The Pennsylvania State University

The Graduate School

College of Medicine

USE OF ATYPICAL ANTIPSYCHOTIC MEDICATION AMONG CHILDREN IN A COMMERCIALLY INSURED POPULATION

A Thesis in

Public Health Sciences

by

Benjamin William Novinger

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Master of Science

August 2011

The thesis of Benjamin William Novinger was reviewed and approved* by the following:

Douglas L. Leslie
Professor, Division of Health Services Research
Thesis Adviser

Vernon M. Chinchilli
Distinguished Professor, Division of Biostatistics and Chair, Public Health Sciences

Christopher S. Hollenbeak
Associate Professor, Division of Health Services Research

*Signatures are on file in the Graduate School

Abstract

This study examined the prevalence, trends, and predictors of non-evidenced based atypical antipsychotic use in commercially insured children with mental health conditions between 2003 and 2009. A national administrative claims database was used to identify a sample of 150,272 children with a mental health condition who received a prescription for an atypical antipsychotic medication. Generalized estimating equation models were developed to identify patient factors associated with non-evidenced based use. Non-evidenced based use was common in this sample (34%-62% of subjects depending on the specific medication). Adjustment reaction, anxiety disorder, attention-deficit disorder, conduct disorder, depression, eating disorders, obsessive-compulsive disorder, autism spectrum disorders, and tic disorder were all significant predictors of non-evidenced based use. Further studies that evaluate the temporal relationship between the diagnosis, prescription, and presence of an inpatient admission as well as provider factors affecting non-evidenced based use of these drugs, should be considered.

TABLE OF CONTENTS

Introduction

Antipsychotics were first introduced in the 1950's and revolutionized the treatment of schizophrenia. Patients who had been relegated to long-term psychiatric institutions could leave the inpatient setting and lead much more rewarding and productive lives out in the community. Unfortunately, these drugs have significant side effects, including various neurological reactions. Beginning in the 1990's, a second generation of antipsychotics was developed, called "atypical" for their apparent lack of extrapyramidal side effects. However, recent research has shown that even these atypical antipsychotics contain some level of extrapyramidal side effects, as well as other side effects not traditionally associated with the first generation drugs (including metabolic and cardiovascular problems) (1).

Although second generation antipsychotic medications have been approved for use in the treatment of schizophrenia and bipolar disorder, previous studies suggest off-label use of these drugs is common in adults (2-4). Recent studies have demonstrated that rates of off label use of second generation antipsychotics is as high as 60% in adults, with off-label use being the most common among patients diagnosed with posttraumatic stress disorder, depression, and anxiety disorders (2). Dementia, obsessive-compulsive disorder, personality disorders, and autism have also been reported as conditions for which off-label use was more common (4).

However, little is known about the use of these drugs in children. The Food and Drug Administration's (FDA) approval for atypical antipsychotics in children is generally limited to the treatment of schizophrenia for ages 13-17, mania and bipolar disorders for ages 10-17, and irritability associated with autistic disorder for ages 5-17. Select atypical antipsychotics have been shown to be effective in treating a limited set of conditions in children, such as conduct disorder, developmental disorders, obsessive compulsive disorders, and tic disorders. Although these drugs

currently are not FDA approved for these conditions, their use in such circumstances is supported by clinical evidence. It is unclear, however, how often these drugs are prescribed for conditions for which such evidence does not exist.

The number of children who became new users of atypical antipsychotics is increasing in Medicaid populations, where the number of new users approximately doubled between 1996 and 2001 (5, 6). However, the extent to which this increase was for non-evidenced based treatment is not known. Non-evidenced based use can have two important negative consequences. First, atypical antipsychotics represent a significant cost to the U.S. healthcare system, where $14.6 billion was spent on these drugs in 2009 (7), much of it for off-label use (8, 9). Second, atypical antipsychotics can have serious side effects in adults, including weight gain, diabetes mellitus, hyperlipidemia, and extrapyramidal symptoms (10), as well as increased risk of sudden cardiac death (11). Among children, a number of studies have documented similar side effects associated with these drugs, particularly weight gain, prolactin elevation, glucose dysregulation, and dyslipidemia (14). The risk of these and other side effects of these medications needs to be weighed against their clinical benefit.

