JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 21, Number 4, 2011

Pp. 311–319
DOI: 10.1089/cap.2010.0138

Original Articles

Clinical Characteristics of Children Receiving Antipsychotic Medication

Robert L. Findling, M.D., M.B.A.,[1] Sarah McCue Horwitz, Ph.D.,[2] Boris Birmaher, M.D.,[3] Robert A. Kowatch, M.D., Ph.D.,[4] Mary A. Fristad, Ph.D., ABPP,[5] Eric A. Youngstrom, Ph.D.,[6] Thomas W. Frazier, Ph.D.,[7] David Axelson, M.D.,[3] Neal Ryan, M.D.,[3] Christine A. Demeter, M.A.,[1] Judith Depew,[4] Benjamin Fields, M.A., M.Ed.,[8] Mary Kay Gill, MSN,[3] Elizabeth A. Deyling M.A.,[1] Brieana M. Rowles, M.A.,[1] and L. Eugene Arnold, M.D.[5]

Abstract

This study explored the demographic and diagnostic features of children who were currently receiving antipsychotics compared to children who were receiving other psychotropics in a cohort of children with and without elevated symptoms of mania (ESM). Participants were recruited from 10 child outpatient mental health clinics associated with four universities. Guardians with children between 6–12 years who presented for new clinical evaluations completed the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M). All children who scored ≥ 12 on the PGBI-10M and a select demographically matched comparison group of patients who scored ≤ 11 were invited to participate. Children were divided into two groups: those receiving at least one antipsychotic medication and those receiving other psychotropic medications. The groups were compared on demographics, diagnoses, psychiatric symptoms, functioning, and past hospitalizations. Of the 707 children enrolled in the Longitudinal Assessment of Manic Symptoms (LAMS) study, 443 (63%) were prescribed psychotropic medication at baseline: 157 (35%) were receiving an antipsychotic and 286 (65%) were prescribed other agents. Multivariate results indicated that being prescribed antipsychotics was related to being white, previous hospitalization, having a psychotic or bipolar 1 disorder and the site where the child was receiving services ($p < 0.001$). In this sample, it is relatively common for a child to be prescribed an antipsychotic medication. However, the only diagnoses associated with a greater likelihood of being treated with an antipsychotic were psychotic disorders or unmodified DSM-IV bipolar 1 disorder.

Introduction

There is a growing body of data suggesting there has been a significant increase in the rates at which antipsychotics are prescribed to children (Cooper et al. 2004; Cooper et al. 2006; Olfson et al. 2006; Patel et al. 2006; Pathak et al. 2010). In addition, data suggest that a substantial number of children may be receiving antipsychotic medications for indications that do not have regulatory approval (Patel et al. 2006; Aparasu & Bhatara 2007; Domino & Swartz 2008; Crystal et al. 2009). Perhaps more disconcerting is the observation that some children may be receiving atypical antipsychotics for reasons not supported by scientific evidence. Specifically, concerns have been raised about the rates at which atypical antipsychotics are prescribed to children with attention-deficit/hyperactivity disorder (ADHD) and, although there is speculation that antipsychotics may be prescribed to control disruptive behaviors, this possibility has not been specifically investigated (Cooper et al. 2004; Crystal et al. 2009).

Given that antipsychotics are prescribed for bipolar disorder and given the rapid increase in the diagnosis of bipolar disorder in children and adolescents, a plausible but unexplored contributor to the increased prescribing of antipsychotics could be the increase in the diagnosis of bipolar disorder in youth (Moreno et al. 2007). Furthermore, there is evidence to suggest

[1]University Hospitals Case Medical Center/Case Western Reserve University.
[2]Department of Pediatrics and Stanford Health Policy, Stanford University School of Medicine.
[3]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh.
[4]Dr. Kowatch and Ms. Depew are with Cincinnati Children's Hospital.
[5]Department of Psychiatry, Division of Child and Adolescent Psychiatry, Ohio State University.
[6]Department of Psychology at University of North Carolina at Chapel Hill and Case Western Reserve University.
[7]Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic.
[8]Nationwide Children's Hospital.

This study was supported by the National Institute of Mental Health (R01-MH073967; R01-MH073801; R01-MH073953; R01-MH073816). We thank them for their support but acknowledge that the findings and conclusions presented in this paper are those of the authors alone, and do not necessarily reflect the opinions of NIMH.

that the bipolar spectrum has, in a sense, broadened. For example, children and adolescents who show symptoms of subsyndromal bipolar disorder or cyclothymic disorder may be given a diagnosis of bipolar disorder not-otherwise-specified (BP-NOS) (Youngstrom et al. 2008a; Goldstein 2010). Given that antipsychotics are frequently used as a treatment for bipolar disorder, it may be that some of the increase in antipsychotic prescriptions is driven by the treatment of youth with a bipolar spectrum diagnosis who may not have narrowly defined bipolar 1 disorder (Miller 2010; Waters 2010).

