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Aberrant Behaviors and Co-occurring Conditions as Predictors of Psychotropic Polypharmacy among Children with Autism Spectrum Disorders

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Abstract

Objectives: The purpose of this study was to identify rates and predictors of psychotropic medication polypharmacy among Medicaid-eligible children in South Carolina with autism spectrum disorder (ASD) from 2000 to 2008.
Methods: Population-based surveillance data were linked with state Medicaid records to obtain a detailed demographic, behavioral, educational, clinical, and diagnostic data set for all Medicaid-eligible 8-year-old children ($n = 629$) who were identified and diagnosed with ASD using standardized criteria. Polypharmacy was defined as having interclass psychotropic medication claims overlapping for ≥ 30 consecutive days at any time during the 2-year study period. Multivariable logistic regression was used to model predictors of any polypharmacy, and for the three most common combinations.
Results: Overall, 60% ($n = 377$) used any psychotropic medication, and 41% ($n = 153$) of those had interclass polypharmacy. Common combinations were attention-deficit/hyperactivity disorder (ADHD) medications with an antidepressant (A/AD), antipsychotic (A/AP) or a mood stabilizer (A/MS). Black children had lower odds of any polypharmacy, as did those eligible for Medicaid because of income or being foster care versus those eligible because of disability. There were no significant associations between polypharmacy and social deficits in ASD for any combination, although children with communication deficits diagnostic of ASD had lower odds of any polypharmacy and A/AP polypharmacy. Children with argumentative, aggressive, hyperactive/impulsive, or self-injurious aberrant behaviors had higher odds of polypharmacy, as did children with diagnosed co-occurring ADHD, anxiety or mood disorders, or conduct/oppositional defiant disorder (ODD) in Medicaid records.
Conclusions: Future research is warranted to investigate how child-level factors impact combination psychotropic medication prescribing practices and outcomes in ASD.

Introduction

Autism spectrum disorders (ASD) are a group of neurological developmental disorders that manifest in early life as core deficits in socialization, communication, and odd behaviors or interests along with debilitating aberrant behaviors and co-occurring conditions (Johnson et al. 2007; Myers et al. 2007). Although there is no cure, early intensive behavioral interventions can maximize the abilities and minimize deficits in social, communicative, and behavioral development (Rogers and Laurie 2008; Dawson et al. 2010). However, behavioral interventions such as Applied Behavior Analysis (ABA) can be costly, time consuming, and difficult to obtain (Shattuck and Grosse 2007; Montes et al. 2009). Therefore, prescribing of psychotropic medication is increasingly common as an alternative or supplement to behavior therapy for managing ASD-associated aberrant behaviors, including but not limited to inattention, hyperactivity, irritability, sleep disruption, aggression, self-injurious behavior (SIB), and obsessions and compulsions (Myers 2007; Charles et al. 2008; Esbensen et al. 2009).

Although there is an increasing amount of evidence in favor of psychotropic medication use in similar childhood conditions such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and major depressive disorder (MDD) (Riddle et al. 2001), less is known regarding combination psychotropic medication use, particularly in ASD.

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Table 1. Data Source and Time Period from which Data Were Obtained

Source	*Information obtained*	*Time period extracted*	
SCADDM Network	Gender, race, aberrant behaviors, DSM-IV criteria, diagnostic history	SY2000 SY2002 SY2004 SY2006 SY2008	Birth through December 31 of the surveillance year.
MMIS Eligibility File	Individual eligibility status, county of residence	SY2000 SY2002 SY2004 SY2006 SY2008	1999/2000 2001/2002 2003/2004 2005/2006 2007/2008
MMIS Pharmacy File	Dispensed date, drug code, therapeutic class, drug name, dosage, quantity, days' supply	SY2000 SY2002 SY2004 SY2006 SY2008	1999/2000 2001/2002 2003/2004 2005/2006 2007/2008

SCADDM, South Carolina Autism and Developmental Disabilities Monitoring; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.; SY- surveillance year; MMIS, Medicaid Management Information System.

Although previous psychotropic medication utilization studies in ASD mention polypharmacy, only one study reported the details of common drug combinations that have been prescribed (Logan et al. 2012). However, only limited variables were assessed, and exact prescription dates were unavailable to identify *overlapping* prescriptions to determine true instances of polypharmacy. The remaining relevant studies are of two main types: Administrative claims or parent surveys. The current study adds to the literature by examining medication use among children who may meet diagnostic criteria for ASD, but may not have been identified by official medical diagnoses or diagnostic codes (Centers for Disease Control 2009, 2012;). Treatment-related surveys in ASD have had low response rates and relied on volunteer participation or parent recall (Martin et al. 1999; Aman et al. 2005; Esbensen et al. 2009; Rosenberg et al. 2009).

Therefore, the goal of this study was to use population-based surveillance data collected from 2000 to 2008 from the South Carolina Autism and Developmental Disabilities Monitoring (SC ADDM) Network regarding 8- year-old children with ASD linked to Medicaid claims, to produce a detailed behavioral, educational, clinical, and medical history database to address gaps in the ASD treatment literature. Factors associated with polypharmacy in ASD or similar conditions (e.g., ADHD, anxiety disorder, epilepsy, bipolar disorder, conduct disorder, OCD) were explored (Moore et al. 2009). Given that psychotropic medication polypharmacy has not been systematically evaluated in children with ASD, a detailed assessment is warranted. For the current study, we defined polypharmacy as the simultaneous use of two or more different classes of psychotropic medication for a period of at least 30 consecutive days at any time during the 2 year study period for each child. This definition of polypharmacy was chosen based on what has been described in the literature in similar populations (Safer et al. 2003), and most recently in a manuscript by Spencer et al. (2013).

Methods

Study design and population

This study described psychotropic medication polypharmacy and potential associated factors among Medicaid-eligible children with ASD at 7 or 8 years of age who were identified between 2000

Table 2. Characteristics of the Study Population, $N=629$

Variable	*Total (*n*=629)*
Gender	
Male	510 (81%)
Race	
White	193 (31%)
Black	160 (25%)
Other[a]	276 (44%)
Residency	
Urban	436 (69%)
Rural	193 (31%)
Eligibility category	
Disability	465 (74%)
Income	152 (24%)
Foster care	10 (2%)
Surveillance year identified	
2000	119 (19%)
2002	103 (16%)
2004	92 (15%)
2006	129 (21%)
2008	186 (30%)
Community ASD diagnosis[b]	411 (65%)
Special education services	
Autism-specific	266 (42%)
ASD-related[c]	71 (11%)
Any other[d]	190 (30%)
None	102 (16%)

[a]Other race includes Hispanic, Asian/Pacific Islander, and 1 unknown.
[b]Community ASD diagnosis reflects if a child had evidence of a previous ASD diagnosis in educational or medical records as collected and recorded by the surveillance network.
[c]ASD-related special education services include other health impairment ($n=47$), preschool child with a disability ($n=2$), speech delay ($n=20$), and developmentally disabled not otherwise specified ($n=2$).
[d]"Any other" special education category includes deaf-blindness, hearing impairment, mental retardation, multiple disabilities, orthopedic impairment, traumatic brain injury, and visual impairment.
ASD, Autism spectrum disorder.

and 2008 by the Centers for Disease Control (CDC)-sponsored, population-based SC ADDM Network ($n=629$), which is part of the larger ADDM Network. Surveillance data were linked with Medicaid to obtain a comprehensive demographic, behavioral, and clinical database.