The objective of this cross-sectional, retrospective study is to determine the prevalence, trends, and predictors of non-evidenced based atypical antipsychotic use in commercially insured children with mental health conditions. In contrast to earlier studies by Domino and Swartz (3) and Cooper et al. (5) that focused on new users and to Pathak et al. (6) that included only Medicaid enrollees from a single state and focused on new users (that is, those receiving their first prescription in the study period) this study evaluates all users of these medications and broadens the investigation to a large, national commercially-insured population. Additionally, this study explores whether the effect of patient characteristics on the likelihood of non-evidenced based use differs by medication or is

consistent across all of the drugs in the class. Finally, more recent findings are provided by using data through calendar year 2009.

Methods

Sources of data

Data for this study came from the Thomson/Reuters MarketScan® database, which contains de-identified medical and pharmacy utilization and enrollment information from approximately 100 private health insurance plans. The data set contains claims information for individuals across the United States who are insured through the benefit plans of large employers. The covered individuals include employees, their dependents, and early retirees of companies who participate in the database. Thomson/Reuters collects the claims data, standardizes and combines them, and then reports back to the firms who participate. Information about the firms is unavailable for reasons of confidentiality. The database contains information for more than 500 million claim records for the period 2003-2009. The study was approved by the Institutional Review Board of the Penn State College of Medicine.

Inclusion Criteria

The study sample consists of all individuals in the database 17 years and younger who were continuously enrolled for one year between 2003 and 2009 and had a mental health diagnosis based on the International Classification of Diseases 9th Edition (ICD-9) as outlined in Appendix A. Individuals were identified as having a mental health disorder if they had at least 1 inpatient claim or 2 outpatient claims on different dates of service for the disorder. Individuals were also required to have had at least 1 prescription for any atypical antipsychotic. Medications in the evaluation included aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Inclusion criteria for each study year were evaluated independently. Individuals could appear in the sample in multiple years.

Measures

Dichotomous variables were created to indicate whether an individual received each of the antipsychotic medications, as well as for whether they had any diagnosis during the year for which

there was scientific evidence that the drug was effective. Use under this scenario is considered evidenced based. Use of the drugs in individuals who did not have a diagnosis for a condition for which they have been FDA approved or for which evidence of effectiveness has not been shown in the literature was considered non-evidenced based use. The lists of conditions for which use of an antipsychotic was considered evidenced based were based on a study by Pathak and colleagues (6) in which a literature search was performed to identify the strength of evidence of clinical effectiveness. Evidenced-based use was then expanded to include recent FDA approvals for these drugs. Although epilepsy was indicated by Pathak et al. to show weak support for treatment with risperidone, the literature actually shows that risperidone does not appear to induce seizures and hence is safe for use in children with epilepsy (rather than being effective in reducing seizures); hence, epilepsy alone was not included as an evidenced base use. Age of the individual in relationship to the specific age ranges approved by the FDA for each medication was not evaluated. That is, if there was evidence of effectiveness among children of any age, then any use among children was considered evidenced-based. This approach yields the most liberal assignment of approved indications as certain FDA approvals are restricted by age. Dichotomous variables were also created to indicate whether the child had each of the mental health conditions listed in Appendix A. Patients could belong to multiple mental health diagnostic groups. Categorical variables were created to assign the level of evidence for each drug for each mental health condition, following the methods used by Pathak et al. outlined in Appendix B. The variable "year" represents a calendar year.

Analysis

The number and proportion of individuals with a mental health condition, and with a mental health condition and receiving any atypical antipsychotic, were calculated, as were the number and proportion of children who received an antipsychotic for a non-evidence based use. The Mantel-Haenszel chi-square test was performed to test for association between calendar year and non-

evidenced based antipsychotic use separately for each medication and overall across all medications. Next, regression analysis was used to identify individual level factors associated with non-evidenced base use. In order to correct for the correlated nature of these data, a generalized estimating equation (12) model was applied separately for each medication using the genmod procedure in SAS. Individual models predicting non-evidenced based use were run for each medication with age, gender, geographic region, inpatient mental health admission, and calendar year included as independent variables. A model was not run for clozapine because only 377 children (0.25% of the sample) were prescribed this drug. Only mental health conditions not related to the medication for evidenced based indications were included in each individual model and therefore we were not able to run a model for atypical antipsychotics as a class because evidenced based conditions differ by drug within the class. A very small percentage of records where region was not indicated in the data were excluded from the models. All data analysis was performed using SAS version 9.2.