The substantive risks associated with antipsychotic treatment in children make understanding the apparent increase in rates of prescriptions critically important (Cooper et al. 2006; Crystal et al. 2009). Many concerns that have been raised about the indications for which antipsychotics are prescribed to children have come from studies of large administrative databases (Cooper et al. 2004; Cooper et al. 2006; Olfson et al. 2006; Pathak et al. 2010). Although the size and coverage of these databases are important strengths, reliance on diagnoses of unknown accuracy and the lack of precise information about key clinical characteristics are distinct shortcomings (Schwartz et al. 1980; Domino & Swartz 2008; Rettew et al. 2009; Pathak et al. 2010). For example, diagnoses recorded in these data sets might not be complete (Cooper et al. 2004). This may, in part, be due to the lack of information about co-morbidities (Rettew et al. 2009). It is also possible that these co-morbidities, and not the principal diagnosis in the administrative database, may be associated with antipsychotic use. Also, it is possible that providers record only reimbursable diagnoses (Goldstein 2010) or those they perceive to be associated with less stigma.

Thus, this study explored the demographic and diagnostic features of children who were currently receiving antipsychotics compared to children who were receiving other psychotropics in a sample of children selected to have high or low ''manic'' symptomatology. In addition, this study specifically examined whether children who met diagnostic symptom criteria for ADHD only were receiving antipsychotic medications. All diagnoses were based on semi-structured research interviews, complementing prior work by ensuring that all requisite symptoms were assessed, using formal DSM criteria, with comorbidities systematically considered regardless of presenting problem.

Methods

Study sites and subject ascertainment

The children examined in this study are patients who received an initial evaluation under the auspices of the NIMH-supported Longitudinal Assessment of Manic Symptoms (LAMS) study. The LAMS study was designed to examine the characteristics of children with elevated symptoms of mania (ESM) and to examine the relationship between manic symptoms and bipolarity. All procedures were reviewed and approved by the Institutional Review Boards at each site of the four university affiliated sites where LAMS is being conducted. Written informed consent from the parents/guardians and assent from the participants were obtained before any study-related procedures were performed.

Study participants were recruited from 10 child outpatient mental health clinics (2 in Northeast Ohio, 1 in Pittsburgh, 5 in Columbus, and 2 in Cincinnati) associated with four universities in Ohio and Western Pennsylvania (Case Western Reserve University, University of Pittsburgh, Ohio State University and University of Cincinnati).

Eligible children were between the ages of 6 years 0 months and 12 years 11 months and were new evaluations at the LAMS outpatient clinics. Parents/guardians accompanying eligible children were approached and asked to complete the 10-item Parent-Completed General Behavior Inventory Mania Form (PGBI-10M) (Youngstrom et al. 2005; Youngstrom et al. 2008b) to screen for ESM. The items that comprise the PGBI-10M describe hypomanic, manic, and biphasic symptomatology and discriminate bipolar disorder from other diagnoses (Youngstrom et al. 2008b). Each item is scored from 0 (''never or hardly ever'') to 3 (''very often or almost constantly''); total scores range from 0 to 30. All patients whose parent/guardian rated the child at or above a score of 12 (ESM+) on the PGBI-10M were invited to participate in the longitudinal portion of the LAMS study. In addition, a comparison group of patients who scored 11 or lower (ESM-) were selected to enroll in the longitudinal portion of the study. Details about subject ascertainment and the rationale for the cut score of 12 on the PGBI-10M are described in Horwitz et al. (2010).

Baseline assessment

Patients rated positively by their parents/guardians for ESM (scoring 12 or higher on the PGBI-10M), and the selected patients who served as the comparison group who did not present with ESM, were given an initial interview. In order to assign diagnoses, participants were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL) (Kaufman et al. 1997) with additional mood onset and offset items derived from the Washington University in St. Louis Kiddie Schedule for Affective Disorders (WASH-U K-SADS) (Geller et al. 1998; Geller et al. 2001).

The LAMS study used the following criteria for BP-NOS: (a) elated mood plus two associated symptoms of mania (e.g., grandiosity, decreased need for sleep, pressured speech, racing thoughts, increased goal-directed activity), or irritable mood plus three associated symptoms of mania; (b) change in the participant's level of functioning (increase or decrease); (c) symptoms must be present for a total of at least four hours within a 24-hour period; and (d) the participant must have had at least four episodes of four hours duration or a total of four days of the above-noted symptom intensity in his/her lifetime. These criteria were also used in the Course and Outcome of Bipolar Youth study (COBY) (Axelson et al. 2006). A licensed child psychiatrist or psychologist reviewed and confirmed all diagnoses. In addition, inter-rater reliability was performed by the interviewers rating taped administrations of the K-SADS-PL-W, Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al. 1984), and the Young Mania Rating Scale (YMRS) (Young et al. 1978). The kappa for K-SADS-PL-W psychiatric diagnoses was 0.82 and more specifically, the kappa for bipolar diagnoses was 0.93. In addition, the kappa for the CDRS-R and the YMRS were ($k = 0.47$) and ($k = 0.41$) respectively, which are within the acceptable levels of item level weighted kappa suggested in the literature (Siegel & Castellan 1988; Cicchetti et al. 2006).