The SC ADDM Network is an active and ongoing surveillance system that is an invaluable resource for health services and epidemiological research, capable of providing extensive child-level data (Yeargin-Allsopp 2003; Durkin et al. 2008; King et al. 2008; Nicholas et al. 2008; Van Naarden Braun 2008; Yeargin-Allsopp 2008; Bilder et al 2009; Mandell 2009; Nicholas et al., 2009; Shattuck et al 2009; Pinborough-Zimmerman et al. 2009; Wiggins and Baio 2009; Durkin et al. 2010; Kalkbrenner et al. 2010; Levy et al. 2010; Powell et al 2010). Furthermore, in South Carolina, the majority of cases are eligible for Medicaid because of disability, income, or out-of-home placement (Logan et al. 2012), allowing detailed assessments of healthcare utilization patterns in populations not limited to those of low socioeconomic status. The SC ADDM Network has, since 2000, documented the prevalence of ASD via public health surveillance, using consistent methodology at multiple health and educational sources, to identify both previously diagnosed cases of ASD and those who meet diagnostic criteria but have not been diagnosed. Details of the methodology have been published previously (Rice et al. 2007; Nicholas et al. 2008, 2009) and are briefly outlined here. South Carolina employs a full case review process regardless of previous diagnoses, of all children who have key words in medical or education records that may indicate an ASD. All potential cases undergo the same diagnostic review. No child is assumed to be a case until ADDM definition of case status is met.

Surveillance data for each ASD case were linked with South Carolina Medicaid Management Information System (MMIS) eligibility files and the MMIS pharmacy claims. All protected health information (PHI) was removed to produce a large, high quality, de-identified database. Table 1 provides a summary of the databases from which data were derived.

Table 3. Details of Symptoms and Co-occurring Conditions Among the Study Population, $N=629$

Variable	n *(%)*
Aberrant behaviors as evidenced in each child's SC ADDM record	
Temper tantrums	363 (58%)
Sensory issues	309 (49%)
Seizure-like activity/staring spells	181 (29%)
Mood abnormalities	375 (60%)
Argumentative, defiant behavior	347 (55%)
Aggression	311 (49%)
Eating/drinking abnormalities	340 (54%)
Abnormal cognitive development	334 (53%)
Clumsiness, motor delays	393 (62%)
Hyperactivity, impulsivity	533 (85%)
Abnormal response to fear	234 (37%)
Self-injurious behavior	233 (37%)
Diagnostic criteria as evidenced in each child's SC ADDM record	
Socialization deficits	
Nonverbal behaviors	541 (86%)
Poor peer relationships	456 (72%)
Failure to share interests	376 (60%)
Emotional reciprocity abnormalities	545 (87%)
Communication deficits	
Delayed spoken language	593 (94%)
Conversational deficits	533 (85%)
Repetitive language	469 (75%)
Imaginative play deficits	400 (64%)
Unusual behaviors	
Restricted interests	387 (62%)
Routines or ritualistic behaviors	486 (77%)
Stereotyped mannerisms	459 (73%)
Preoccupation with parts	376 (60%)
Co-occurring conditions by ICD9 code in Medicaid claims files	
Any mental health related disorder	588 (93%)
ADHD	242 (38%)
Anxiety or mood disorder	76 (12%)
Communication disorder	410 (65%)
Conduct disorder/ODD	88 (14%)
Developmental disability	145 (23%)
Epilepsy	86 (14%)
Intellectual disability	396 (63%)
Learning disability	172 (27%)
Other mental health disorder[a]	103 (16%)

[a]"Other mental health disorders" include adjustment disorder ($n=21$), delirium, dementia ($n=3$), motor skills disorder ($n=5$), elimination disorder ($n=9$), separation anxiety ($n=3$), emotional disorder not otherwise specified ($n=2$), catatonic disorder ($n=3$), schizophrenia ($n=1$), psychogenic disorder ($n=2$), sleep disorder ($n=15$), and somatoform disorder ($n=2$).

SC ADDM, South Carolina Autism and Developmental Disabilities Monitoring Network; ICD-9, International Classification of Diseases, 9th Revision; ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder.

Variables

Child characteristics. Child characteristics included race, gender, year identified by the surveillance network, presence of ASD-associated aberrant behaviors, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) diagnostic criteria (American Psychiatric Association 1994), mental health and previous ASD diagnostic history, Medicaid eligibility category (disability versus income or foster care status), and residence (urban versus rural, as defined by the South Carolina Department of Commerce).

A dichotomous variable indicated when a previous ASD diagnosis was present based on data in each child's SC ADDM or

Table 4. Number and Percent of Children Who Had Claims for Any Medication, Any Psychotropic, and Psychotropic Polypharmacy

Medication and or combination	n	%
Any prescription[a]	554	88%
Any psychotropic	377	60%
Any psychotropic polypharmacy[b]	153	41%
Specific combinations[b]		
A/AD	74	20%
A/AP	73	19%
A/MS	48	13%
AD/AP	33	9%
MS/AD	29	8%
MS/AP	28	7%

[a]Number and percentage reflects the total number and percentage of all 629 children in the study.

[b]Percentage calculated by dividing the number of children taking each specific combination by those taking any psychotropic.

A/AD, attention-deficit/hyperactivity disorder (ADHD) medication and antidepressant; A/AP, ADHD medication and antipsychotic; A/MS, ADHD medication and mood stabilizer; AD/AP, antidepressant and antipsychotic; MS/AD, mood stabilizer and antidepressant; MS/AP, mood stabilizer and antipsychotic.

Table 5. Simple And Multiple Logistic Regression Analyses to Determine Associations Between Predictors and *Any* Polypharmacy, $N=629$

