

Psychotropic Medication Use and Polypharmacy in Children With Autism Spectrum Disorders

AUTHORS: Donna Spencer, PhD,^a Jaclyn Marshall, MS,^b Brady Post, BA,^b Mahesh Kulakodlu, MS,^a Craig Newschaffer, PhD,^c Taylor Dennen, PhD,^b Francisca Azocar, PhD,^d and Anjali Jain, MD^b

^a*OptumInsight, Life Sciences, Eden Prairie, Minnesota;* ^b*The Lewin Group, Falls Church, Virginia;* ^c*Drexel University School of Public Health, Philadelphia, Pennsylvania;* and ^d*OptumHealth Behavioral Solutions, San Francisco, California*

KEY WORDS

administrative claims, autism spectrum disorder, commercially insured, psychotropic polypharmacy

ABBREVIATIONS

ADD—attention-deficit disorder

ASD—autism spectrum disorders

ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*

VIF—variance inflation factor

Dr Spencer drafted the study design and analytical plan, supervised the analysis and interpretation of results, and contributed to the writing of the manuscript; Ms Marshall contributed to the overall study and approach as well as the study design and analytical plan, and critically reviewed the initial manuscript; Mr Post documented background literature and contributed to the study methods, and drafted and reviewed the initial manuscript; Mr Kulakodlu oversaw claims data programming, conducted the data analysis, and reviewed and contributed to revising the manuscript; Dr Newschaffer consulted on study methods, contributed to interpretation of results, and reviewed the manuscript; Dr Dennen contributed to the overall study and approach, and reviewed and revised the manuscript; Dr Azocar reviewed and contributed to the study design, provided guidance on study execution, and revised drafts of the manuscript; and Dr Jain contributed to the overall study design and writing of the manuscript, including the interpretation of the data and the implications of the study findings. All authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Psychotropic use is common and increasing in children with mental disorders but little is known about the long-term patterns of psychotropic use and polypharmacy among commercially insured children with autism spectrum disorders.



WHAT THIS STUDY ADDS: Among 33 565 children with autism spectrum disorders, 64% used psychotropic medications and 35% had evidence of polypharmacy. Older children and those who had seizures, attention-deficit disorders, anxiety, bipolar disorder, or depression had increased risk of psychotropic use and polypharmacy.

abstract



OBJECTIVE: The objectives of this study were to examine rates and predictors of psychotropic use and multiclass polypharmacy among commercially insured children with autism spectrum disorders (ASD).

METHODS: This retrospective observational study used administrative medical and pharmacy claims data linked with health plan enrollment and sociodemographic information from 2001 to 2009. Children with ASD were identified by using a validated ASD case algorithm. Psychotropic polypharmacy was defined as concurrent medication fills across ≥ 2 classes for at least 30 days. Multinomial logistic regression was used to model 5 categories of psychotropic use and multiclass polypharmacy.

RESULTS: Among 33 565 children with ASD, 64% had a filled prescription for at least 1 psychotropic medication, 35% had evidence of psychotropic polypharmacy (≥ 2 classes), and 15% used medications from ≥ 3 classes concurrently. Among children with polypharmacy, the median length of polypharmacy was 346 days. Older children, those who had a psychiatrist visit, and those with evidence of co-occurring conditions (seizures, attention-deficit disorders, anxiety, bipolar disorder, or depression) had higher odds of psychotropic use and/or polypharmacy.

CONCLUSIONS: Despite minimal evidence of the effectiveness or appropriateness of multidrug treatment of ASD, psychotropic medications are commonly used, singly and in combination, for ASD and its co-occurring conditions. Our results indicate the need to develop standards of care around the prescription of psychotropic medications to children with ASD. *Pediatrics* 2013;132:833–840

