the need for efforts to improve these rates.

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Attention-deficit hyperactivity disorder (ADHD) is a prevalent and morbid neurobiological disorder estimated to affect up to 11% of children in the United States (1–4). ADHD has been associated with a wide range of adverse outcomes, including educational and occupational underattainment (5); family disruption; interpersonal deficits (6–8); mood and anxiety disorders (9); addictions to cigarettes, drugs, and alcohol (10); injuries and accidents; automobile accidents (11); traumatic brain injury (12–14); posttraumatic stress disorder (9); premature death (5, 15); and suicide (16, 17).

At the same time, ADHD is among the most treatable of all psychiatric disorders, with the documented safety and efficacy of stimulants (18–27). Emerging data also document that treatment with stimulants decreases the risks for many ADHD-associated adverse outcomes, including addictions (28, 29), smoking initiation (7), mood and anxiety disorders

HIGHLIGHTS

- The objective of this study was to evaluate rates and correlates of adherence to stimulant medication among children and adolescents by using data derived from the electronic medical record (EMR) of a large health care organization in a large metropolitan area.
- A novel definition of medication adherence was operationalized as a timely renewal of an index prescription of a stimulant as documented in the EMR.
- EMR data showed that only 46% of more than 2,000 pediatric patients were adherent to treatment with stimulants.
- Rates of treatment adherence were lower in the primary care setting, in older patients, and in female patients and did not appear to be influenced by racial-ethnic group, economic class, stimulant type, or medication formulation (short or long acting).

(30), criminality (31), accidents and injuries (32, 33), and traumatic brain injury (34).

A limited literature suggests that compliance with stimulants is low (35, 36). Likely contributors to poor compliance include parental biases (37) and inadequate parental supervision (38). Perwien et al. (39) showed that patients with ADHD took stimulants consistently for 2 months or less, indicating that pharmacologic treatment in newly treated ADHD patients may be suboptimal and may adversely affect outcomes, including effectiveness of the treatment. Unfortunately, most of the literature on the subject of nonadherence to stimulants in ADHD does not provide specific rates in the general population, focusing instead on specific subpopulations (40, 41), such as those receiving public assistance (42–45); specific ethnic groups, such as African Americans (46); and specific stimulant formulations, such as long- versus short-acting medications (47–50). These findings call for improved efforts to better quantify the magnitude of the problem of low adherence to stimulants in broader populations of patients with ADHD.

Although the advent of electronic medical records (EMRs) offers a unique opportunity to investigate adherence to stimulants in pediatric populations, this technology has not been adequately utilized in the scientific literature. One of the few studies that used EMR data to quantify rates of adherence to stimulants among patients with ADHD reported that 84% of children were nonadherent to prescribed stimulant medication therapy during the first 2 months of treatment (39), suggesting that nonadherence can be observed shortly after initiation of stimulant treatment. This finding is noteworthy because short-term compliance with treatment may reflect the patient's overall adherence to treatment. As shown in the literature, patients who adhere to treatment have better clinical outcomes than those who do not (51).

Further efforts to quantify and better understand rates of patient adherence to stimulant treatments could have important implications. If new insights can be gleaned regarding risk factors for low adherence, then efforts could be made to help mitigate this problem.

The main aim of this study was to quantify rates and correlates of patient adherence to stimulant treatment for ADHD. We conducted a systematic search of EMR from a large health care organization for children ages 4–17 years who had been prescribed an amphetamine or methylphenidate product between January 1, 2015, and December 31, 2016. We defined the children as adherent to stimulant medication treatment if the first prescription (hereafter referred to as the index prescription) was renewed in a timely fashion. On the basis of the literature, we hypothesized that adherence to stimulant medication for ADHD would be low.

METHODS

Sample

Prescription and sociodemographic data were extracted from the Partners Health Care Research Patient Data Registry (RPDR) of Massachusetts General Hospital (MGH) for patients ages 4–17 years who had been prescribed a stimulant from January 1, 2015, to December 31, 2016. This period was based on the time when the newest EMR system from Epic Systems Corporation was implemented. Epic is one of the largest providers of health information technology used to access, organize, store, and share EMRs. Prescription information in Epic before January 1, 2015, was considered incomplete. This study was approved by the institutional review board at MGH.

Patients were included in the study sample if they had been prescribed any of the following formulations of stimulants (short- or long-acting): amphetamine/dextroamphetamine, dextroamphetamine or lisdexamfetamine, dexmethylphenidate, or methylphenidate. We included medications prescribed as a single prescription (30-day supply) and medications with prescriptions postdated by up to three months (60- or 90-day supply).

Index Prescription

We defined a patient's index prescription as the first time a stimulant was prescribed for him or her during the study period of January 1, 2015, to December 31, 2016. This period was chosen because prescription data prior to January 1, 2015, were incomplete in the system, prohibiting differentiation between newly treated patients and patients who had received any treatment prior to the study period.