	Simple regression[a]		*Final model*[b]	
Variable	*OR (95% CI)*	p	*OR (95% CI)*	p
Demographics				
Gender (ref., male)	0.89 (0.56, 1.4)	0.64	–	–
Surveillance year identified (ref., 2000)		0.17	–	–
2002	1.9 (1.1, 3.5)		–	–
2004	1.0 (0.54, 2.0)		–	–
2006	1.2 (0.65, 2.2)		–	–
2008	1.1 (0.63, 1.9)		–	–
Residency (ref., urban)	0.78 (0.52, 0.12)	0.23	–	–
Medicaid eligibility category (ref., disability)[c]	0.57 (0.36, 0.90)	0.02	0.40 (0.21, 0.77)	0.01
Race (ref., white)		0.08		0.01
Black	0.57 (0.34, 0.94)		0.44 (0.23, 0.86)	
Other[d]	0.77 (0.51, 0.170		0.42 (0.24, 0.74)	
Special education services (ref, autism)		0.13	–	–
ASD- Related[e]	1.3 (0.72, 2.5)		–	–
Any other[f]	1.7 (1.1, 2.6)		–	–
None	1.2 (0.70, 2.1)		–	–
Community assigned ASD diagnosis[g]	0.96 (0.66, 1.4)	0.85	–	–
Aberrant behaviors as evidenced in each child's SC ADDM record				
Temper tantrums	1.8 (1.2, 2.6)	<0.01	–	–
Sensory issues	1.5 (1.0, 2.1)	0.04	–	–
Staring spells/seizure-like activity	2.4 (1.6, 3.5)	<0.01	–	–
Mood abnormalities	2.0 (1.4, 3.0)	<0.01	–	–
Argumentative, defiant behavior	2.8 (1.9, 4.2)	<0.01	1.6 (0.92, 2.6)	0.10
Aggression	4.1 (2.8, 6.2)	<0.01	2.3 (1.4, 4.0)	<0.01
Abnormal eating/drinking/sleeping	1.9 (1.3, 2.7)	<0.01	–	–
Abnormal cognitive development	1.0 (0.71, 1.5)	0.89	–	–
Motor development delays	1.1 (0.75, 1.6)	0.64	–	–
Abnormal fear response	1.5 (1.0, 2.2)	0.03	–	–
Hyperactivity, inattention	1.9 (1.1, 3.4)	0.03	–	–
Self-injurious behavior	2.6 (1.8, 3.7)	<0.01	1.3 (0.77, 2.1)	0.36
ASD-specific DSM-IV diagnostic criteria as evidenced in SC ADDM records				
Social deficits				
Deficits in nonverbal behaviors	1.1 (0.65, 1.9)	0.71	–	–
Poor peer relationships	1.0 (0.67, 1.5)	0.99	–	–
Failure to share interests	.80 (0.55, 1.2)	0.22	–	–
Lack of or deficient emotional reciprocity	.89 (0.53, 1.5)	0.67	–	–
Communication deficits				
Delayed spoken language	1.1 (0.51, 2.5)	0.76	–	–
Conversational deficits	0.59 (0.37, 0.94)	0.03	0.44 (0.24, 0.79)	0.01
Repetitive language	0.77 (0.51, 1.1)	0.20	–	–
Deficits in imaginative play skills	0.92 (0.63, 1.3)	0.66	–	–
Unusual behaviors				
Restricted interests	1.1 (0.74, 1.6)	0.72	–	–
Abnormal routines and/or rituals	1.4 (0.90, 2.3)	0.14	–	–
Stereotyped motor mannerisms	0.97 (0.65, 1.5)	0.89	–	–
Abnormal preoccupation with parts of objects	1.0 (0.70, 1.5)	0.92	–	–
Co-occurring conditions by ICD9 code in Medicaid claims files				
Any PDD	1.4 (0.96, 2.1)	0.08	–	–
ADHD	6.7 (4.4, 10.0)	<0.01	4.1 (2.5, 6.7)	<0.01
Anxiety or mood disorder	4.1 (2.5, 6.7)	<.001	2.5 (1.3, 4.7)	0.01
Communication disorder	1.4 (0.93, 2.1)	0.11	–	–
Conduct disorder/ODD	8.5 (5.2, 13.9)	<0.01	4.0 (2.2, 7.5)	<0.01
Developmental disability	1.2 (0.78, 1.8)	0.41	–	–

(*continued*)

Table 5. (Continued)

Variable	*Simple regression*[a]		*Final model*[b]	
	OR (95% CI)	p	*OR (95% CI)*	p
Epilepsy	8.1 (4.9, 13.2)	<0.01	7.3 (4.0, 13.5)	<0.01
Intellectual disability	1.7 (1.1, 2.5)	0.01	–	
Learning disability	1.2 (0.84, 1.9)	0.28	–	–
Other mental health disorder[h]	2.4 (1.5, 3.7)	<0.01	–	–

[a]Simple logistic regression between predictor and outcome.
[b]Final model: variables significantly associated with outcome after adjusting for demographic variables (0.10 level).
[c]Disability versus foster care/income because of the small numbers in foster care.
[d]''Other race'' = Hispanic, Asian/Pacific Islander, 1 missing.
[e]''ASD related'' special education = other health impairment ($n=47$), preschool child with disability ($n=2$), speech delay ($n=20$), developmentally disabled ($n=2$).
[f]''Any other'' special education = deaf-blindness, hearing impaired, mental retardation, multiple disabilities, orthopedic impairment, brain injury, visual impairment.
[g]Community assigned diagnosis based on evidence of a previous ASD diagnosis in educational or medical records.
[h]''Other mental health disorders'' included adjustment disorder ($n=21$), delirium, dementia ($n=3$), motor skills disorder ($n=5$), elimination disorder ($n=9$), separation anxiety ($n=3$), emotional disorder not otherwise specified ($n=2$), catatonic disorder ($n=3$), schizophrenia ($n=1$), psychogenic disorder ($n=2$), sleep disorder ($n=15$), and somatoform disorder ($n=2$).

ASD, autism spectrum disorder; SC ADDM, South Carolina Autism & Developmental Disabilities Monitoring Network; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders;* 4*th* ed.; ICD9, International Classification of Diseases, 9th Revision; PDD, pervasive developmental disorder; ADHD, attention-deficit/hyperactivity disorder; ODD- oppositional defiant disorder.

Medicaid record. Indicators of behavioral and emotional problems were assessed from SC ADDM data, including 12 aberrant behaviors and 12 DSM-IV criteria. Co-occurring mental health disorders were identified by primary or secondary diagnostic codes 290.xx–319.xx.

Psychotropic medication classification. The Specific Therapeutic Class (STC) Code was used to identify medications by class. A dichotomous variable indicated if each child had a prescription for any psychotropic medication during the study period, defined as the year identified and 1 year prior (at age 7 or 8 years of age). Specific psychotropic medication classes were chosen based on a literature review of commonly prescribed medications in ASD: Antipsychotics (e.g., aripiprazole and risperidone); antidepressants (e.g., citalopram and sertraline); ADHD medications (i.e., stimulants and nonstimulants); mood stabilizers (e.g., carbamazepine and levetiracetam); antihypertensives (e.g., clonidine and guanfacine); anxiolytics (e.g., buspirone and lorazepam); sedatives or hypnotics (e.g., chloral hydrate and ramelteon); anticholinergics (e.g., benztropine and amantadine); and Alzheimer's medications (memantine and galantamine). Over-the-counter medications such as antacids, omega-3 fatty acids, and other nutritional supplements were not included.

Definition of polypharmacy. A dichotomous variable was used to indicate if at any time during the 2 year study period a child had medication claims for more than one psychotropic medication class of interest that overlapped for a period of at least 30 days, which is consistent with the definition of polypharmacy used in recent previous studies of polypharmacy (Safer et al. 2003; Zito et al. 2003; dosReis et al. 2005, 2011).

Data analysis

The analytical goals of this study were to describe and determine predictors of psychotropic medication polypharmacy for each of the following outcomes: Any polypharmacy, and the three most common combinations. We first performed descriptive statistics for each variable, followed by a series of bivariate associations between outcomes and predictors using simple logistic regression. Separate logistic regression models were first fit for each outcome, with predictors that were associated with each outcome at the 0.10 level of significance from the bivariate analysis. A final model was then fit for each outcome with variables that remained significant after adjusting for demographic variables. To determine the best method of operationalizing each variable, models were assessed for possible collinearity between predictors using the tolerance and variance inflation factor (TOL/VIF) method, and the predictive ability of each model was noted using the area under the receiver operator characteristic (ROC) curve (AUC). The TOL/VIF values were examined and the variable with the lowest TOL or highest VIF was removed in a stepwise fashion, to find the best model until all variables had VIF values <3.0. Statistical significance was set at 0.05 for the final models, and analyses were performed using SAS version 9.2 and R version 2.1.2.0.