Additionally, demographic information including age, sex, race, ethnicity, and health insurance status were obtained from parents/guardians. A brief medical history was collected and each patient's parent/guardian was asked to provide a complete history of the child's past and currently prescribed psychotropic medications. A more detailed description of the baseline assessment and a description of the 707 children and adolescents who constitute the LAMS cohort are outlined in Findling et al. (2010).

Psychometric scales

Overall functioning was measured by the Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983). Manic and behavioral dysregulation symptoms, regardless of etiology were assessed by parent report with the PGBI-10M as well as the YMRS that was administered to both the parent and child. Similarly, the presence and severity of depressive symptoms, regardless of etiology were assessed using the CDRS-R. Parent-reported scores of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD) subscales were examined with the Child and Adolescent Symptom Inventory-4-Parent Version (CAASI-4R) (Gadow & Sprafkin 2005). Finally, a modified questionnaire that contained the four items from the Outward Irritability Subscale of the Irritability, Depression, Anxiety Scale (IDA) (Snaith et al. 1978) was used to measure irritability.

Service utilization

Information about current and lifetime psychiatric hospitalizations was obtained at baseline using the Services Assessment of Children and Adolescents (SACA). The parent report version of the SACA was used to gather information about the use of child inpatient, outpatient, and school mental health services (Hoagwood et al. 2009).

Statistical analysis

Descriptive statistics, including means and percentages, described the demographic, functional and diagnostic variables. Children and adolescents were divided into two medication groups to be compared; those youth receiving antipsychotic medications and those children receiving other psychotropic medications. Fisher's exact test evaluated associations among categorical variables and medication groups. In addition, independent t-tests examined differences in medication groups on continuous variables. Logistic regression analyses evaluated the relationships of demographic and functional characteristics to the prescription of antipsychotics. The data were modeled in a forward hierarchical fashion beginning with demographic variables entered first followed by diagnostic information, ESM status, aggression and irritability symptoms, and adding site location of the participant last. Variables that had a p value of ≤ 0.15 were retained in subsequent analyses (Hosmer & Lemeshow 2000). Given that prescribing practices might vary by site of service, site was also examined. Finally, exploratory analyses, including independent t-tests and Fisher's exact tests, were performed to examine the differences between the medication groups within youth with an ADHD diagnosis. Analyses were conducted with SPSS Statistics 17.0.

Results

Participant demographics

Of the 707 children and adolescents with an overall mean age of 9.4 (1.9) years, 443 (63%) reported having been prescribed a medication at the baseline assessment. Of these 443 youth, 157 (35%) were currently receiving an antipsychotic and 286 (65%) were prescribed medication other than an antipsychotic. Of note, with the exception of 6 children, all youths had been prescribed their medications prior to their first visit to one of the participating outpatient clinics. Table 1 shows the demographics and functioning characteristics of children prescribed antipsychotics or other psychotropic medications. Youth who were white ($p = 0.004$), covered by non-Medicaid insurance ($p = 0.017$), or had a previous psychiatric hospitalization ($p < 0.001$) were significantly more likely to be prescribed an antipsychotic compared to other psychotropic medications. In addition, youth currently prescribed an antipsychotic received significantly lower CGAS scores (M = 52.4; SD = 9.9) compared to children receiving other medications (M = 55.1; SD = 10.1: t = 2.682, df = 438, $p = 0.008$), indicative of lower overall psychosocial functioning. The two medication groups did not significantly differ in mean age, sex, having ESM of mania at screen or current number of diagnoses.

DSM-IV psychiatric disorders and symptoms

Current diagnoses are shown in Table 2. Children with a diagnosis of psychosis ($p = 0.016$) or bipolar disorder ($p < 0.001$) were more likely to receive an antipsychotic rather than other

Table 1. Demographics of Participants Prescribed Medication at Baseline (N = 443)

n (%) unless otherwise specified	*Not currently prescribed an antipsychotic (n = 286)*	*Currently prescribed an antipsychotic (n = 157)*	*Statistic, p value*
Male (n = 315)	201 (70%)	114 (73%)	Fisher's Exact, p = 0.662
White (n = 321)	194 (68%)	127 (81%)	Fisher's Exact, p = 0.004
Age, mean (standard deviation)	9.4 (1.9)	9.4 (1.9)	t = 0.23, df = 441, p = 0.820
Insurance Status			
Medicaid Only (n = 207)	146 (51%)	61 (39%)	Fisher's Exact, p = 0.017
Other Insurance (n = 236)	140 (49%)	96 (61%)	
Ever Hospitalized	15 (5%)	37 (24%)	Fisher's Exact, p < 0.001
Elevated Symptoms of Mania at screen	244 (85%)	143 (91%)	Fisher's Exact, p = 0.100
Number of Current Diagnoses at Baseline, mean (standard deviation)	2.5 (1.2)	2.6 (1.3)	t = 1.22, df = 441, p = 0.223
Current Children's Global Assessment Scale Score, mean (standard deviation)	55.1 (10.1)	52.4 (9.9)	t = 2.68, df = 438, p = 0.008
University Site Location			
Case Western Reserve University	70 (57%)	53 (43%)	
Ohio State University	84 (71%)	34 (29%)	
University of Cincinnati	67 (55%)	54 (45%)	
University of Pittsburgh	65 (80%)	16 (20%)	Chi-square, p < 0.001