Results

Overall, 150,272 children met the inclusion criteria of being continuously enrolled during the year, having a mental health condition and receiving a prescription for an atypical antipsychotic. The average age for these children was 12 with a large majority being male (66%). Compared to other children without a mental health condition or those not receiving an atypical antipsychotic medication, these children were generally older and more likely to be male. Eighteen percent of those receiving antipsychotic medications had at least 1 inpatient admission for a mental disorder compared to just 4% of those not receiving the medications. The complete demographic distributions of these subgroup samples are shown in Table 1.

Table 1: Characteristics of the sample stratified by all children, children with a Mental Health Diagnosis, and those with a Mental Health diagnosis and an atypical anti-psychotic prescription (member-years, 2003 - 2009)

	Total Under 18 Continuously Enrolled Population		**Subgroup of those with MH Diagnosis**		**Subgroup of those with Atypical Antipsychotic**	
	N	%	N	%	N	%
N	38,869,659		2,071,362	5%*	150,272	7%**
Age						
Mean ± SD	9.2 ± 5.1		10.9 ± 4.2		12.2 ± 3.5	
0-9	19,235,666	49%	738,122	36%	35,435	24%
10-13	9,379,362	24%	610,663	29%	48,569	32%
14-17	10,254,631	26%	722,577	35%	66,268	44%
Gender						
Male	19,858,528	51%	1,241,958	60%	98,779	66%
Female	19,011,131	49%	829,404	40%	51,493	34%
At least 1 inpatient stay for a mental health condition			91,159	4%	26,309	18%

* Prevalence of mental health diagnosis among total population

**Prevalence of atypical antipsychotic use among mental health population

Table 2 shows the distribution of mental health conditions by gender among antipsychotic users. Males tended to have a higher prevalence of attention-deficit hyperactivity disorder (46% vs. 26%) and autism spectrum disorders (16% vs. 6%) while females tended to have a higher prevalence of adjustment reaction (17% vs. 11%), depression (42% vs. 23%), and mania and bipolar disorders (33% vs. 24%).

Table 2: Number and percent of specific mental health diagnoses among those receiving atypical antipsychotic

	Male		Female	
	N	**% of Males**	**N**	**% of Females**
Adjustment Reaction	10,454	10.7%	8,571	16.6%
Anxiety Disorders	9,918	10.1%	7,110	13.8%
Attention-deficit hyperactivity disorder	44,742	45.6%	13,183	25.6%
Autism spectrum disorders	15,677	16.0%	3,047	5.9%
Conduct Disorder	7,927	8.1%	2,911	5.7%
Depression	22,041	22.5%	21,542	41.8%
Development Disorders	2,926	3.0%	1,060	2.1%
Eating Disorders	250	0.3%	1,640	3.2%
Mania and bipolar disorders	23,095	23.5%	17,174	33.4%
Obsessive-compulsive disorder	3,654	3.7%	2,141	4.2%
Oppositional defiant disorder	7,878	8.0%	3,375	6.6%
Personality disorders	871	0.9%	790	1.5%
Posttraumatic stress disorder	128	0.1%	1,843	3.6%
Psychoses	4,257	4.3%	2,739	5.3%
Substance Abuse	3,840	3.9%	2,481	4.8%
Tic Disorder	2,229	2.3%	484	0.9%

The number and percent of individuals receiving each medication by strength of evidence is shown in Table 3. Overall quetiapine had the highest level of non-evidenced based use at 62%, while paliperidone had the highest proportion of those with at least plausible evidence of effectiveness (32% with plausible evidence and 30% with strong evidence). Risperidone was the most prescribed drug with 69,975 patients receiving this medication, although 50% was non-evidenced based. Clozapine was not included in the analyses since only 377 children received the drug during the study period.

Table 3: Unique number and percent of patients receiving atypical antipsychotics by level of evidence in total study period.