Research shows increasing rates of psychotropic use and the simultaneous use of multiple psychotropic medications (polypharmacy) among children overall^{1–5} and in children with autism spectrum disorders (ASD).^{6–12} General concerns about these medications include the lack of evidence documenting the safety or effectiveness of psychotropic treatment during childhood, when developing brains and bodies may be particularly vulnerable to environmental or biological influences.^{7,8,13} For ASD treatment in particular, the only US Food and Drug Administration–approved medications are risperidone and aripiprazole (indicated for the treatment of irritability [including symptoms of aggression] in 2006 and 2009, respectively). However, physicians often prescribe nonindicated medications to children in an “off-label,” trial-and-error fashion to help manage troublesome symptoms in patients, especially if other treatments are not available or accessible.^{10,14} There is even less information about the safety and effectiveness of psychotropic polypharmacy and potential interactions between and among medications that may affect patients with complex psychiatric disorders, including ASD.¹⁵ For these reasons, detailing psychotropic use and polypharmacy among children with ASD is crucial for informing families, clinicians, and researchers.

Current estimates of psychotropic use among children with ASD vary widely. Reported rates of use among children with ASD have ranged from 27% to 83%, with polypharmacy ranging from 10% to 20%.^{6–12} The rates reported to date have either been based on a fairly limited time period (1 year) or reflect a single point in time and therefore do not yield information about the chronic use of psychotropic medications. Furthermore, all previous studies about psychotropic use and related factors for

children who are commercially insured (who comprise the majority of children in the United States¹⁶) have been based on parental report and included relatively small sample sizes (from 326 to 5181). The only large study⁷ ($N = 60\,641$) of psychotropic medication use among children with ASD was based on Medicaid claims and dates back to 2001, which likely does not reflect current usage. Therefore, we examined the use of psychotropic medications and polypharmacy by using a large and heterogeneous data set of medical and pharmacy claims for commercially insured children with ASD, with more objective and accurate documentation of psychotropic use than is possible from parental report. We were also able to quantify use over longer periods of time compared with previous studies, allowing for a more nuanced understanding of the predictors, extent, nature of psychotropic use, and polypharmacy among children with ASD.

METHODS

This retrospective observational study was conducted by using an administrative claims database associated with a large US commercial health plan. Only claims occurring at least 6 months earlier were used in the analysis to allow for claims adjudication. Using medical and pharmacy claims data with linked enrollment information, a total of 33 565 children with ASD who had at least 6 months of continuous medical, pharmacy, and behavioral health care coverage between January 2001 and December 2009 were identified. Subjects with ASD were identified by using a validated algorithm¹⁷ requiring ≥ 2 medical claims with a diagnosis code in any position for autistic disorder, other specified pervasive developmental disorder, or unspecified pervasive developmental disorder (*International Classification of Diseases, Ninth Revision,*

Clinical Modification [ICD-9-CM] codes 299.0x, 299.8x, and 299.9x) on separate dates of service. In addition, eligible subjects had to be between the age of 0 and 20 years as of their first day of health plan enrollment during the study (ie, index date) and without claims for childhood disintegrative disorder (ICD-9-CM code 299.1x) or Rett syndrome (ICD-9-CM code 330.8x). Because a medical chart validation study has shown that requiring at least 2 claims for ASD in any position generated a positive predictive value approaching 90%,¹⁷ children who met the eligibility requirements but had only 1 ASD claim ($n = 12\,671$) were excluded from the analysis.

Each subject's total study observation time was the sum of all of his or her enrollment time between 2001 and 2009, during which the subject had simultaneous medical, pharmacy, and behavioral health coverage. Subjects were required to have 1 period of at least 6 months of continuous enrollment but may have had more enrollment time (either a longer single period or multiple enrollment periods or both) with all 3 types of coverage during the study. Gaps in enrollment had to be at least 33 days for periods to be considered discontinuous. Only claims with a date of service that occurred during enrollment periods were used in the analysis.

The study was exempted by the New England Institutional Review Board, and it was reviewed and approved by OptumInsight's Disclosure Limitation Program in November 2011.

Study Variables

The primary outcomes of interest were whether a subject had any psychotropic use and whether a subject had at least 1 episode of multiclass psychotropic polypharmacy. Psychotropic use was defined as at least 1 pharmacy claim for a psychotropic medication.