Prescription Refills and Medication Adherence

We defined a stimulant prescription refill as receipt of another prescription for any stimulant medication regardless of the medication type (amphetamine or methylphenidate), dose, or formulation (short- versus long-acting). We defined a patient as being adherent if the index stimulant prescription was refilled in one of the following three ways: a single index prescription was followed by a second prescription issued within 90 days; index prescriptions postdated by 2 months (i.e., two prescriptions in the system with the same prescribing date for medications of the same dose, formulation, and type) were followed by a third prescription issued between 31 and 120 days after the date of the index prescription; or index prescriptions postdated by 3 months (i.e., three prescriptions in the system with the same prescribing date for medications of the same dose, formulation, and type) were followed by a fourth prescription issued between 61 and 150 days after the date of the index prescription. If patients had more than one medication prescribed on the date of the index prescription (i.e., medications with different dosages or formulations), they had to refill only one of the medications to be considered adherent. Additionally, if patients had more than one medication prescribed on the date of the index prescription and one was postdated, we followed the rules for postdated prescriptions. Patients were excluded if the window of time to refill their prescriptions extended beyond the endpoint of our study.

Variable Derivation for Correlates and Prediction Analysis

We used patients' zip codes to identify the median incomes for the towns in which they lived (52). We split the median incomes into terciles to classify patients as lower (≤\$61,391), middle (>\$61,391 to <\$89,271), or upper (≥\$89,271) class. We categorized index prescriptions as prescribed from a psychiatric or nonpsychiatric clinic on the basis of the clinic reported in the EMR. If patients had more than one medication prescribed on the date of the index prescription and at least one was from a nonpsychiatric clinic, we categorized that prescription as having a nonpsychiatric source .

Statistical Methods

Of the available pool of 2,206 participants, a minority (N=741, 34%) had unspecified data for at least one of the following demographic or treatment characteristics: race (N=81, 4% missing), clinic source (N=678, 31% missing), primary language (N=20, <1% missing), and economic status (N=2, <1% missing). Therefore, we used multivariate imputation with chained equations to impute the missing data for these independent variables. Using Stata's "mi impute" command with 20 imputations, we implemented logistic regression imputation methods for race, clinic source, and primary language (binary variables) and ordered logistic regression imputation methods for economic status (ordinal variable). In addition to the imputed variables, we included the following predictors in our imputation models: sex, age, medication formulation (long- versus short-acting), medication type (methylphenidate versus amphetamine), and medication adherence.

We first compared rates of medication adherence between patients with different demographic (e.g., boys versus girls) and treatment (e.g., short- versus long-acting formulation) characteristics by using logistic regression models. We then used a multivariable logistic regression model to predict medication adherence from the demographic characteristics that were associated with adherence at the level of $p \leq 0.10$ in the bivariate analyses and all of the treatment characteristics. We generated an area-under-the-curve (AUC) statistic for the multivariable model to examine how well these characteristics predicted medication adherence. An AUC of 0.5 means the combined characteristics do not exceed chance in predicting adherence, and an AUC of 1.0 means they predict adherence perfectly.

To assess the robustness of the findings in our primary analysis, we performed five sensitivity analyses: the first excluded patients who had an unspecified prescribing clinic; the second excluded patients with an unclear ADHD diagnosis; the third excluded patients who had index prescriptions prior to January 1, 2016, thus ensuring 1 year of lead-in time without stimulant medication for all included patients; the fourth used a 45-day window to define medication adherence; and the fifth used a 37-day window to define medication adherence.

We also analyzed the data using a discovery and replication set approach, which allowed us to build a model to predict medication adherence in one data set and evaluate how well the model worked in a separate, unbiased data set. To do this, we randomly selected 75% of the patients for the discovery set and 25% of the patients for the replication set. Using the same approach as stated above, we built a multivariable logistic regression model and generated an AUC statistic using the discovery set. We then applied the multivariable logistic regression model developed in the discovery set to the replication set to see how well it predicted adherence in the replication set. This approach is used routinely in predictive analytics to protect against drawing conclusions from false-positive results.

For all analyses, standard errors were adjusted by using Stata's "mi estimate" command to account for the variability between imputations. All tests were two-tailed and performed at the 0.05 alpha level in Stata (version 15.1).

RESULTS

Sample

We identified 2,206 children and adolescents with prescriptions for stimulant medication; of these, a putative diagnosis of ADHD could be confirmed in 1,355 (61%). Of the 2,206 patients, 95% had single index prescriptions, 4.9% had prescriptions that were postdated by 2 months, and 0.5% had prescriptions postdated by 3 months.

Medication Adherence

Only 46% (N=1,023) of patients met our definition of medication adherence, indicating that they refilled their stimulant prescriptions quickly enough to be considered consistently medicated.