	Total	**Level of Evidence:**			
	Receiving	**Strong**	**Plausible**	**Weak**	**None**
Aripiprazole	48,060	0 0%	23,350 49%	0 0%	24,710 51%
Olanzapine	11,339	710 6%	4,043 36%	0 0%	6,586 58%
Paliperidone	2,096	635 30%	681 32%	68 3%	712 34%
Quetiapine	39,531	13,847 35%	1,247 3%	0 0%	24,437 62%
Risperidone	69,975	20,273 29%	11,209 16%	3,280 5%	35,213 50%
Ziprasidone	10,926	0 0%	4,854 44%	0 0%	6,072 56%

Overall, rates of non-evidence based use by year were fairly constant; however, there were statistically significant changes by year for some drugs. When looking at specific medications, there was a significant increase in the non-evidence based use of aripiprazole, both in terms of percentage (45% in 2003 to 54% in 2009) and number (580 in 2003 to 7,254 in 2009)of patients receiving the drug . Use of olanzapine dropped during the study period from 1,159 patients in 2003 to 908 in 2009. This was the only medication to show a decrease. Paliperidone was not approved by the FDA until 2006. It should be noted that even thought the any atypical antipsychotic results is statistically significant this is due in large part to the sample size and may not be clinically significant.

Table 4: Unique number and percent of patients receiving atypical antipsychotics with no evidence based indications by calendar year (1).

		2003	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**p (2)**
Aripiprazole	# No Evidence	580	1,670	2,563	3,077	3,348	6,218	7,254	
	Total Receiving	1,294	3,437	5,069	6,259	6,814	11,737	13,450	
	% No Evidence	45%	49%	51%	49%	49%	53%	54%	<.0001
Olanzapine	# No Evidence	1,159	1,159	963	760	708	929	908	
	Total Receiving	1,947	1,963	1,558	1,350	1,256	1,624	1,641	
	% No Evidence	60%	59%	62%	56%	56%	57%	55%	0.0008
Paliperidone	# No Evidence					134	302	276	
	Total Receiving					406	843	847	
	% No Evidence					33%	36%	33%	0.6286
Quetiapine	# No Evidence	1,613	2,508	3,092	3,501	3,699	4,997	5,027	
	Total Receiving	2,624	4,066	5,003	5,767	6,009	8,081	7,981	
	% No Evidence	61%	62%	62%	61%	62%	62%	63%	0.0907
Risperidone	# No Evidence	2,612	3,758	4,322	4,547	5,097	7,232	7,645	
	Total Receiving	5,180	7,321	8,338	9,012	10,133	14,475	15,516	
	% No Evidence	50%	51%	52%	50%	50%	50%	49%	0.0005
Ziprasidone	# No Evidence	430	680	810	875	907	1,162	1,208	
	Total Receiving	723	1,165	1,398	1,664	1,639	2,142	2,195	
	% No Evidence	59%	58%	58%	53%	55%	54%	55%	0.0042
Any Atypical Antipsychotic	# No Evidence	5,322	8,148	9,929	10,948	11,886	17,819	19,205	
	Total Receiving	9,468	14,487	17,564	19,947	21,779	32,234	34,793	
	% No Evidence	56%	56%	57%	55%	55%	55%	55%	0.0016

(1) Denominator in percent calculation is unique number of recipients receiving associated atypical antipsychotic

(2) Mantel-Haenszel Chi Square

Table 5 shows the results of the generalized estimating equation models predicting non-evidenced based use of each medication. We find that children age 0-9 and 10-13 were significantly more likely to receive aripiprazole, olanzapine, and quetiapine for non-evidenced based use than children aged 14-17. Children aged 0-9 were less likely to receive risperidone for a non-evidenced based use, but there were no other significant differences by age. Females were more likely to receive aripiprazole and risperidone for a non-evidence based use, whereas males were more likely to receive quetiapine and ziprasidone for a non-evidenced based use. No significant gender differences were found for olanzapine and paliperidone. Patients that had an inpatient admission for a mental health condition were significantly less likely to have a non-evidenced based use in all the models. Diagnosis was also a significant predictor of non-evidenced based use for many of the medications. Patients diagnosed with adjustment reaction, anxiety disorder, attention-deficit disorder, conduct disorder, depression, eating disorders, obsessive-compulsive disorder, autism spectrum disorders, or tic disorder were all significantly more likely to be prescribed an antipsychotic medication for a non-evidenced based use. Having an eating disorder was the strongest predictor of non-evidence based use of aripiprazole, olanzapine, paliperidone, and quetiapine, while attention-deficit disorder was the strongest predictor for risperidone and tic disorder was the strongest predictor for ziprasidone. There were few consistent trends across years.