Results

Characteristics of the study population

The study included 510 (81%) males and 193 (31%) rural residents. Medicaid eligibility was the result of disability for 465 (74%), for 152 (24%) eligibility was the result of income, and for 10 (2%) eligibility was the result of the children being in foster care. There were 193 (31%) white children, 160 (25%) black children, and 275 (44%) children for whom race was recorded as ''other'' (including Hispanic and Asian/Pacific Islanders, and one patient of unknown race). Demographic variables are summarized in Table 2.

Common aberrant behaviors were hyperactivity or impulsivity ($n=533$, 85%), delayed motor milestones ($n=393$, 62%), mood abnormalities ($n=375$, 60%), temper tantrums ($n=363$, 58%), argumentative behavior ($n=347$, 55%), and eating/sleeping abnormalities ($n=340$, 54%). Most children (93%) had at least one mental health disorder based on diagnostic codes in Medicaid records; most commonly, this was a communication disorder ($n=410$, 65%), intellectual disability ($n=396$, 63%), or any pervasive developmental disorder (PDD) ($n=381$, 61%). Additional details of symptoms and co-occurring diagnoses are presented in Table 3.

Table 6. Simple and Multiple Logistic Regression to Determine Associations Between Predictors and Attention-Deficit/Hyperactivity Disorder (ADHD) Medications and Antidepressant (A/AD) Polypharmacy, $N=629$

	Simple logistic regression[a]		*Final model 2*[b]	
Variable	*OR (95% CI)*	p	*OR (95% CI)*	p
Demographics				
Gender (ref, male)	0.64 (.32, 1.3)	0.21	–	–
Surveillance year identified (ref, 2000)		0.02		0.01
2002	4.1 (1.7, 10.1)		3.2 (1.2, 9.0)	
2004	2.4 (0.91, 6.4)		2.1 (0.72, 6.4)	
2006	1.8 (0.69, 4.7)		1.1 (0.35, 3.1)	
2008	2.0 (0.84, 5.0)		0.82 (0.29, 2.3)	
Residency (ref, urban)	0.59 (0.33, 1.1)	0.07	–	–
Medicaid eligibility category (ref, disability)[c]	1.2 (0.73, 2.1)	0.42	–	–
Race (ref, white)		0.02		0.02
Black	0.39 (0.20, 0.79)		0.37 (0.16, 0.84)	
Other[d]	0.57 (0.33, 0.98)		0.49 (0.26, 0.92)	
Special education services (ref, autism)		0.64	–	–
ASD- related[e]	1.3 (0.62, 2.7)		–	–
Any other[f]	0.83 (0.46, 1.5)		–	–
None	0.77 (0.36, 1.6)		–	–
Community assigned ASD diagnosis[g]	0.91 (0.55, 1.5)	0.73	–	–
Aberrant behaviors as evidenced in each child's SC ADDM record				
Temper tantrums	2.3 (1.3, 4.0)	<0.01	–	–
Sensory issues	1.5 (0.92, 2.5)	0.10	–	–
Staring spells/seizure-like activity	1.3 (0.78, 2.2)	0.31	–	–
Mood abnormalities	1.8 (1.1, 3.1)	0.03	–	–
Argumentative, defiant behavior	4.4 (2.4, 8.2)	0.01	2.2 (1.1, 4.6)	0.03
Aggression	3.7 (2.1, 6.4)	<0.01	1.7 (0.89, 3.4)	0.11
Abnormal eating/drinking/sleeping	2.5 (1.5, 4.4)	<0.01	–	–
Abnormal cognitive development	1.3 (0.82, 2.2)	0.24	–	–
Motor development delays	0.67 (0.41, 1.1)	0.11	–	–
Abnormal fear response	1.7 (1.1, 2.8)	0.03	–	–
Hyperactivity, inattention	1.6 (0.72, 3.4)	0.26	–	–
Self-injurious behavior	1.9 (1.2, 3.2)	0.01	–	–
ASD-specific DSM-IV diagnostic criteria as evidenced in SC ADDM records				
Social deficits				
Deficits in nonverbal behaviors	1.2 (0.57, 2.5)	0.63	–	–
Poor peer relationships	1.2 (0.69, 2.1)	0.51	–	–
Failure to share interests	0.82 (0.50, 1.3)	0.41	–	–
Lack of or deficient emotional reciprocity	1.1 (0.54, 2.4)	0.75	–	–
Communication deficits				
Delayed spoken language	0.65 (0.26, 1.6)	0.35	–	–
Conversational deficits	0.83 (0.43, 1.6)	0.56	–	–
Repetitive language	0.78 (0.46, 1.3)	0.37	–	–
Deficits in imaginative play skills	1.1 (0.68, 1.9)	0.62	–	–
Unusual behaviors				
Restricted interests	1.1 (0.67, 1.8)	0.71	–	–
Abnormal routines and/or rituals	1.6 (.84, 3.1)	0.16	–	–
Stereotyped motor mannerisms	1.3 (.72, 2.3)	0.40	–	–
Abnormal preoccupation with parts of objects	1.7 (1.0, 2.9)	0.05	2.2 (1.1, 4.2)	0.02
Co-occurring conditions by ICD9 code in Medicaid claims files				
Any PDD	1.7 (1.0, 3.0)	0.04	1.5 (.78, 3.0)	0.22
ADHD	10.8 (5.7, 20.5)	<0.01	6.4 (3.2, 13.1)	<0.01
Anxiety or mood disorder	3.9 (2.2, 7.0)	<0.01	2.4 (1.2, 5.0)	0.02
Communication disorder	1.3 (0.77, 2.2)	0.33	–	–
Conduct disorder/ODD	6.8 (4.0, 11.6)	<0.01	2.8 (1.5, 5.3)	<0.01
Developmental disability	0.68 (0.36, 1.3)	0.24	–	–

(*continued*)

Table 6. (Continued)

Variable	*Simple logistic regression*[a]		*Final model 2*[b]	
	OR (95% CI)	p	*OR (95% CI)*	p
Epilepsy	2.1 (1.2, 3.8)	0.02	–	–
Intellectual disability	1.4 (0.80, 2.3)	0.26	–	–
Learning disability	0.98 (0.57, 1.7)	0.95	–	–
Other mental health disorder[h]	1.8 (1.0, 3.1)	0.04	–	–

[a]Simple logistic regression between predictor and outcome.
[b]Final model: variables significantly associated with outcome after adjusting for demographic variables (0.10 level).
[c]Disability versus foster care/income because of small numbers in foster care.
[d]''Other race'' = Hispanic, Asian/Pacific Islander, 1 missing.
[e]''ASD related'' special education = other health impairment ($n = 47$), preschool child with disability ($n = 2$), speech delay ($n = 20$), developmental disability ($n = 2$).
[f]''Any other'' special education = deaf-blindness, hearing impaired, mental retardation, multiple disabilities, orthopedic impairment, brain injury, visual impairment.
[g]Community assigned diagnosis based on previous ASD diagnosis in education or medical records.
[g]''Other mental health disorders'' = adjustment disorder ($n = 21$), delirium, dementia ($n = 3$), motor skills disorder ($n = 5$), elimination disorder ($n = 9$), separation anxiety ($n = 3$), emotional disorder ($n = 2$), catatonic disorder ($n = 3$), schizophrenia ($n = 1$), psychogenic disorder ($n = 2$), sleep disorder ($n = 15$), and somatoform disorder ($n = 2$).
ASD, autism spectrum disorder; SC ADDM-, South Carolina Autism and Developmental Disabilities Monitoring Network; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; ICD9, International Classification of Diseases, 9th Revision; PDD, pervasive developmental disorder; ODD, oppositional defiant disorder.