Psychotropic medications included: (1) anticonvulsants/antiepileptics; (2) antidepressants; (3) antipsychotics; (4) anxiolytics; (5) attention-deficit disorder (ADD) medications (both stimulants and nonstimulants); (6) lithium; and (7) anticholinergic/antiparkinsonian medications. (The Supplemental Information presents a list of these medications.) Polypharmacy was defined as at least 1 episode of multiclass polypharmacy. An episode of multiclass polypharmacy was defined as overlapping fills of medications across ≥ 2 classes for at least 30 days. Different definitions of polypharmacy were considered based on the literature, including a lower minimum of 14 days of overlap, which was used in another psychotropic polypharmacy study by Ganguly et al.¹⁸ The Medicaid claims-based ASD polypharmacy study by Mandell et al.⁷ also used a 30-day definition.

Episodes were identified by using the prescription fill date and days' supply information available on pharmacy claims. Before measuring episodes, overlapping fills of the same medication were pushed out (ie, extended) to the sum of both fills. If multiple fills for the same medication occurred on the same day, the claim for the longest day's supply was used. Inpatient stays occurring during a fill were added to the overall length of the fill (with the assumption that the hospital administered the medication and the child continued outpatient use after hospitalization). Gaps in fills of the same medication of ≤ 7 days were permitted and were included in the calculation of days of overlapping fills (ie, 2 fills for the same medication for 15 days each, separated by 6 days totaled 36 days in length).

No single medication within a class needed to overlap by 30 days with a particular medication in another class. Only unique combinations of classes of at least 30 days were considered. This

could include cases in which ≥ 2 drugs within a class contributed to the overlap with another class. Any change in the combination of classes indicated the end of the episode and possibly the start of a new episode (if there was a new combination of classes and it lasted at least 30 days).

Information on these outcomes was combined to form the following 5 mutually exclusive categories: 0, no psychotropic fills; 1, at least 1 psychotropic medication without multiclass polypharmacy; 2, multiclass polypharmacy involving no more than 2 medication classes; 3, multiclass polypharmacy involving 3 classes; and 4, multiclass polypharmacy with ≥ 4 classes. The group with psychotropic use without polypharmacy included both children with evidence of only 1 psychotropic medication and children with multiple psychotropic medications but whose use did not meet the definition of multiclass polypharmacy. For subjects with evidence of polypharmacy, the polypharmacy episode with the highest number of classes was used to categorize subjects with > 1 episode. Secondary outcomes of interest were the total number of multiclass polypharmacy episodes a subject had and the total length, in days, of all episodes combined.

Independent Variables

Potential predictors of psychotropic use and/or episodes of multiclass psychotropic polypharmacy were identified through a review of the literature and included gender, household income, race/ethnicity, geographic region, age at index date, whether a child had at least 1 medical claim for a psychiatrist visit during the study, and indicator variables for neurologic and psychiatric conditions that often co-occur with ASD and are commonly treated with psychotropic medications and thus may be independently related to the outcome.^{1,3,7,11} These conditions included seizures/

epilepsy, ADD, anxiety, depression, and bipolar disorder. For depression, anxiety, and bipolar disorder, subjects had to have at least 2 medical claims with the relevant diagnosis codes in any position at least 30 days apart. For ADD and seizures, subjects had either ≥ 2 claims with the relevant diagnosis codes in any position at least 30 days apart or 1 claim with the relevant diagnosis code in any position along with a pharmacy claim for an ADD medication or anticonvulsant, respectively. Race/ethnicity and household income variables were derived through a marketing database (KBM Group; <http://www.kbmg.com/>) that relies on a variety of sources including self-report, modeling, US Census, and imputed data. These data have been used extensively in market and population segmentation analyses. Although these data have application to health research, certain limitations exist, including potential inaccuracies in socioeconomic status assignment, inability to determine whether data for a particular person were imputed, missing data, and predefined categorizations (eg, income level). Race/ethnicity and income category are populated for 65% to 70% of patients included in the claims database used in this study. Results shown here provide the number of subjects for whom these data were missing.