Table 2. Current Diagnoses of Participants Prescribed Medication at Baseline (n = 443)

	Not currently prescribed an antipsychotic (n = 286)	*Currently prescribed an antipsychotic (n = 157)*	*Fisher's Exact Test, p value*
Current Diagnostic Groups			
Any Psychotic Disorder* (n = 13)	4 (31%)	9 (69%)	.016
No Psychotic Disorder (n = 430)	282 (66%)	148 (34%)	
Bipolar Disorder Group Comparisons			
Bipolar 1 Disorder (BP1) (n = 60)	15 (25%)	45 (75%)	< .0005
No BP1 Disorder (n = 383)	271 (71%)	112 (29%)	
Other Bipolar Diagnoses (n = 56)	35 (63%)	21 (38%)	.766
Non-Other Bipolar Diagnoses (n = 387)	251 (65%)	136 (35%)	
Any Bipolar Diagnosis (n = 116)	50 (43%)	66 (57%)	< .0005
No Bipolar Diagnosis (n = 327)	236 (72%)	91 (28%)	
Any Disruptive Behavior Disorder (n = 214)	143 (67%)	71 (33%)	.371
No Disruptive Behavior Disorder (n = 229)	143 (62%)	86 (38%)	
Any Pervasive Developmental Disorder (n = 37)	20 (54%)	17 (46%)	.208
No Pervasive Developmental Disorder (n = 406)	266 (66%)	140 (35%)	
Any Tourette's/Tic Disorder (n = 15)	13 (87%)	2 (13%)	.098
No Tourette's/Tic Disorder (n = 428)	273 (64%)	155 (36%)	
ADHD Group Comparisons			
Any Attention-Deficit Hyperactivity Disorder (ADHD) (n = 361)	252 (70%)	109 (30%)	< 0.0005
No ADHD (n = 82)	34 (42%)	48 (59%)	
ADHD only** (n = 62)	49 (79%)	13 (21%)	.010
No ADHD only diagnosis (n = 381)	237 (62%)	144 (38%)	
Any Depressive Disorder (n = 69)	51 (74%)	18 (26%)	.100
No Depressive Disorder (n = 374)	235 (63%)	139 (37%)	
Any Anxiety Disorder (n = 127)	79 (62%)	48 (38%)	.512
No Anxiety Disorder (n = 316)	207 (66%)	109 (35%)	
More than one current diagnosis at baseline (n = 350)	227 (65%)	123 (35%)	.808
One or no current diagnosis at baseline (n = 93)	59 (63%)	34 (37%)	
Does not meet DSM-IV criteria for a Current Diagnosis (n = 4)	2 (50%)	2 (50%)	.617
Meets DSM-IV criteria for a Current Diagnosis (n = 439)	284 (65%)	155 (35%)	

*One child met criteria for a psychotic disorder and BP1 and 2 children met criteria for a psychotic disorder and BP-NOS, these children were included in the psychotic diagnosis diagnostic group only; **Children in this group may have also met criteria for enuresis or encopresis diagnoses.

medications, but children with a diagnosis of ADHD only ($p = 0.010$) or ADHD diagnosis plus another diagnosis ($p < 0.001$) were more likely to be treated with other medications.

The children receiving antipsychotics at baseline had higher scores on the P-GBI-10M ($p < 0.001$) and YMRS ($p < 0.001$) and scored significantly higher on the ODD ($p = 0.004$) and CD ($p = 0.016$) CAASI-4R subscales compared to youth prescribed other medications. In addition, significantly higher irritability scores were found on the IDA outward irritability subscale in children who were prescribed antipsychotics compared to youth

Table 3. Psychiatric Symptom Measures of Participants Currently Prescribed Medication at Baseline

mean (standard deviation)	*Not currently prescribed an antipsychotic*	*Currently prescribed an antipsychotic*	*t Statistic (df), p value*
Mood Symptoms*			
Baseline P-GBI-10M total score	12.6 (7.0)	15.1 (7.3)	3.62 (438), p < .001
Baseline CDRS-R total score	34.7 (10.7)	34.8 (10.5)	0.10 (441), p = 0.917
Baseline YMRS total score	15.8 (8.2)	21.0 (10.4)	5.81 (441), p < 0.001
CAASI-4R Subscale Scores			
ODD Subscale	15.0 (5.8)	16.6 (5.6)	2.89 (436), p = 0.004
CD Subscale	5.2 (4.9)	6.5 (5.4)	2.42 (437), p = 0.016
ADHD Inattentive Subscale	19.1 (5.9)	18.3 (6.3)	1.21 (438), p = 0.227
ADHD Hyperactive Subscale	17.4 (6.5)	16.5 (7.1)	1.39 (438), p = 0.165
ADHD Combined Subscale	36.5 (10.7)	34.8 (12.2)	1.48 (438), p = 0.141
Irritability, Depression, Anxiety Scale- Outward Irritability Subscale	8.7 (2.6)	9.4 (2.5)	2.86 (440), p = 0.004