During the study period, 377 (60%) of children had a psychotropic medication claim; most commonly for an ADHD medication ($n = 281$), antidepressant ($n = 108$), antipsychotic ($n = 102$), mood stabilizer ($n = 101$), sedative or hypnotic ($n = 63$), anxiolytic ($n = 56$), or anticholinergic ($n = 12$). Of those, interclass polypharmacy was identified in 41% ($n = 153$) of children. Common combinations were ADHD medications and an antidepressant (A/AD), antipsychotic (A/AP), or a mood stabilizer (A/MS) (Table 4).

Any polypharmacy

After adjusting for demographics, aberrant behaviors, diagnostic criteria, and co-occurring conditions, children who were Medicaid eligible because of income had 0.40 times lower odds of any psychotropic medication polypharmacy compared with those who were eligible because of disability (OR 0.40, 95% CI 0.21, 0.77). Black children had 0.44 times lower odds of polypharmacy compared with white children (OR 0.44, 95% CI 0.23, 0.86), and children in the ''other'' race category had 0.42 times lower odds of any polypharmacy compared with white children (OR 0.42, 95% CI 0.24, 0.74). Children with aggressive behaviors had 2.3 times higher odds of any polypharmacy compared with those without (OR 2.3, 95% CI 1.4, 4.0), and the odds of any interclass polypharmacy among children with conversational deficits were 0.44 times lower (OR 0.44, 95% CI 0.24, 0.79) compared with those without.

By International Classification of Diseases, 9th Revision (ICD-9) codes in Medicaid claims files, children with diagnosed ADHD had 4.1 times higher odds of any polypharmacy (OR 4.1, 95% CI 2.5, 6.7), and those with an anxiety or mood disorder had 2.5 times higher odds (OR 2.5, 95% CI 1.3, 4.7). Diagnosed conduct disorder or ODD was associated with 4.0 times higher odds of polypharmacy (OR 4.0, 95% CI 2.2, 7.5), and children with epilepsy had 7.3 times higher odds of any polypharmacy compared with those without (OR 7.3, 95% CI 4.0, 13.5). These results are shown in Table 5.

ADHD and antidepressant polypharmacy

After the same model building techniques set forth previously, in the final model, we found that compared with children identified with an ASD at 8 years of age in 2000, those in 2002 had 3.2 higher odds of A/AD polypharmacy (OR 3.2, 95% CI 1.2, 9.0). Black children had 0.37 times lower odds of A/AD polypharmacy (OR 0.37, 95% CI 0.16, 0.84), and children in the ''other'' race category had 0.49 lower odds of A/AD polypharmacy (0.49, 95% CI 0.26, 0.92) compared with whites. Children with argumentative behavior had 2.2 times higher odds of A/AD polypharmacy (OR 2.2, 95% CI 1.1, 4.6) compared with children without.

The only ASD-specific diagnostic criterion significantly associated with A/AD polypharmacy in the adjusted final model was an abnormal preoccupation with parts of objects; children with this behavior had 2.2 times higher odds of A/AD polypharmacy compared with those without (OR 2.2, 95% CI 1.1, 4.2).

Significant diagnoses in Medicaid records by ICD-9 code associated with A/AD polypharmacy were ADHD (OR 6.4, 95% CI 3.2, 13.1), anxiety or mood disorder (OR 2.4, 95% CI 1.2, 5.0), and a conduct disorder or ODD (OR 2.8, 95% CI 1.5, 5.3). These results are summarized in Table 6.

A/AP polypharmacy

Although the final adjusted model for A/AP polypharmacy found no demographic variables significantly associated with A/AP polypharmacy, hyperactivity and/or inattention (OR 5.7, 95% CI 1.1, 30.7) and self-injurious behavior (OR 2.3, 95% CI 1.3, 4.2) remained statistically significant. The presence of a conversational deficit was the only ASD-specific diagnostic criteria that also remained significantly associated with A/AP polypharmacy (OR 0.28, 95% CI 0.13, 0.61), although an abnormal preoccupation with routines and rituals neared statistical significance (OR 2.4, 95% CI 1.0, 5.9).

Co-occurring conditions from Medicaid records associated with A/AP polypharmacy were ADHD (OR 6.6, 95% CI 3.2, 13.9), and conduct disorder or ODD (OR 4.6, 95% CI 2.5, 8.7). These results are shown in Table 7.

ADHD and mood stabilizers

The final model for A/MS polypharmacy suggested that children with staring spells or seizure-like activity (as documented in SC ADDM records) had 3.3 times higher odds of A/MS polypharmacy

Table 7. Simple and Multiple Logistic Regression Analyses to Determine Associations Between Predictors and Attention-Deficit/ Hyperactivity Disorder (ADHD) Medications and Antipsychotic Polypharmacy (A/AP), $N = 629$

	Simple logistic regression[a]		*Final model*[b]	
Variable	*OR (95% CI)*	p	*OR (95% CI)*	p
Demographics				
Gender (ref, male)	0.74 (0.38, 1.4)	0.38	–	–
Year identified (ref, 2000)		0.37	–	–
2002	2.4 (1.0, 5.7)		–	–
2004	1.7 (0.66, 4.2)		–	–
2006	1.5 (0.62, 3.6)		–	–
2008	1.6 (0.73, 3.7)		–	–
Residency (ref, urban)	0.97 (0.57, 1.7)	0.91	–	–
Medicaid eligibility category (ref, disability)[c]	0.59 (0.31, 1.1)	<0.01	–	–
Race (ref, white)		0.46	–	–
Black	0.68 (0.34, 1.4)		–	–
Other[d]	0.99 (0.57, 1.7)		–	–
Special education category (ref, autism)		0.45	–	–
Related[e]	1.1 (0.49, 2.6)		–	–
Any[f]	1.5 (0.87, 2.7)		–	–
None	0.96 (0.45, 2.1)		–	–
Community assigned ASD diagnosis[g]	1.2 (0.70, 2.0)	0.55	–	–
Aberrant behaviors as evidenced in SC ADDM record				
Temper tantrums	2.3 (1.3, 3.9)	<0.01	–	–
Sensory issues	1.4 (.84, 2.3)	0.20	–	–
Staring spells/seizure-like activity	2.1 (1.3, 3.5)	<0.01	–	–
Mood abnormalities	2.7 (1.5, 4.8)	<0.01	–	–
Argumentative, defiant behavior	3.9 (2.1, 7.2)	<0.01	1.7 (0.81, 3.4)	0.17
Aggression	4.6 (2.6, 8.4)	<0.01	1.7 (0.87, 3.5)	0.12
Abnormal eating/drinking/sleeping	2.5 (1.4, 4.3)	<0.01	–	–
Abnormal cognitive development	0.74 (0.46, 1.2)	0.24	–	–
Motor development delays	1.2 (0.70, 2.0)	0.54	–	–
Abnormal fear response	1.7 (1.0, 2.7)	0.05	–	–
Hyperactivity, inattention	7.2 (1.7, 29.9)	0.01	5.7 (1.1, 30.7)	0.04
Self-injurious behavior	3.6 (2.2, 6.00)	<0.01	2.3 (1.3, 4.2)	0.01
ASD-specific DSM-IV diagnostic criteria as evidenced in SC ADDM record				
Social deficits				
Deficits in nonverbal behaviors	1.0 (0.51, 2.1)	0.94	–	–
Poor peer relationships	1.3 (0.72, 2.3)	0.39	–	–
Failure to share interests	1.0 (0.62, 1.7)	0.93	–	–
Lack of or deficient emotional reciprocity	1.8 (0.75, 4.3)	0.18	–	–
Communication deficits				
Delayed spoken language	0.80 (0.30, 2.1)	0.66	–	–
Conversational deficits	0.55 (0.30, 0.99)	0.05	0.28 (0.13, 0.61)	<0.01
Repetitive language	0.97 (0.55, 1.7)	0.90	–	–
Deficits in imaginative play skills	1.1 (0.67, 1.9)	0.68	–	–
Unusual behaviors				
Restricted interests	1.2 (0.74, 2.1)	0.43	–	–
Abnormal routines and/or rituals	2.6 (1.2, 5.6)	0.01	2.4 (1.0, 5.9)	0.05
Stereotyped motor mannerisms	1.3 (0.71, 2.2)	0.45	–	–
Abnormal preoccupation with parts of objects	1.4 (0.85, 2.4)	0.18	–	–
Co-occurring conditions by ICD9 code in Medicaid claims files				
Any PDD	1.8 (1.1, 3.2)	0.03	–	–
ADHD	13.3 (6.7, 26.5)	<0.01	6.6 (3.2, 13.9)	<0.01
Anxiety or mood disorder	3.1 (1.7, 5.6)	<0.01	–	–
Communication disorder	1.4 (0.80, 2.3)	0.25	–	–
Conduct disorder/ODD	8.7 (5.1, 15.0)	<0.01	4.6 (2.5, 8.7)	<0.01