Statistical Analysis

Descriptive analyses were conducted to examine the frequency of outcomes across subjects in different demographic and clinical subgroups defined by using the aforementioned variables. Multinomial logistic regression models were used to estimate the association between independent variables and the 5-level outcome variable. In addition to the demographic and clinical covariates, the model also controlled for subjects' total duration of health plan enrollment during the study (categorized into 5 binary variables based on enrollment quintiles).

Regression diagnostics (eg, likelihood ratio) were examined to assess goodness-of-fit and are provided with the results. To detect multicollinearity, correlations among the model variables and variance inflation factors (VIFs) were examined. Generally, correlations ≥ 0.80 signal a strong linear relationship between 2 variables.^{19,20} Although there is no agreed-upon criterion for which the VIF level indicates multicollinearity, some believe VIF values exceeding 10 warrant concern.²¹ All of the correlations and VIF values observed fell below these thresholds, indicating no concern. Type I error was set at .05 for all *P* values and confidence intervals. Analyses were conducted by using SAS 9.2 software (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 33 565 children with ASD aged 0 to 20 years at index date (first day of enrollment during the study) were identified. More than 80% of subjects had only 1 period of continuous enrollment with simultaneous medical, pharmacy, and behavioral health coverage during the study. Of those who had >1 period of enrollment, >90% had only 1 additional period. The mean enrollment time during the study was 43.5 months (>3.5 years). Only 5.7% of the sample had <1 year of enrollment, and just over one-half had ≥ 3 years; 75% had ≥ 2 years of enrollment during the study.

Table 1 presents the demographic and clinical characteristics of the sample of children with ASD as well as the unadjusted results of psychotropic use and psychotropic polypharmacy for select subgroups. Of the 33 565 children with ASD, 21 334 (64%) had evidence of at least 1 psychotropic prescription fill, and 11 598 (35%) exhibited multiclass psychotropic polypharmacy. Among those with polypharmacy, the total number of polypharmacy episodes per subject

TABLE 1 Demographic and Clinical Composition of ASD Sample and Psychotropic Drug Use and Multiclass Polypharmacy by Demographic and Clinical Characteristics

Characteristic	Total ASD Subjects (<i>n</i> = 33 565) (<i>N</i> [%])	Proportion of ASD Subjects With Any Psychotropic Use (%) ^a	Proportion of ASD Subjects With Evidence of Multiclass Polypharmacy (%) ^b
Overall	33 565 (100)	21 334 (63.56)	11 598 (34.55)
Gender			
Male	27 479 (82)	63.55	34.36
Female	6086 (18)	63.60	35.41
Geographic region			
Northeast	5271 (16)	56.04	28.44
Midwest	11 561 (34)	67.79	39.35
South	12 090 (36)	65.96	34.99
West	4643 (14)	55.33	28.43
Race/ethnicity ^c			
White	17 796 (53)	67.33	38.03
African American/black	691 (2)	59.91	28.94
Asian	466 (1)	45.71	15.24
Hispanic	1366 (4)	55.93	25.99
Other	339 (1)	47.49	17.99
Unknown	12 907 (38)	60.43	32.10
Household income, \$			
<50 000	3090 (9)	66.50	35.99
50 000–74 999	5149 (15)	67.37	36.71
75 000–99 999	4838 (14)	64.92	35.66
100 000–124 999	3596 (11)	63.01	34.43
$\geq 125 000$	2915 (9)	63.67	37.12
Unknown	13 977 (42)	61.15	32.56
Age group at index date ^d			
0–1 y	5609 (17)	33.77	9.89
2–10 y	19 987 (60)	63.51	32.33
11–17 y	7277 (22)	84.46	57.07
18–20 y	692 (2)	86.71	61.85
Co-occurring conditions			
Epilepsy/seizure	2554 (8)	95.65	64.21
ADD	13 018 (39)	93.42	57.54
Anxiety	5507 (16)	86.73	59.32
Depression	4065 (12)	89.96	68.02
Bipolar disorder	3089 (9)	96.41	86.66
Psychiatrist visit	15 207 (45)	84.73	57.55

^a This column presents the percentage of ASD subjects with evidence of psychotropic drug use according to demographic and clinical subgroups. The differences in percentages were statistically significant for all characteristics (*P* < .05) except gender (*P* = .9361).