*P-GBI-10M = Parent-Completed General Behavior Inventory Mania Form; CDRS-R = Children's Depression Rating Scale-Revised; YMRS = Young Mania Rating Scale; CAASI-4R = Child and Adolescent Symptom Inventory-4-Parent Version Oppositional Defiant Disorder, Conduct Disorder, Attention Deficit Hyperactivity Disorder Subscales.

Table 4. Multivariate Results Examining Factors Associated with Antipsychotic Prescriptions at Baseline

	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			
Variables	*B*	*SE*	*p value*	*B*	*SE*	*p value*	*B*	*SE*	*p value*	*B*	*SE*	*p value*	*B*	*SE*	*p value*	*B*	*SE*	*p value*	*Odds Ratio (95% confidence interval)*
Step 1																			
Sex	−.18	0.24	0.46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
White only race*	0.64	0.27	0.02	0.65	0.28	0.02	0.63	0.28	0.03	0.68	0.29	0.02	0.72	0.29	0.01	.840	0.27	0.002	2.32 (1.37-3.91)
Insured by Medicaid	0.47	0.23	0.04	0.46	0.24	0.05	0.44	0.24	0.06	0.5	0.25	0.04	0.31	0.25	0.21	-	-	-	-
Ever hospitalized	1.9	0.34	<0.001	1.32	0.37	<0.001	1.31	0.38	0.001	1.25	0.38	0.001	1.35	0.38	<0.001	1.32	0.37	<0.001	3.74 (1.80-7.78)
Step 2																			
Bipolar Type 1	-	-	-	1.70	0.34	<0.001	1.72	0.37	<0.001	1.63	0.35	<0.001	1.53	0.35	<0.001	1.51	0.35	<0.001	4.51 (2.27-8.97)
Diagnosis only																			
Other Bipolar Diagnoses excluding BP 1	-	-	-	-	-	-	0.47	0.33	0.16	-	-	-	-	-	-	-	-	-	-
Diagnoses																			
Any Psychosis Diagnosis	-	-	-	1.75	0.64	0.01	1.77	0.65	0.01	1.81	0.65	0.01	1.73	0.65	0.01	1.70	0.65	0.01	5.49 (1.55-19.53)
Any DBD Diagnosis	-	-	-	-	-	-	−.02	0.26	0.95	-	-	-	-	-	-	-	-	-	-
Any PDD Diagnosis	-	-	-	-	-	-	0.53	0.40	0.18	-	-	-	-	-	-	-	-	-	-
Any Tourette's or Tic Diagnosis	-	-	-	-	-	-	−1.10	0.78	0.16	-	-	-	-	-	-	-	-	-	-
ADHD only Diagnosis	-	-	-	-	-	-	−.17	0.40	0.66	-	-	-	-	-	-	-	-	-	-
Step 3																			
ODD CAASI-4R	-	-	-	-	-	-	-	-	-	0.02	0.03	0.59	-	-	-	-	-	-	-
Subscale																			
CD CAASI-4R	-	-	-	-	-	-	-	-	-	−.003	0.03	0.92	-	-	-		-	-	-
Subscale																			
IDA – Outward	-	-	-	-	-	-	-	-	-	0.06	0.06	0.33	-	-	-	-	-	-	-
Irritability																			
Step 4																			
Site				-	-	-	-	-	-	-	-	-	−0.24	0.11	0.03	−0.28	0.11	0.01	0.76 (0.61-0.93)
Model	$X^2=47.46$, $p<.001$, $R^2=0.14$			$X^2=79.53$, $p<.001$, $R^2=0.23$			$X^2=86.23$, $p<.001$, $R^2=0.24$			$X^2=81.76$, $p<.001$, $R^2=0.24$			$X^2=84.17$, $p<.001$, $R^2=0.24$			$X^2=82.57$, $p<.001$, $R^2=0.23$			

*Coding of variables includes: race: 0=other race, 1=white only; insurance variable 0=Medicaid only, 1=other insurance coverage; CGAS: lower scores are indicative of poorer functioning (0-100); Ever hospitalized: 0=no, 1=yes; Diagnosis variables: 0=diagnosis not present, 1=diagnosis present.