(*continued*)

Table 7. (Continued)

Variable	*Simple logistic regression*[a]		*Final model*[b]	
	OR (95% CI)	p	*OR (95% CI)*	p
Developmental disability	1.1 (0.63, 2.0)	0.73	–	–
Epilepsy	2.8 (1.6, 5.0)	< 0.01	–	–
Intellectual disability	1.8 (1.0, 3.1)	0.04	–	–
Learning disability	0.85 (0.49, 1.5)	0.58	–	–
Other mental health disorder[h]	2.0 (1.1, 3.4)	0.02	–	–

[a]Simple logistic regression.
[b]Final model: Variables significantly associated with outcome, adjusted for demographic variables (0.10 level).
[c]Disability versus foster care/income because of small numbers in foster care.
[d]''Other race'' = Hispanic, Asian/Pacific Islander, 1 missing.
[e]''ASD related'' special education = other health impairment ($n = 47$), child with disability ($n = 2$), speech delay ($n = 20$), developmentally disabled ($n = 2$).
[f]''Any other'' special education = deaf-blindness, hearing impaired, mental retardation, multiple disabilities, orthopedic impairment, brain injury, visual impairment.
[g]Community assigned ASD diagnosis in ADDM data.
[h]''Other mental health disorders'' = adjustment disorder ($n = 21$), delirium, dementia ($n = 3$), motor disorder ($n = 5$), elimination disorder ($n = 9$), separation anxiety ($n = 3$), emotional disorder ($n = 2$), catatonic disorder ($n = 3$), schizophrenia ($n = 1$), psychogenic disorder ($n = 2$), sleep disorder ($n = 15$), and somatoform disorder ($n = 2$).

ASD, autism spectrum disorder; SC ADDM, South Carolina Autism and Developmental Disabilities Monitoring Network; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders* 4th ed.; ICD9, International Classification of Diseases, 9th Revision; PDD, pervasive developmental disorder; ODD- oppositional defiant disorder.

than did those without (OR 3.3, 95% CI 1.4, 7.6). Although aggressive behavior was associated with A/MS polypharmacy (OR 2.9, 95% CI 1.1, 7.5), there were no ASD-specific diagnostic criteria associated with A/MS polypharmacy. Diagnoses within Medicaid records by ICD-9 code significantly associated with A/MS polypharmacy were ADHD (OR 3.6, 95% CI 1.4, 9.4), conduct disorder or ODD (OR 4.3, 95% CI 1.8, 10.5), and epilepsy (OR 13.6, 95% CI 5.8, 31.8). These results are shown in Table 8. See Table 9 for a summary of results related to any polypharmacy, and for the three most common combinations.

Discussion

To the authors' knowledge, this is the first study to examine child-level demographics, ASD-associated aberrant behaviors, diagnostic criteria, and co-occurring mental health-related disorders in reference to interclass psychotropic medication polypharmacy in a population-based study sample of Medicaid-eligible children with ASD who were diagnosed using consistent criteria over time. Of the 629 Medicaid-eligible children who met CDC surveillance criteria of an ASD in South Carolina between 2000 and 2008, 377 (60%) had a claim for a psychotropic medication at age 7 or 8 years; 153 (41%) of those had interclass polypharmacy. The most common combinations were ADHD medications and an antidepressant, antipsychotic, or mood stabilizer.

Although initial analyses suggested that several symptoms and conditions were associated with specific interclass polypharmacy, in the final adjusted models this was not the case. For example, although AP use in ASD shows promise for treating irritability (Erickson et al. 2007), the only behaviors associated with A/AP were SIB and hyperactivity. Similarly, mood abnormalities were not associated with A/MS, although a diagnosed mood disorder neared significance. The higher odds of polypharmacy in the current study were similar to findings in other chronic childhood conditions with mental health-related comorbidities. Specifically co-occurring ADHD and conduct disorder or ODD were associated with higher odds of any and all combinations of polypharmacy. Mood disorders were positively associated with A/AP polypharmacy only. Findings were not a surprise, because aggressive children or those with severe behavior problems would be more likely to receive medications to target aggressive and challenging behaviors. Similarly, because mood stabilizers can be used to manage epilepsy it is not surprising that diagnosed epilepsy was associated with A/MS polypharmacy only.

Interestingly, we primarily found a lack of association with demographic variables and psychotropic medication polypharmacy. We did not find gender differences consistent with previous ASD psychotropic medication studies, although these studies addressed *any* polypharmacy, and not specific combinations (Mandell et al. 2008; Rosenberg et al. 2009). Another surprise finding in our study was the lack of an urban versus rural association even after controlling for race, as, like minorities, children in rural areas may have less access to behavioral services and rely more on medications for behavior management. Furthermore, because children with a diagnosed ASD are eligible for several services in South Carolina, we expected that children with a previously documented ASD diagnosis in educational or medical records from SC ADDM files or Medicaid claims would have lower odds of polypharmacy, given the greater access to behavioral services, although this was not the case. Also interesting was that compared with white children, black and ''other race'' children had much lower odds of *any*, and A/AD polypharmacy. We considered this unexpected, under the premise that as with those in rural areas, minorities may have diminished access to behavioral services that could decrease reliance on medication behavior management. However, minority groups may be less likely to embrace psychotropic medication and have a more skeptical attitude toward psychopharmacological treatments, particularly antidepressants (Stevens et al. 2009), which could explain these findings.