^b This column presents the percentage of ASD subjects with evidence of psychotropic polypharmacy according to demographic and clinical subgroups. The differences in percentages were statistically significant for all characteristics (*P* < .05) except gender (*P* = .1210).

^c From merged socioeconomic data.

^d Mean \pm SD: 6.73 \pm 4.93 years.

averaged 5.63 (median: 4.00), and the total number of days of polypharmacy (from all episodes combined for a given subject) averaged 525 days, with a median of 346 days (data not shown). The maximum number of classes and medications per episode averaged 2.6 and 3.3, respectively (data not shown). Common class combinations were antidepressants and ADD medications (38% of subjects), antipsychotic and ADD

medications (28%), antipsychotics and antidepressants (20%), and antipsychotic, antidepressant, and ADD medications (18%).

Psychotropic use and polypharmacy varied according to region of the country, race/ethnicity, age, and co-occurring conditions. Lower proportions of children in the northeast and west had evidence of psychotropic use and polypharmacy. More white children and more children aged ≥ 11 years had

evidence of both psychotropic use and polypharmacy. A large proportion of children with evidence of epilepsy/seizures, ADD, anxiety, depression, and/or bipolar disorder were psychotropic users, and one-half or more had evidence of polypharmacy. In addition, the majority of children who had seen a psychiatrist had evidence of psychotropic use.

Table 2 displays the results of the multinomial logistic regression model of psychotropic use and multiclass polypharmacy. Thirty-six percent of the

sample had no psychotropic use, 29.0% had psychotropic use without polypharmacy, 19.7% had polypharmacy with only 2 classes, 10.4% had polypharmacy with 3 classes, and 4.5% had polypharmacy with ≥ 4 classes. All comparisons were made versus children with ASD without psychotropic use. The columns in Table 2 present the results for each comparison examined. Household income, race/ethnicity, geographic region, age at index date, co-occurring conditions, and having had a psychiatrist visit were found to

be significantly related to psychotropic use and polypharmacy. Barring just a few exceptions, children of older age, those who had a psychiatric visit, and those with evidence of co-occurring conditions had higher odds across all outcomes relative to no psychotropic use. In fact, the odds ratios for the covariates were highest in the comparisons between the more complicated polypharmacy and no psychotropic use. Although the effects of race/ethnicity and region were inconsistent across the comparisons, Hispanic children were

TABLE 2 Multinomial Logistic Regression for Psychotropic Use and Combination-Specific Multiclass Polypharmacy Among ASD Group