BP-NOS, Cyclothymic Disorder, Bipolar Type II; DBD=disruptive behavior diagnoses; PDD=pervasive developmental disorders; ADHD=attention-deficit/hyperactivity disorder; CAASI-4R=Child and Adolescent Symptom Inventory-4-Parent Version; Outward Irritability Subscale of the Irritability, Depression, Anxiety Scale (IDA).

treated with other medications ($p = 0.004$). Participants in both medication groups did not differ in depressive symptomatology measured by the CDRS-R or the three CAASI-4R ADHD subscales (see Table 3).

Multivariate results (Table 4) indicated that being prescribed antipsychotics was independently related to being white, having been previously hospitalized, having a psychotic or bipolar disorder, and differed by site. The child's sex, ESM at screen, Disruptive Behavior Disorders (DBD) diagnoses, Pervasive Developmental Delay (PDD), Tourette's/Tic Disorders, ADHD, irritability symptoms, ODD and CD symptoms did not predict antipsychotic prescriptions for youth in this study. It should be noted that insurance other than Medicaid was related to being prescribed an antipsychotic until site was introduced into the model (see Table 4, Model 5). At two of the sites participants insured exclusively by Medicaid were more frequently prescribed an antipsychotic, whereas at the other two sites the participants were more frequently prescribed an antipsychotic when insured by other insurance providers.

When examining the bipolar diagnoses in detail, we first restricted the bipolar diagnoses to only bipolar 1 disorder in the multivariate model instead of any bipolar disorder diagnoses (Table 4, Model 2). Finally, when examining other bipolar diagnoses excluding bipolar type 1 (BP1) diagnoses (i.e., BP-NOS, BP2, and Cyclothymia) (Table 4, Model 3), other bipolar diagnoses were not associated with the youth being prescribed an antipsychotic.

Variables associated with ADHD and antipsychotic prescriptions

Exploratory analyses indicate that participants with any ADHD diagnosis who were treated with antipsychotics were found to have lower psychosocial functioning as measured by the CGAS ($p = 0.009$), more manic symptoms on the P-GBI-10M ($p = 0.001$) and YMRS ($p < 0.001$), scored significantly higher on the ODD ($p = 0.001$) and CD ($p = 0.005$) CAASI-4R subscales, and higher irritability of the outward irritability subscale of the IDA ($p = 0.004$) compared to children with an ADHD diagnosis not prescribed an antipsychotic as part of their medication regimen (see Table 5). In addition, the ADHD group who were prescribed antipsychotics were also diagnosed with significantly more diagnoses at baseline compared to the ADHD group not prescribed an antipsychotic ($p < 0.001$). Of the 62 with ADHD alone (no comorbidity), 13 (21%) were receiving an antipsychotic. Again, as with the overall sample, youth diagnosed with ADHD did not differ in mean age, depressive symptomatology measured by the CDRS-R or the three CAASI-4R ADHD subscales across medication groups (see Table 5).

When examining comorbid diagnoses, those youth diagnosed with ADHD being treated with antipsychotics were more likely to have a comorbid diagnosis of a bipolar disorder ($p < 0.001$). However, if a child with ADHD was diagnosed with a comorbid diagnosis other than a bipolar diagnosis, he or she was more likely to be treated by a medication other than an antipsychotic. More specifically, children in the ADHD group being treated with a medication other than an antipsychotic were more likely to have a co-morbid disruptive behavior disorder ($p = 0.003$). There were no differences in the number of participants with comorbid psychotic or PDD diagnoses between the ADHD groups (see Table 5).

When examining the subset of 13 children with only ADHD who were prescribed antipsychotics more closely, 12 of the 13 either currently or in the past had a psychostimulant trial. The one child

Table 5. Characteristics and Psychiatric Symptoms in Children Diagnosed with ADHD diagnoses Who Are versus Are Not Prescribed Antipsychotic Medication at Baseline (n = 361)

Characteristics and Psychiatric Symptoms M (SD)	*Not currently prescribed an antipsychotic (n = 252)*	*Currently prescribed an antipsychotic (n = 109)*	*t Statistic (df), p value*
Number of Current Diagnoses at Baseline	2.5 (1.1)	3.0 (1.3)	3.77 (359), p < 0.001
Current CGAS	54.9 (9.9)	52.0 (9.2)	2.61 (358), p = 0.009
Age	9.3 (1.9)	9.2 (1.9)	0.42 (359), p = 0.677
Comorbid Diagnoses n (%)			Fisher's Exact, p value
Any bipolar diagnosis (n = 87)	41 (16%)	46 (42%)	< .001
Any comorbid disorder except bipolar diagnoses (n = 209)	161 (64%)	48 (44%)	< .001
Any disruptive behavior disorder (n = 144)	113 (45%)	31 (28%)	.003
Any psychotic disorder* (n = 8)	4 (2%)	4 (4%)	.250
Any pervasive developmental disorder (n = 15)	11 (4%)	4 (4%)	1.000
Mood Symptoms M (SD)			t Statistic (df), p value
Baseline YMRS** total score	15.9 (8.1)	21.8 (9.6)	6.10 (359), p < .001
Baseline P-GBI-10M total score	12.8 (6.9)	15.6 (7.3)	3.38 (356), p = 0.001
Baseline CDRS-R total score	34.6 (10.6)	34.8 (10.0)	0.11 (359), p = 0.916
CAASI-4R Subscale Scores M (SD)			
ODD Subscale	14.8 (5.8)	17.1 (5.2)	3.49 (354), p = .001
CD Subscale	5.3 (4.9)	7.0 (5.5)	2.81 (355), p = .005
ADHD Hyperactive Subscale	18.3 (6.0)	18.2 (6.4)	0.11 (356), p = 0.916
ADHD Inattentive Subscale	19.6 (5.5)	19.6 (5.2)	0.02 (356), p = 0.984
ADHD Combined Subscale	37.8 (9.6)	37.8 (10.4)	0.05 (356), p = 0.957
Irritability, Depression, Anxiety Scale- Outward Irritability Subscale M (SD)	8.7 (2.6)	9.6 (2.4)	2.89 (358), p = 0.004