Sociodemographic Correlates of Medication Adherence

As shown in Table 1, there were small but statistically significant differences in the rates of medication adherence by age, sex, racial-ethnic group, and economic status. Patients who were older, female, Caucasian, or middle or upper class were less likely to adhere to the medication regimen. Patients who were taking methylphenidate instead of amphetamines and those who received prescriptions from psychiatric clinics rather than nonpsychiatric clinics had a small but significantly greater likelihood of adherence to treatment (Table 1). There were no other meaningful differences.

Predictors of Medication Adherence

We used a multivariable logistic regression model to predict medication adherence from all demographic characteristics that had $p \leq 0.10$ in the bivariate analyses and all treatment characteristics (Table 2). After the analyses controlled for all other variables, the characteristics that remained significantly associated with adherence to treatment were age, sex, and prescription source. Older patients were significantly less likely to adhere to treatment, while male patients and patients who got their prescriptions from a psychiatry clinic were significantly likelier to adhere to treatment. Overall, however, this model yielded an AUC statistic of 0.57, indicating that these demographic and treatment characteristics were only modestly better than chance at predicting medication adherence.

TABLE 1. Rates of stimulant medication adherence among 2,206 children and adolescents, by demographic and treatment characteristic

Characteristic	Total N	Nonadherent to treatment (N=1,183) N	%[a]	Adherent to treatment (N=1,023) N	%[a]	p
Age (M±SD)		12.5±3.0		12.1±3.0		.003
Age group						.04
Child (age <12)	897	457	51	440	49	
Adolescent (age ≥12)	1,309	726	55	583	45	
Sex						.009
Male	1,624	844	52	780	48	
Female	582	339	58	243	42	
Racial-ethnic group[b]						.01
Caucasian	1,568	869	55	699	45	
Not Caucasian	638	314	49	324	51	
Primary language						.51
English	2,015	1,085	54	930	46	
Not English	191	98	51	93	49	
Economic class						.03
Lower	739	367	50	372	50	
Middle	730	401	55	329	45	
Upper	737	415	56	322	44	
Medication formulation						.29
Long-acting	1,639	868	53	771	47	
Short-acting	567	315	56	252	44	
Medication type						.02
Methylphenidate	1,573	819	52	754	48	
Amphetamine	633	364	58	269	42	
Prescription source						.001
Psychiatric clinic	926	449	48	477	52	
Nonpsychiatric clinic	1,280	734	57	546	43	

[a] Row percentages. Denominator is total N for each characteristic.
[b] Racial-ethnic group combined into Caucasian versus non-Caucasian for analysis. Breakdown was as follows: Caucasian, N=1,511 (68.5%); black, N=138 (6.3%); Asian American, N=50 (2.3%); Hispanic, N=352 (15.8%); Native American: N=5 (.3%); other: N=69 (3.1%), not reported, N=81 (3.6%).

Discovery and Replication Set Analysis

We randomly assigned 1,662 patients (75%) to the discovery set and 544 patients (25%) to the replication set. Medication adherence rates in the discovery and replication sets were 46% and 48%, respectively. The multivariable logistic regression model predicting medication adherence from age, sex, race, medication formulation, medication type, and prescribing clinic yielded an AUC statistic of 0.59 in the discovery set and 0.58 in the replication set (see the online supplement).

Sensitivity Analysis Results

To assess the robustness of the results in our primary analysis, we reran our analyses after excluding 678 patients with unspecified prescribing clinics. Medication adherence remained low (53%) and our model predicting adherence from age, sex, medication formulation, medication type, and prescribing clinic yielded a low AUC statistic of 0.57. As a second sensitivity analysis, we reran our analyses after excluding 851 patients with no recorded psychiatric diagnoses in the EMR. Adherence remained low (59%), and our model predicting medication adherence from age, economic status, medication formulation, medication type, and prescribing clinic yielded a low AUC statistic of 0.56. In a third sensitivity analysis, we excluded 1,035 patients with index prescriptions prescribed prior to January 1, 2016, to help mitigate the problem of being unable to differentiate between newly treated patients and patients who had received treatment before the study period. This exclusion ensured that all patients included in the analysis had at least one year of lead-in time without stimulant prescriptions. Again, adherence to medication remained low (59%), and our model predicting adherence from age, sex, race, primary language, economic status, medication formulation, medication type, and prescribing clinic yielded a low AUC statistic of 0.60.

In the fourth sensitivity analysis, we narrowed the prescription refill window from 90 days to between 7 and 45 days of the index prescription, making an additional assumption that prescriptions refilled within the first 7 days were not actually refills, but likely reprints of lost prescriptions. We decided to give a 15-day window beyond the date the medication ran out to allow some margin of error for minor delays or problems with obtaining the new prescription exactly when the medication ran out. With this new definition, medication adherence dropped to 30%, and our model predicting adherence from age, race, medication formulation, medication type, and prescribing clinic yielded a low AUC statistic of 0.54.