Independent Variables	1 vs 0		2 vs 0		3 vs 0		4 vs 0		Overall <i>P</i>
	Odds Ratio	<i>P</i>	Odds Ratio	<i>P</i>	Odds Ratio	<i>P</i>	Odds Ratio	<i>P</i>	
Gender									
Female	Ref.	—	Ref.	—	Ref.	—	Ref.	—	
Male	1.02	.60	1.04	.47	1.16	.03	1.00	.96	.16
Household income, \$ ^a									
<50 000	Ref.	—	Ref.	—	Ref.	—	Ref.	—	
50 000–74 999	1.02	.77	1.06	.46	0.91	.33	0.96	.78	.48
75 000–99 999	0.97	.67	1.06	.48	0.88	.23	0.84	.22	.21
100 000–124 999	0.89	.08	0.98	.83	0.76	.01	0.82	.18	.04
$\geq 125 000$	0.83	.02	1.01	.95	0.99	.93	0.95	.74	.05
Unknown	0.97	.67	1.02	.83	0.89	.26	0.92	.53	.65
Race/ethnicity ^a									
White	Ref.	—	Ref.	—	Ref.	—	Ref.	—	
African American/black	0.87	.20	0.78	.08	0.77	.14	0.71	.20	.43
Asian	0.86	.25	0.45	<.001	0.46	.003	0.49	.10	<.001
Hispanic	0.85	.04	0.76	.008	0.57	<.001	0.75	.14	.002
Other	0.86	.32	0.62	.02	0.41	.006	0.26	.02	.02
Unknown	0.92	.12	0.92	.15	0.88	.10	1.02	.81	.25
Geographic region									
Northeast	0.68	<.001	0.60	<.001	0.53	<.001	0.52	<.001	<.001
Midwest	0.88	<.001	0.95	.23	0.92	.17	0.85	.04	.008
South	Ref.	—	Ref.	—	Ref.	—	Ref.	—	
West	0.72	<.001	0.67	<.001	0.59	<.001	0.57	<.001	<.001
Age at index date (continuous)	1.13	<.001	1.22	<.001	1.28	<.001	1.35	<.001	<.001
Comorbid conditions									
Seizure	16.78	<.001	37.37	<.001	79.54	<.001	153.57	<.001	<.001
ADD	10.68	<.001	17.79	<.001	21.61	<.001	25.05	<.001	<.001
Anxiety	1.64	<.001	2.26	<.001	2.09	<.001	1.87	<.001	<.001
Depression	0.95	.48	1.24	.006	1.23	.02	1.41	<.001	<.001
Bipolar	1.24	.08	3.22	<.001	8.48	<.001	24.25	<.001	<.001
Psychiatrist visit	2.26	<.001	5.24	<.001	9.28	<.001	14.15	<.001	<.001
Total enrollment during study ^b									
1st quintile	Ref.	—	Ref.	—	Ref.	—	Ref.	—	
2nd quintile	1.14	.008	1.03	.63	1.21	.02	1.41	.005	.003
3rd quintile	1.24	<.001	1.11	.10	1.29	.002	1.88	<.001	<.001
4th quintile	1.36	<.001	1.30	<.001	1.7	<.001	2.71	<.001	<.001
5th quintile	1.78	<.001	1.87	<.001	2.55	<.001	4.14	<.001	<.001

Outcome information was combined to form the following 5 mutually exclusive categories: 0, no psychotropic fills; 1, at least 1 psychotropic medication without multiclass polypharmacy; 2, multiclass polypharmacy involving no more than 2 medication classes; 3, multiclass polypharmacy involving 3 classes; and 4, multiclass polypharmacy with ≥ 4 classes. Observations read = 33 565, observations used = 33 565. Likelihood ratio: $\chi^2 = 25123.624$, degrees of freedom = 100, $P \leq .001$. Akaike Information Criterion (AIC) AIC-intercept: 95388.094, AIC-intercept and covariates: 70464.470. Pseudo $R^2 = 0.263$.

^a From merged socioeconomic data.

^b Subjects may have had gap(s) in enrollment during this time. Quintiles calculated for total sample of children with ASD.

more likely than white children to be psychotropic and polypharmacy users, and there is some evidence that Asian children were more likely than white children to have episodes of polypharmacy involving a higher number of drug classes. Children in the south also had higher odds of psychotropic use and polypharmacy. Household income was found to be mostly unrelated to psychotropic use and polypharmacy.

DISCUSSION

Among a sample of 33 565 commercially insured children with ASD in the United States, we found that 64% used at least 1 psychotropic medication, and just more than one-third had evidence of psychotropic polypharmacy during an average length of enrollment of >3 years. Approximately 15% of children had psychotropic polypharmacy that included ≥ 3 classes of medications. Common combinations of classes were antidepressants and ADD medications, antipsychotics and ADD medications, antipsychotics and antidepressants, and all 3 (antipsychotics, antidepressants, and ADD medications). In addition, children with evidence of polypharmacy received the treatments for a long duration, as the median length of polypharmacy was just under 1 year.