*One child met criteria for a psychotic disorder and BP1 and 2 children met criteria for a psychotic disorder and BP-NOS, these children were included in the psychotic diagnosis diagnostic group only; **YMRS = Young Mania Rating Scale; P-GBI-10M = Parent-Completed General Behavior Inventory Mania Form; CDRS-R = Children's Depression Rating Scale-Revised; CAASI-4R = Child and Adolescent Symptom Inventory-4-Parent Version Oppositional Defiant Disorder, Conduct Disorder, Attention Deficit Hyperactivity Disorder Subscales.

not ever treated with a stimulant had persistent ESM with scores greater than 12 on the P-GBI-10M both at screen and at baseline. Past diagnoses in the 13 children included: one who also met DSM-IV criteria for a past diagnosis of depressive disorder not otherwise specified (NOS), another who also met criteria for past diagnoses of transient tic disorder, major depressive disorder (MDD) and anxiety disorder NOS. In terms of current psychiatric symptoms, four of the 13 children had ESM. Three (one of whom also had ESM)) also had elevated scores on the ODD (18 and greater) and/or CD scale (7 and greater). Four of the thirteen children also had high irritability scores (10 and greater) on the Outward Irritability Subscale of the IDA (one of these children also received elevated scores on the ODD and CD scales and another of these children received elevated scores on the ODD, CD scales and had ESM).

Discussion

In our initial description of the 707 youth who comprise the LAMS cohort, we had observed that a substantial number of these children had been receiving an antipsychotic medication, most commonly an atypical antipsychotic agent, at the time of their baseline assessment (Findling et al. 2010). Due to the concerns about the use of this class of drug in young people, particularly in pre-adolescents, a careful examination of factors associated with the prescription of antipsychotics seemed warranted.

Results of bivariate and multivariate analyses showed that several demographic characteristics were associated with the use of antipsychotics in this patient population. These included being white and having a prior psychiatric hospitalization (the latter suggesting greater prior symptom severity). Although other studies have signaled concerns about rates at which antipsychotics are prescribed to children based on Medicaid claims data (Cooper et al. 2004; Olfson et al. 2006; Crystal et al. 2009; Halloran et al. 2010), the LAMS data suggest that having Medicaid as a child's only form of health insurance may not be associated with receiving an antipsychotic medication.

Bivariate analyses showed that more manic symptoms as well as higher degrees of disruptive behavioral difficulties were linked with more frequent antipsychotic treatment. However, based on the multivariate analyses, only children with either a psychotic disorder or those who had strictly-defined, unmodified DSM-IV BPI were found more likely to be treated with an antipsychotic. Perhaps more salient were the findings that antipsychotic medication prescriptions were not associated with ADHD symptoms, an ADHD diagnosis, a disruptive behavior diagnosis or a diagnosis of BP-NOS.

These findings are noteworthy, as they do not fully coincide with results previously reported in studies of claims-based data. Consistent with previous reports, it was relatively common in the LAMS cohort for a child to be prescribed antipsychotic medication in general and an atypical antipsychotic in particular (Findling et al. 2010). However, current results do not support the possible explanation we posed in the Introduction; namely that the increased rates at which a bipolar spectrum diagnosis, rather than a BPI diagnosis, are used on claims data are driving increased antipsychotic use. In addition, in this study, having only an ADHD diagnosis was not predictive of a child receiving an antipsychotic. In fact, the rate of antipsychotic medication in those with ADHD alone (21%) was *lower* than the rate in the whole sample (33%). Of the 707 children participating in LAMS, only 13 had a diagnosis of ADHD without current comorbidity and were receiving an antipsychotic. Moreover, having a disruptive behavior disorder diagnosis, or higher levels of anger and irritability were also not found to be associated with higher rates of antipsychotic use.