For more than a decade, studies have documented an increasing in use of polypharmacy in ASD (Esbensen et al. 2009). Therefore, we expected to see that over time, more children would be prescribed interclass polypharmacy. This was not found. Surveillance year 2000 was compared with 2002 for any polypharmacy, but not for any specific combination, nor was comparison made between any other surveillance years.

Table 8. Results of Simple and Multiple Logistic Regression Analyses to Determine Associations Between Predictors and Attention-Deficit/Hyperactivity Disorder (ADHD) Medications and Mood Stabilizer (A/MS) Polypharmacy, $N = 629$

	Simple logistic regression[a]		*Final model*[b]	
Variable	*OR (95% CI)*	p	*OR (95% CI)*	p
Demographics				
Gender (ref, male)	1.3 (0.64, 2.6)	0.46	–	–
Year identified (ref, 2000)		0.06		0.08
2002	1.4 (0.62, 3.2)		1.4 (0.43, 4.6)	
2004	0.41 (0.13, 1.3)		0.79 (0.19, 3.2)	
2006	0.67 (0.27, 1.6)		0.93 (0.27, 3.2)	
2008	0.45 (0.19, 1.1)		0.25 (0.07, 0.85)	
Residency (ref, urban)	0.93 (0.48, 1.8)	0.81	–	–
Medicaid eligibility category (ref, disability)[c]	0.64 (0.30, 1.4)	0.25	–	–
Race (ref, white)		0.38	–	–
Black	0.83 (0.34, 2.0)		–	–
Other[d]	1.4 (0.69, 2.8)		–	–
Special education category (ref, autism)		0.15	–	–
Related[e]	2.1 (0.82, 5.6)		–	–
Any[f]	2.3 (1.1, 4.7)		–	–
None	1.7 (0.67, 4.1)		–	–
Community assigned ASD diagnosis[g]	.80 (0.44, 1.5)	0.46	–	–
Aberrant behaviors as evidenced in SC ADDM records				
Temper tantrums	1.9 (0.98, 3.5)	0.06	–	–
Sensory issues	1.6 (0.90, 3.0)	0.11	–	–
Staring spells/seizure-like activity	7.2 (3.7, 13.7)	<0.01	3.3 (1.4, 7.6)	0.01
Mood abnormalities	2.8 (1.3, 5.6)	0.01	–	–
Argumentative, defiant behavior	3.3 (1.6, 6.8)	<0.01	1.3 (0.48, 3.3)	0.63
Aggression	5.7 (2.6, 12.4)	<0.01	2.9 (1.1, 7.5)	0.03
Abnormal eating/drinking/sleeping	2.2 (1.1, 4.2)	0.02	–	–
Abnormal cognitive development	1.1 (0.58, 1.9)	0.88	–	–
Motor development delays	1.7 (0.87, 3.2)	0.12	–	–
Abnormal fear response	1.6 (0.89, 2.9)	0.11	–	–
Hyperactivity, inattention	4.4 (1.1, 18.6)	0.04	–	–
Self-injurious behavior	3.1 (1.7, 5.7)	<0.01	–	–
ASD-specific DSM-IV diagnostic criteria as evidenced in SC ADDM record				
Social deficits				
Deficits in nonverbal behaviors	1.2 (0.47, 2.8)	0.76	–	–
Poor peer relationships	0.92 (0.48, 1.8)	0.79	–	–
Failure to share interests	0.94 (0.52, 1.7)	0.83	–	–
Lack of or deficient emotional reciprocity	0.56 (0.27, 1.2)	0.12	–	–
Communication deficits				
Delayed spoken language	1.4 (0.33, 6.1)	0.63	–	–
Conversational deficits	1.3 (0.53, 3.1)	0.58	–	–
Repetitive language	0.60 (0.32, 1.1)	0.11	–	–
Deficits in imaginative play skills	0.79 (0.43, 1.4)	0.43	–	–
Unusual behaviors				
Restricted interests	1.2 (0.62, 2.1)	0.65	–	–
Abnormal routines and/or rituals	1.5 (0.69, 3.3)	0.30	–	–
Stereotyped motor mannerisms	0.59 (0.32, 1.1)	0.09	–	–
Abnormal preoccupation with parts of objects	1.0 (0.56, 1.9)	0.93	–	–
Co-occurring conditions by ICD9 code in Medicaid claims files				
Any PDD	0.99 (.54, 1.8)	0.98	–	–
ADHD	7.0 (3.4, 14.4)	<0.01	3.6 (1.4, 9.4)	0.01
Anxiety or mood disorder	4.3 (2.3, 8.4)	<0.01	2.6 (0.95, 6.9)	0.06
Communication disorder	1.9 (0.94, 3.8)	0.08	–	–
Conduct disorder/ODD	11.0 (5.8, 20.6)	<0.01	4.3 (1.8, 10.5)	<0.01
Developmental disability	.65 (.30, 1.4)	0.28	–	–

(*continued*)

Table 8. (Continued)

Variable	*Simple logistic regression*[a]		*Final model*[b]	
	OR (95% CI)	p	*OR (95% CI)*	p
Epilepsy	21.9 (11.2, 42.9)	<0.01	13.6 (5.8, 31.8)	<0.01
Intellectual disability	2.1 (1.0, 4.2)	0.04	–	–
Learning disability	1.1 (0.58, 2.1)	0.77	–	–
Other mental health disorder[h]	3.0 (1.6, 5.5)	<0.01	–	–

[a]Simple logistic regression between predictor and outcome.
[b]Final model: Variables significantly associated with outcome after adjusting for demographic variables (0.10 level).
[c]Disability versus foster care/income because of small numbers in foster care.
[d]"Other race" = Hispanic, Asian/Pacific Islander, 1 missing.
[e]"ASD related" special education = other health impairment ($n=47$), preschool child with disability ($n=2$), speech delay ($n=20$), developmental disability ($n=2$).
[f]"Any other" special education = deaf-blindness, hearing impairment, mental retardation, multiple disabilities, orthopedic impairment, brain injury, visual impairment.
[g]Community assigned diagnosis based on previous ASD diagnosis in education or medical records.
[h]"Other mental health disorders" = adjustment disorder ($n=21$), delirium, dementia ($n=3$), motor skills disorder ($n=5$), elimination disorder ($n=9$), separation anxiety ($n=3$), emotional disorder ($n=2$), catatonic disorder ($n=3$), schizophrenia ($n=1$), psychogenic disorder ($n=2$), sleep disorder ($n=15$), and somatoform disorder ($n=2$).

ASD, autism spectrum disorder; SC ADDM, South Carolina Autism and Developmental Disabilities Monitoring Network; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.; ICD9, International Classification of Diseases, 9th Revision; PDD, pervasive developmental disorder; ODD, oppositional defiant disorder.

Limitations

This study had several limitations. If not identified or included as an ASD case by the SC ADDM network, the child was not included in the current study, an inherent limitation in the study methodology from which the data were derived. However, we believe that the completeness of case ascertainment using the SC ADDM methodology is high (Nicholas et al. 2012). Also, the ADDM methodology does not allow for face-to-face interaction to confirm the ASD diagnosis. It is important to note that although the study population was a Medicaid-only population, only 24% of children were eligible for Medicaid because of low income. In other words, nearly three quarters of the children in the study were eligible because of their disability. This is likely because of South Carolina's Katie Beckett Waiver program, which is not an income-based program, but rather a program that covers children based on functional disability (Logan et al. 2012). Therefore, the study was not limited to a low-income population and this limitation of relying on Medicaid claims is likely minimal. Further support of this statement is that we found no statistically significant differences between a subgroup of children identified as ASD cases by SC ADDM who were not eligible for Medicaid and those who were eligible for Medicaid. Another example of the minimal impact of this possible limitation is the similar polypharmacy rates among children with ASD from a community-based survey of children with various insurance programs compared with polypharmacy rates to Mandell et al.'s (2008) Medicaid population (Rosenberg et al. 2009).