Our findings are consistent with, but slightly higher than, previously reported rates based on Medicaid claims data⁷ or parental report^{11,12} for similarly aged samples of children with ASD. Our increased rates may reflect the longer time periods over which many of our study subjects were observed (>3 years on average compared with 1 year or a single point in time in other studies). The analysis of Mandell et al⁷ of Medicaid claims data from 2001 found 56% of children with ASD (aged 0–21 years) used a psychotropic medication, and 11% used ≥ 3 medications concurrently, suggesting

some similarity between children who are privately and publicly insured. Rosenberg et al¹¹ analyzed data from the Interactive Autism Network, an Internet-based parental survey tool, from April 2007 through October 2008 for children aged 0 to 18 years; they found that 35% of children with ASD were reported to have used psychotropic medications (60% of 939 privately insured children) and 10% used medications in ≥ 3 classes concurrently (21% of privately insured children). Coury et al¹² analyzed data from the autism registry maintained by the Autism Treatment Network from December 2007 to April 2011 for children aged 2 to 17 years, and they found much lower rates of psychotropic use; 28% of privately insured children used a psychotropic medication and only 12% used ≥ 2 medications. These lower rates may be due to a smaller proportion of older children (children aged ≥ 11 years totaled 10% compared with 20% of the sample of Rosenberg et al and 24% of our sample) but is also likely related to parents reporting current, 1-time use (only at the time of enrollment in the registry).

As expected and similar to the literature,^{7,11,12} we found that co-occurring conditions were among the strongest and most consistent predictors of psychotropic use and polypharmacy, and, in the case of our study, seizures, ADD, and bipolar disorder were highly associated. Although we did not correlate the use of a particular class of medication with the diagnosis for which it was given, it is likely that some of the commonly used medications such as ADD medications are prescribed for symptoms fitting a diagnosis of ADD. The appropriate reasons and indications for antipsychotic medications and antidepressants, however, are less clearly defined; these medications could have been given for a wide variety of symptoms among children with ASD,¹³ without proven benefit or safety.²²

Although older age was significantly associated with both psychotropic use and polypharmacy, consistent with the literature,^{7,11,12} polypharmacy was still significant among the younger age groups (33% of children aged 2–10 years and 10% of 0- to 1-year-olds) for whom safety concerns are increased and evidence of benefit even more sparse.^{23–25} Also in keeping with findings described in the literature,¹¹ children from the southern region were significantly more likely than children from the northeast and west to be multiclass polypharmacy users, raising questions about the availability of non-pharmacologic, behaviorally based services and treatments in the south, where other health outcomes and health care services have been found to be poorer than in other parts of the country.^{26,27} White race/ethnicity and having had a psychiatrist visit were also related to polypharmacy duration; these variables may serve as markers for access to services or clinical complexity, respectively.

Our study is not without limitations. For example, although the claims-based ASD case-identifying algorithm used in this study demonstrates strong positive predicted value,¹⁷ misclassification of subjects with and without ASD is nonetheless still possible. In addition, administrative claims data can be used to document prescription fills but not whether the patient actually took the prescribed medication or as directed, and claims do not capture over-the-counter medications (although very few psychotropic medications are available without a prescription). However, pharmacy claims are likely more reliable than parent or provider report, and repeated fills of the same medication are likely to be highly correlated with actual use. Furthermore, polypharmacy can be quantified more precisely with claims data because actual days' supply and days of medication

overlap are documented. We also did not examine dose or appropriateness of dose for a particular child or a particular diagnosis because appropriate dosing often depends on a child's weight. This omission could have resulted in an overestimation of psychotropic use and polypharmacy when a medication was being tapered but still prescribed, although our definition of polypharmacy as 30 days of overlap is similar to that of Mandell et al⁷ and appropriately excludes most cross-titration of psychotropic medications (which typically takes 2–3 weeks⁵). Pharmacy claims often have incomplete prescriber information, which inhibited our ability to examine the number and type of prescribers for the children with psychotropic claims. Lastly, we were only able to examine findings in the 4 major US regions, without greater specificity in geographic location such as state or county, which may be important determinants of policies and patterns of care. Although existing evidence for the effectiveness of multidrug treatment of children with ASD has been described as “woefully inadequate,”¹ psychotropic medications are commonly used for ASD and its co-occurring conditions. Additional research is needed to understand why they are being used (for which symptoms, behaviors, or diagnoses, and by which providers) and whether current practices are a result of trial-and-error in individual children or whether there is a more systematic perception of need and