Table 5: Generalized estimating equation regression models of non-evidenced base use

	Aripiprazole			Olanzapine			Paliperidone			Quetiapine			Risperidone			Ziprasidone		
N=	47,774			11,240			2,088			39,247			69,469			10,849		
Effect	Est.	SE	p	Est.	SE	p	Est.	SE	p	Est.	SE	p	Est.	SE	p	Est.	SE	p
Age																		
0-9	**0.09**	0.03	0.0012	**0.39**	0.06	<.0001	0.26	0.16	0.1105	**0.26**	0.04	<.0001	**-0.13**	0.02	<.0001	0.06	0.07	0.3608
10-13	**0.08**	0.02	0.0009	**0.35**	0.05	<.0001	0.01	0.13	0.9286	**0.15**	0.03	<.0001	-0.02	0.02	0.4854	0.07	0.05	0.1543
14-17 (ref)																		
Gender																		
Male	**-0.06**	0.02	0.0169	0.05	0.05	0.3072	-0.11	0.12	0.3851	**0.13**	0.03	<.0001	**-0.16**	0.02	<.0001	**0.25**	0.05	<.0001
Female (ref)																		
Region [1]																		
North East	**0.20**	0.04	<.0001	0.07	0.09	0.4225	0.09	0.26	0.7217	**0.29**	0.05	<.0001	-0.01	0.04	0.8747	**0.20**	0.09	0.0268
North Central	**0.34**	0.03	<.0001	**0.26**	0.06	<.0001	0.34	0.17	0.0505	**0.42**	0.04	<.0001	**0.25**	0.03	<.0001	**0.37**	0.07	<.0001
South	**0.26**	0.03	<.0001	**0.16**	0.06	0.0077	0.25	0.16	0.1227	**0.31**	0.03	<.0001	**0.18**	0.03	<.0001	**0.22**	0.07	0.0009
West (ref)																		
IP admission																		
Yes	**-1.60**	0.03	<.0001	**-1.78**	0.06	<.0001	**-2.16**	0.19	<.0001	**-1.52**	0.03	<.0001	**-1.72**	0.04	<.0001	**-1.59**	0.06	<.0001
No (ref)																		
Diagnosis [2]																		
Adjustment Reaction	**0.61**	0.03	<.0001	**0.35**	0.07	<.0001	**0.58**	0.19	0.0028	**0.51**	0.04	<.0001	**0.87**	0.03	<.0001	**0.40**	0.07	<.0001
Anxiety Dis.	**0.62**	0.03	<.0001	**0.66**	0.08	<.0001	**0.56**	0.18	0.0024	**0.67**	0.04	<.0001	**0.81**	0.03	<.0001	**0.51**	0.07	<.0001
Attention-deficit Dis.	**1.02**	0.02	<.0001	**0.94**	0.05	<.0001	**1.59**	0.12	<.0001	**0.78**	0.03	<.0001	**1.75**	0.02	<.0001	**0.54**	0.05	<.0001
Autism Spectrum Dis.				**1.23**	0.09	<.0001				**1.05**	0.05	<.0001				**1.30**	0.08	<.0001
Conduct Dis.	**0.45**	0.04	<.0001	**0.24**	0.08	0.0024				**0.24**	0.05	<.0001				**0.42**	0.09	<.0001
Depression	**1.06**	0.03	<.0001	**0.78**	0.06	<.0001	**1.43**	0.15	<.0001	**0.97**	0.03	<.0001	**1.30**	0.03	<.0001	**0.68**	0.05	<.0001
Development Dis.	-0.07	0.07	0.3098	**0.48**	0.15	0.0019				**0.48**	0.10	<.0001				**0.65**	0.16	<.0001
Eating Dis.	**1.30**	0.12	<.0001	**2.30**	0.18	<.0001	**1.75**	0.67	0.0087	**1.27**	0.12	<.0001	**1.35**	0.13	<.0001	**0.84**	0.22	0.0001
Obsessive-compulsive Dis.	**0.99**	0.06	<.0001	**0.66**	0.13	<.0001				**0.77**	0.08	<.0001				**1.12**	0.14	<.0001
Oppositional Defiant Dis.	**0.44**	0.04	<.0001	0.06	0.09	0.5250	**0.65**	0.23	0.0055	**0.19**	0.05	0.0001	**0.66**	0.04	<.0001	0.12	0.08	0.1429
Personality Dis.	0.14	0.09	0.1122	0.03	0.21	0.8963	0.86	0.49	0.0806	-0.02	0.11	0.8796	**0.27**	0.11	0.0159	-0.08	0.18	0.6532
Posttraumatic Stress Dis.	0.22	0.22	0.3215	-0.79	0.58	0.1738	0.95	1.15	0.4114	-0.25	0.23	0.2829	0.13	0.23	0.5740	-0.53	0.39	0.1771
Psychoses																**0.62**	0.09	<.0001
Substance Abuse	**0.40**	0.05	<.0001	**0.32**	0.11	0.0022	**0.85**	0.35	0.0152	**0.47**	0.05	<.0001	**0.49**	0.07	<.0001	0.19	0.12	0.1074
Tic Dis.	**1.26**	0.10	<.0001	**0.71**	0.22	0.0012				**0.67**	0.16	<.0001				**1.42**	0.20	<.0001
Year																		
2003 (ref)																		
2004	0.11	0.06	0.0683	-0.08	0.06	0.1959				0.01	0.05	0.7662	0.01	0.03	0.6738	-0.02	0.09	0.7922
2005	-0.02	0.06	0.7598	**-0.16**	0.07	0.0178				**-0.11**	0.05	0.0249	**-0.10**	0.04	0.0041	**-0.20**	0.09	0.0298
2006	0.10	0.06	0.0976	**-0.22**	0.07	0.0016				-0.03	0.05	0.5487	-0.04	0.04	0.2345	**-0.21**	0.09	0.0160
2007	0.08	0.06	0.1623	**-0.18**	0.07	0.0158	0.07	0.14	0.5840	-0.01	0.05	0.8569	**-0.08**	0.03	0.0179	-0.15	0.09	0.0854
2008	**0.17**	0.06	0.0040	**-0.19**	0.07	0.0078	0.13	0.10	0.1759	-0.05	0.05	0.3254	**-0.15**	0.03	<.0001	**-0.29**	0.09	0.0009
2009	**0.16**	0.06	0.0053	**-0.27**	0.07	0.0002				-0.03	0.05	0.5234	**-0.20**	0.03	<.0001	**-0.20**	0.09	0.0196