Most children with only a diagnosis of ADHD who are receiving an antipsychotic were not receiving the antipsychotic as first-line pharmacotherapy. The past diagnoses in these 13 children did not provide strong evidence for antipsychotic medication. However, it appears that based on symptom ratings, it may be that eight of the 13 children had been prescribed an antipsychotic for manic, irritable or disruptive behavior symptoms. The other five children did not score highly on the symptom scales and thus, the justification for their antipsychotic medication prescriptions was not readily apparent.

Compared to claims-based studies, LAMS, despite its size, encompasses a smaller number of children. In addition, LAMS was conducted at only 10 outpatient sites, all of which were affiliated with academic medical centers, in a relatively narrow geographic range (Ohio and Western Pennsylvania). Although it may be asserted that these factors might limit generalizability to some degree, it should also be noted that all first time users of the 10 participating outpatient clinics in the appropriate age range were eligible for screening and about 80% agreed to complete the screening instrument. These factors allow us to aver that those patients who were screened are representative of children visiting the clinics. Analyses examining demographic characteristic of those who did and did not agree to participate in the longitudinal portion of the study found no statistically significant differences. However, the LAMS cohort was designed to have a substantial number of children with ESM and a comparable group of children without ESM. Finally, the diagnoses reported in these analyses were generated using carefully trained, reliable interviewers and a structured diagnostic interview. We were not able to search children's charts for clinician generated diagnoses and, given that virtually all the children were on their medications prior to the LAMS generated diagnoses, no information was available as to the diagnoses or symptom clusters that generated the prescriptions. In addition, we were not able to determine what effects, if any, the pharmacotherapy had on subsequent symptom expression or diagnostic evolution over time.

Conclusion

As noted above, atypical antipsychotics were commonly prescribed to the group of children who participated in the LAMS study. Interestingly, BPI and psychotic disorders were the only conditions associated with a higher likelihood of being treated with an antipsychotic. As such, these data add to what has been reported in claims-based publications.

The LAMS cohort has several key strengths that allow it to complement data from claims-based studies. First, it was not a sample of convenience *per se*, but was an epidemiologically-ascertained cohort of outpatients (see Horwitz et al. (2010)). Moreover, LAMS participants had meticulous assessments that support the reliability of the diagnoses ascribed and the symptomatic characterization of the study patients. At present, in the absence of additional corroborating data, it would be premature to assert that results of LAMS data and claims-based studies diverge due to a lack of external validity in claims-based studies. However, the result of the LAMS study suggest that such external validation studies of claims-based data could be a meaningful endeavor in the future, particularly when diagnostic- and comorbidity-related questions are being considered.

Clinical Significance

In short, these data suggest that only a few key factors increase the likelihood of a child receiving an antipsychotic medication. The data yielded results that were not necessarily expected. Antipsychotics were not prescribed to the majority of the sample, and these medications were most likely to be prescribed to those with a higher socioeconomic status, psychotic disorders, or BPI. As the LAMS study will be following this group of children longitudinally (Findling et al. 2010; Horwitz et al. 2010), it will be important to consider those parameters associated with continued antipsychotic treatment, new antipsychotic therapy, and discontinuation of antipsychotic medications in this group of children over time. Perhaps, even more importantly, these data will allow careful examination over time of the relationship of use, timing and duration of antipsychotic treatment to symptoms, functioning, and health events in young children.

Disclosures

Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Merck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Rhodes Pharmaceuticals, Sanofi-Aventis, Schering-Plough, Seaside Therapeutics, Sepracore, Shire, Solvay, Sunovion, Supernus Pharmaceuticals, Transcept Pharmaceuticals, Validus, and Wyeth. Dr. Youngstrom has received travel support from Bristol-Myers Squibb. Dr. Birmaher receives or has received research support, and/or acted as a consultant for Schering Plough. He receives royalties from Random House and Lippincott Williams & Wilkins. Dr. Arnold receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Celgene, Cure Mark, Lilly, McNeil, Novartis, Noven, Neuropharm, Organon, Shire, Sigma Tau, and Targacept. Dr. Frazier has received federal funding or research support from, acted as a consultant to, or received travel support from Shire Development, Inc., Bristol-Myers Squibb, National Institute of Health, and NARSAD. Dr. Kowatch receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Forest, AstraZeneca, Current Psychiatry, Merck, Medscape, NARSAD, NICHD, NIMH, Physicians Postgraduate Press and the Stanley Foundation. Drs. Fristad, Axelson, Ryan, and Horwitz and the other authors have no financial interests to disclose.

Statistical Consultants

Eric A. Youngstrom, Ph.D., Department of Psychology at University of North Carolina at Chapel Hill and Case Western Reserve University and Thomas W. Frazier, Ph.D., Center for Pediatric Behavioral Health and Center for Autism, Cleveland Clinic.

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Address correspondence to:
Robert L Findling, M.D.
University Hospitals Case Medical Center
Case Western Reserve University School of Medicine
Child and Adolescent Psychiatry
10524 Euclid Avenue, Suite 1155
Cleveland, OH 44106

E-mail: robert.findling@uhhospitals.org