benefit. Safety concerns are worrisome because many of these medications have already exhibited safety issues when used by themselves,^{15,28} and the potential for toxicity could increase when medications are combined.²⁹ A next step using claims data would be to link medication use with symptoms and diagnostic indications as well as monitor both short- and long-term outcomes such as adverse effects, medication changes, acute care visits, and overall health and morbidity outcomes. In addition, information about the secular trends in the use of psychotropic medications is contained within claims data and remains unexplored. Finally, claims-linked patient registries may hold promise for understanding the diverse needs and outcomes of heterogeneous children with ASD.

CONCLUSIONS

Children with ASD and their families often struggle to achieve normality in many realms, including physical and mental health and everyday functioning. ASD and its common co-occurring conditions are associated with challenging symptoms, including irritability, anxiety, sadness, aggression and inattention, and ongoing social and/or intellectual difficulties. The few ASD treatments thought to be effective are intended to be early, intensive, and behaviorally based, and they are thus taxing, expensive, and difficult to access.¹⁵ It is perhaps not surprising then

that so many of the children with ASD in our study received psychotropic medications, alone and in combination, over long periods of time despite the paucity of evidence supporting their effectiveness or safety. Some clinicians caring for children with ASD may not be aware of the extent and effects of psychotropic use and polypharmacy because many of these complex children see multiple providers. Our study highlights the need for primary care providers to carefully elicit medication histories and monitor symptoms for evidence of effectiveness. Our study underscores an immediate need to develop standards of care around the prescription of psychotropic medications based on the best available evidence and a coordinated, multidisciplinary approach to improving the health and quality of life of children with ASD and their families. Lastly, it calls for additional research investigating current practice patterns and access to services and emphasizes the need for rigorous trials of psychotropic medications for children with ASD and other psychiatric disorders to assess the value of these medications when weighed against their potential for harm.

ACKNOWLEDGMENTS

The authors acknowledge the following individuals for their contribution to the manuscript: Jonathan Kelly, Grace Yang, Lindsay Lawer, James Burke, Tom Horstman, James Hartje, Jonathan Johnson, Lee Brekke, and Feng Cao.

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(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2012-3774

doi:10.1542/peds.2012-3774

Accepted for publication Aug 19, 2013

Address correspondence to Anjali Jain, MD, The Lewin Group, 3130 Fairview Park Dr, Suite 600, Falls Church, VA 22042. E-mail: anjali.jain@lewin.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Sponsored by the National Institute of Mental Health (NIMH), National Institutes of Health, Department of Health and Human Services (HHSN-271-2010-00033-C). The NIMH was given a copy of the final draft of the manuscript, but the content of the manuscript is solely the responsibility of the authors and does not necessarily represent the views of the NIMH, the National Institutes of Health, or the federal government. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: Ms Marshall, Mr Post, Dr Dennen, and Dr Jain are employees of The Lewin Group. At the time of manuscript preparation and submission, Dr Spencer and Mr Kulakodlu were employees of OptumInsight; Dr Spencer is now an employee of the University of Minnesota-Twin Cities. Dr Azocar is an employee of OptumHealth. OptumInsight and OptumHealth are wholly owned subsidiaries of UnitedHealth Group, and The Lewin Group is an OptumInsight company. The Lewin Group operates with editorial independence. Dr Newschaffer has indicated he has no potential conflicts of interest to disclose.

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Pediatrics 2013;132;833

DOI: 10.1542/peds.2012-3774 originally published online October 21, 2013;

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