(1) Null region codes removed from sample

(2) The reference for each diagnostic group is patients who did not have the specified disorder

Discussion

This study demonstrates a high level of non-evidenced based use of atypical antipsychotics, consistent with trends demonstrated in previous studies (5, 6). Depending on the specific medication, as many as 62% of patients prescribed an antipsychotic had no diagnosis of an approved indication or for which any evidence of clinical effectiveness can be found in the literature. Aripiprazole was the drug associated with the largest increases in total prescriptions and percentage of patients receiving the drug for non-evidence based indications. Mental health conditions that were consistent predictors of non-evidence based use for all medications were many and included adjustment reaction, anxiety disorder, attention-deficit disorder, conduct disorder, depression, eating disorders, obsessive-compulsive disorder, autism spectrum disorders, and tic disorders.

The findings of this study are consistent with results reported in previous studies. Pathak et al. examined new use of non-evidenced based antipsychotic use among Medicaid enrolled children in a single state from 2001 through 2005 (6). They found ranges of non-evidenced based use among these drugs from 30% to 77%, which was similar to rates found in our study (34% to 62%). They also reported statistically significant findings with regard to inpatient psychiatric hospitalizations, where patients who were admitted tended to have very high levels of evidence based use. This finding was also very similar to our study in that point estimates for non-evidenced based use range from -1.52 ($p < .0001$) for quetiapine and up to -2.16 ($p < .0001$) for paliperidone. In contrast to Pathak et al., who reported that aripiprazole was the drug with the largest proportion of non-evidence based use at 77% we found that quetiapine was the largest in at 62%. Of note, Pathak et al. examined only new users of these medications while our study evaluated the total exposure to all individuals diagnosed with a mental health condition over the 7 year study period. In addition, we found significant effects of age and gender in non-evidenced based use of certain drugs, which was not explored in the Pathak et al. study. Alexander et al., who used a physician survey instrument for data collection to extrapolate national estimates of off-label use of atypical antipsychotics for non-