Unfortunately, we were not able to control for behavioral interventions or reasons why children may or may not have access to such interventions that may decrease medication reliance, although we did include special education categories and rural versus urban residency variables.

Likewise, although we were not able to assess the impacts of intelligence quotient (IQ) or severity of impairment directly, we did include mental retardation (MR) and intellectual disability, and the type of special education programs received.

As with other claims-based studies, this study operated on the assumption that one would not continue to refill a prescription if the medication were not intended to be taken, although we were not able to confirm this. However, administrative claims-based studies of medication use, particularly adherence and compliance studies, have been validated by numerous methods both directly through biological assays, and indirectly through pill counts and electronic monitors (Karve et al. 2008); therefore, we feel confident that this study represents an accurate portrayal of medication use.

Another important limitation is that ASD case status was not confirmed via comprehensive evaluation. Therefore, the ability to interpret findings between polypharmacy and behavior is limited. The dichotomous measure of polypharmacy is consistent with what has been used in the literature (Spencer et al. 2013); however, this methodology did not allow us to distinguish between children who were prescribed a corresponding number of medications and diagnoses. For example, we could not differentiate children who were prescribed two medications for two diagnoses from children prescribed three or more medications for one diagnosis. Lastly, the study population was entirely based in South Carolina. Given previously noted possible regional variations in psychotropic medication use, variations in the current study underscore the need for small area variation studies (dosReis et al. 2005; Mandell et al. 2008; Rosenberg et al. 2009; Rubin et al. 2009).

Strengths

Despite these limitations, the study has several strengths. The ability to link population-based data to Medicaid claims increases the completeness of the study population and limits bias from volunteer participation or parent report, and case ascertainment is not reliant on previous diagnoses. The SC ADDM methodology uses consistent diagnostic criteria over time and location across many years, spanning from 2000 to 2008, and across numerous data sources. We were able to include demographics, behaviors, ASD-specific criteria, and co-occurring conditions in relation to medication use, all of which could impact the need psychotropic medication. Lastly, the use of a 2 year prescription history allowed us to capture the variability in medication use, and will help form a foundation to continue studying patterns of medication use.

Table 9. Summary Results of Multiple Logistic Regression Analyses of Polypharmacy for Any Polypharmacy, and the Three Most Common Combinations, $N = 629$

Variable	*Any polypharmacy OR (95% CI)*	p	*A/AD OR (95% CI)*	p	*A/AP OR (95% CI)*	p	*A/MS OR (95% CI)*	p
Demographics								
Year identified (ref, 2000)				0.01				0.08
2002			3.2 (1.2, 9.0)				1.4 (0.43, 4.6)	
2004			2.1 (0.72, 6.4)				0.79 (0.19, 3.2)	
2006			1.1 (0.35, 3.1)				0.93 (0.27, 3.2)	
2008			0.82 (0.29, 2.3)				0.25 (0.07, 0.85)	
Medicaid eligibility category (ref, disability)	0.40 (0.21, 0.77)	0.01						
Race (ref, white)		0.01		0.02				
Black	0.44 (0.23, 0.86)		0.37 (0.16, 0.84)					
Other	0.42 (0.24, 0.74)		0.49 (0.26, 0.92)					
Aberrant behaviors								
Staring spells/seizure-like activity							3.3 (1.4, 7.6)	0.01
Argumentative, defiant behavior	1.6 (0.92, 2.6)	0.10	2.2 (1.1, 4.6)	0.03	1.7 (0.81, 3.4)	0.17	1.3 (.48, 3.3)	0.63
Aggression	2.3 (1.4, 4.0)	<0.01	1.7 (0.89, 3.4)	0.11	1.7 (0.87, 3.5)	0.12	2.9 (1.1, 7.5)	0.03
Hyperactivity, inattention					5.7 (1.1, 30.7)	0.04		
Self-injurious behavior	1.3 (0.77, 2.1)	0.36			2.3 (1.3, 4.2)	0.01		
ASD-specific DSM-IV diagnostic criteria								
Social deficits								
Communication deficits								
Conversational deficits	0.44 (0.24, 0.79)	0.01			0.28 (0.13, 0.61)	<0.01		
Unusual behaviors								
Abnormal routines and/or rituals					2.4 (1.0, 5.9)	0.05		
Abnormal preoccupation with parts of objects			2.2 (1.1, 4.2)	0.02				
Co-occurring conditions by ICD9 code								
Any PDD			1.5 (.78, 3.0)	0.22				
ADHD	4.1 (2.5, 6.7)	<0.01	6.4 (3.2, 13.1)	<0.01	6.6 (3.2, 13.9)	<0.01	3.6 (1.4, 9.4)	0.01
Anxiety or mood disorder	2.5 (1.3, 4.7)	0.01	2.4 (1.2, 5.0)	0.02			2.6 (.95, 6.9)	0.06
Conduct disorder/ODD	4.0 (2.2, 7.5)	<0.01	2.8 (1.5, 5.3)	<0.01	4.6 (2.5, 8.7)	<0.01	4.3 (1.8, 10.5)	<0.01
Epilepsy	7.3 (4.0, 13.5)	<0.01					13.6 (5.8, 31.8)	<0.01

A/AD, ADHD medication plus antidepressant; A/AP, ADHD medication plus antipsychotic; A/MS, ADHD medication plus mood stabilizer; ASD, autism spectrum disorder; SC ADDM, South Carolina Autism and Developmental Disabilities Monitoring Network; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; ICD9, International Classification of Diseases, 9th Revision; PDD, pervasive developmental disorder; ADHD-attention deficit hyperactivity disorder; ODD- oppositional defiant disorder.

Conclusions

Children with ASD are prescribed medication regimens with overlapping interclass medication use. In these data, we found evidence that some symptoms, although not all, are associated with specific medication combinations. This article presents the first detailed report of psychotropic medication polypharmacy among Medicaid-eligible children who were diagnosed with ASD between 2000 and 2008 in SC, and the role of behavioral, social, communicative, and comorbid conditions. Given the unexpected findings regarding associations among demographic variables, ASD-specific diagnostic criteria, and psychotropic polypharmacy, and that many predictors of polypharmacy were behavior related, additional investigation is warranted to better determine patterns and predictors of multiple psychotropic medication use in this population.

Clinical Significance

Because of the access to educational, behavioral, clinical, demographic, and pharmaceutical histories, this may be the most thorough study to date to identify both predictive factors of polypharmacy and specific interclass psychotropic medication combinations. Several questions remain, including the appropriateness of combination medication regimens in this young population. Certainly adherence is a factor in medication efficacy, although this study was not designed to assess the duration of combination use over the entire study period, interclass switching patterns, or additional adherence measures. Future studies will advance the field as patterns of and reasons for over- or underutilization of medications are identified.

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Disclosures

No competing financial interests exist.

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