In our last sensitivity analysis, we narrowed the prescription refill window even more, from 90 days to between 7 and 37 days of the index prescription. Adherence was the lowest with this definition (25%), and our model predicting medication adherence based on age, race, medication formulation, medication type, and prescribing clinic yielded a low AUC statistic of 0.55. As in the primary analysis, the low AUC statistics in all sensitivity analyses indicate that these demographic and treatment characteristics were only modestly better than chance at predicting medication adherence.

TABLE 2. Predictors of adherence to stimulant medication among 2,206 children and adolescents

Characteristic	OR	95% CI	p
Age (continuous)	.97	.94–.99	.03
Male (reference: female)	1.23	1.01–1.49	.04
Caucasian (reference: non-Caucasian)	.83	.67–1.03	.09
Economic class			.07
Middle (reference: lower)	.82	.65–1.02	
Upper (reference: lower)	.77	.61–.97	
Upper (reference: middle)	.95	.77–1.17	
Long-acting formulation (reference: short-acting formulation)	1.13	.93–1.38	.21
Methylphenidate (reference: amphetamine)	1.17	.97–1.42	.10
Prescription from psychiatric clinic (reference: nonpsychiatric clinic)	1.54	1.24–1.91	<.001

DISCUSSION

Using a novel definition of medication adherence that was based on the renewal of the index prescription, a study of 2 years of EMR data from a large health care organization demonstrated that only 46% of 2,206 patients adhered to the medication regimen for treatment with stimulants. These findings provide new and generalizable estimates of low rates of medication adherence among children and adolescents with ADHD.

Strengths of this study included the use of a large EMR data set from a well-defined, representative population of patients seen at a large health care organization in a large metropolitan area representing all socioeconomic and racial-ethnic strata and the use of an objective metric of adherence based on the issuance of a prescription for a stimulant as documented in the EMR. Additionally, data were analyzed by using differing definitions of medication adherence (sensitivity analyses) as well as through a discovery and replication set analysis (see the online supplement), with all analyses leading to similar results showing poor rates of medication adherence.

We found some small but statistically significant demographic and clinical differences between patients who did and did not adhere to stimulant treatment. Children tended to adhere to the medication regimen somewhat more than adolescents (perhaps indicating effects of parental surveillance), adherence was slightly better in boys than in girls, and adherence was somewhat better for patients receiving prescriptions from psychiatric versus nonpsychiatric clinics, which may reflect either the severity of these patient populations or a greater ability of psychiatrists to motivate adherence. The findings show that low adherence to stimulant treatment in ADHD affects all ages, both sexes, and all economic class strata.

Our finding that rates of medication adherence were slightly higher among patients who received prescriptions from psychiatric clinics is novel. This finding may reflect better familiarity with ADHD within psychiatry that may help patients become more adherent to stimulant treatment. These findings suggest that efforts to improve medication adherence for ADHD may be most needed in the primary care setting.

While uncertainty remains as to why medication adherence is low, it is possible that low adherence is driven by the unique complexity of renewing prescriptions for stimulants, which are schedule II medicines; poor tolerability to stimulants, such as lack of appetite and difficulty sleeping; as well as ambivalence of parents about using medications to treat their children. Low adherence may also stem from misinformation or biases about stimulants in the media. Some patients may take stimulant medications on schooldays only; thus, failure to refill a prescription on time may not reflect nonadherence. It is also possible that the diagnosis of ADHD may have been inaccurate, thereby the index prescription may have been inappropriate. More research is needed to clarify the causes of low medication adherence in ADHD to develop appropriate measures to mitigate them (35, 36).

Our results should be seen in the context of methodological limitations. Our definition of medication adherence was based on renewal of the index prescription . Thus we do not know whether other measures of medication adherence, such as those proposed by Simmons et al. (53), would have led to different results. Additionally, no consideration was given to time of year; some pediatric patients do not take their medication during the summer. Because our sample was derived from a single health care organization in New England, the extent to which the results can be generalized to other regions or countries merits further investigation. Another limitation stems from not having access to data about co-occurring conditions, making it difficult to assess the impact of comorbid conditions on our findings. As well, in 30% of cases, the clinic source of prescriber was not noted and was imputed. However, an analysis of our findings excluding this subsample led to the same results.

Notwithstanding these caveats, these EMR-derived data relying on a novel definition of medication adherence and on an objective metric of adherence (issuance of a prescription) indicate that only 46% of 2,206 patients were adherent to stimulant treatment. These findings provide strong evidence of low rates of medication adherence among youths, underscoring the need for active efforts to better understand the problem and develop approaches to help mitigate it, especially in primary care settings.

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