evidenced based reasons, found that 67% of patients under 18 years of age received atypical antipsychotics in 2008 (8). The study found that rates of non-evidenced based use increased from 55% in 1996 to 67% in 2008, rates similar to those seen in our study. However, in contrast, Alexander et al. reported that quetiapine was the most commonly prescribed atypical antipsychotic in 2008, while in our study quetiapine was the 3rd most prescribed drug behind risperidone and aripiprazole. The high rate of non-evidenced based use found in our study exceeds the rates of off-label use in other drug classes as reported by Radley et al. (13). Using data from a physician survey, they reported the highest rates of off-label use to be in cardiac therapy drugs (46%), anticonvulsants (46%), and anti-asthmatics (42%) (11). In contrast, off-label use of psychotropic medications (which included antidepressants, anxiolytics, and antipsychotics) was reported to be 31%. In addition, they found that risperidone was the 5th most commonly prescribed drug off-label across all drug classes (66%).

There were statistically significant differences between medications and certain diagnoses, suggesting that providers may be attempting to target certain conditions with certain medications. For example, children with personality disorders were significantly more likely to receive risperidone (estimate of 0.27, p=0.0159), while this diagnosis was not significant in predicting non-evidenced base use of any of the other medications. There are a number of potential explanations for these results. It is possible that providers may not fully understand the current evidence or approved indications for atypical antipsychotics. Alternatively, providers may also feel that clinical trial data may not be generalizable to real-world patient populations due to overly restrictive inclusion or exclusion criteria and therefore rely on their clinical experience for judgment. The high levels of non-evidenced base use for the treatment of eating disorders, which was the highest predictor in four of the drugs, could be cause for concern. A 2010 literature review found evidence that olanzapine, risperidone, and quetiapine may be beneficial in the treatment of eating disorders, but the findings may be limited to severely underweight patients (15). This review found that the most robust study of atypical antipsychotics in the treatment of eating disorders was a 2008 study by

Bissada and colleagues that conducted a randomized controlled trial of the use of olanzapine in women with anorexia nervosa (16). The study concluded that olanzapine was effective versus placebo in achieving weight gain. However, this study included only women and the average age of the participants was 24 years of age.

Having a psychiatric inpatient admission was one of the strongest predictors of non-evidenced based use. As noted in the results, 18% of children in the study had at least one inpatient admission for a mental health diagnosis. Of these, there was a significant positive relationship between having an admission and evidenced-based use of atypical antipsychotics. It could be speculated that once admitted, children receive care from a clinician more familiar with the appropriate administration of these drugs, or conversely, the most severely ill children could be already taking these medications and are therefore most likely to be admitted for psychiatric reasons. More research is needed to understand the reasons for non-evidenced base prescribing of these drugs.

A number of limitations of the study deserve comment. First, the data for the study were derived from medical claims records. Claims records are designed for billing purposes and hence do not contain detailed clinical information. Without access to the patient's full medical record it is difficult to ascertain the true presence of all medical conditions. It is also unclear whether the time trend results represent changes over time in diagnostic coding methods or other administrative provider practices. In addition, this study took a cross sectional view of the exposed population and it is impossible to infer any causal relationship between the prescriptions and diagnosed conditions, as well as the occurrence of any inpatient mental health admission. In other words, it is unclear whether patients received the appropriate medication before or after their inpatient admission. Further studies are needed to understand the temporal relationship between diagnosis, antipsychotic prescription, and inpatient admission.

Conclusion

Although atypical antipsychotics are clinically effective and an important component of care for some conditions, they can be potentially dangerous medications with severe side effects and considerable costs. Significant questions remain about the safety of these medications, particularly in children. Evidence exists that children are receiving these medications without a diagnosis for which the drug has been approved or for which clinical studies have demonstrated their effectiveness. The number of these non-evidence based prescriptions has increased dramatically between 2003 and 2009, with 34% to 62% of children with a mental health condition being prescribed these drugs with no evidence of clinical effectiveness. Given that these drugs are costly and associated with potentially severe side effects, their use in children should be considered carefully.

Appendix A: Mental Health Categories and Associated ICD9 codes

Adjustment Reaction	309
Anxiety Disorders	300.0, 300.2, 313.0
Attention-deficit hyperactivity disorder	314
Autism Spectrum Disorders	299
Conduct Disorder	312, 314.2
Depression	296.2, 296.3, 300.4, 300.5, 311
Development Disorders	314.1, 315, 317-319
Eating Disorders	307.1, 307.5, 783.0
Mania and bipolar disorders	296.0-296.1, 296.4-296.8
Obsessive-compulsive disorder	300.3
Oppositional defiant disorder	313.81
Personality disorders	301
Posttraumatic stress disorder	308
Psychoses	295, 297, 298
Substance Abuse	291, 292, 303-305
Tic Disorder	307.2

Appendix B: Evidence based mapping of level of evidence of atypical antipsychotics to mental health diagnosis

	Level of Evidence		
Drug	**Strong**	**Plausible**	**Weak**
Aripiprazole		Psychoses Autism Spectrum Disorders Mania and Bipolar	
Olanzapine	Psychoses	Mania and Bipolar	
Paliperidone	Conduct Disorder Development Disorders Autism Spectrum Disorders Psychoses	Mania and Bipolar	Obsessive Compulsive Disorder Tic Disorder
Quetiapine	Mania and Bipolar	Psychoses	
Risperidone	Conduct Disorder Development Disorders Autism Spectrum Disorders Psychoses	Mania and Bipolar	Obsessive Compulsive Disorder Tic Disorder
Ziprasidone		Mania and Bipolar	

References

1. Weiden PJ: EPS Profiles: The Atypical Antipsychotics: Are Not All the Same. Journal of Psychiatric Practice. 13(1):13-24, January 2007
2. Leslie DL, Mohamed S, Rosenheck RA: Off-Label Use of Antipsychotic Medications in the Department of Veterans Affairs Health Care System. Psychiatric Services 60: 1175-1181, 2009
3. Domino ME, Swartz MS: Who are the New Users of Antipsychotic Medications? Psychiatric Services 59: 507-514, 2008
4. Shekelle P, Maglione M, Bagley S, et al: Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics. Rockville, Md, Agency for Healthcare Research and Quality, 2007
5. Cooper WO, Hickson GB, Fuchs C, et al: New Users of Antipsychotic Medications Among Children Enrolled in TennCare. Archives of Pediatric and Adolescent Medicine 158: 753-759, 2004
6. Pathak P, West D, Martin BC, et al: Evidenced-Based Use of Second-Generation Antipsychotics in a State Medicaid Pediatric Population. Psychiatric Services 61: 123-129, 2010
7. "Top Therapuetic Classes by U.S. Sales". IMS Health. http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%20Therapy%20Classes%20by%20U.S.Sales.pdf
8. Alexander GC, Gallagher SA, et al: Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiology and Drug Safety 20: 177-184, 2011
9. Rosenheck RA, Leslie DL, Doshi JA: Second Generation Antipsychotics: Cost-Effectiveness, Policy Options, and Political Decision Making. Psychiatric Services 59: 515-520, 2008
10. Ucok A, Gaebel W: Side effects of atypical antipsychotics: a brief overview. World Psychiatry 7: 58-62, 2008
11. Ray WA, Chung CP, Murray KT, et al: Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death. New England Journal of Medicine 360: 225-235, 2009
12. Liang K, Zeger S: Longitudinal data analysis using generalized linear models. Biometrika 73: 13-22, 1986
13. Radley DC, Finkelstein SN, Stafford RS: Off-label Prescribing Among Office-Based Physicians. Arch Intern Med 166: 1021-1026, 2006
14. Fedorowicz VJ, Fombonne E: Metabolic side effects of atypical antipsychotics in children: a literature review. Journal of Psychopharmacology 19: 533-550, 2005
15. McKnight R, Park R: Atypical Antipsychotics and Anorexia Nervosa: A Review. Eur Eat. Disorders Rev 18: 10-21, 2010
16. Bissada H, Tasca GA, et al: Olanzapine in the Treatment of Low Body Weight and Obsessive Thinking in Women With Anorexia Nervosa: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Psychiatry 165: 1281-1288, 2008