Extent, Time Course, and Moderators of Antipsychotic Treatment in Youth With Mood Disorders:

Results of a Meta-Analysis and Meta-Regression Analyses

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ABSTRACT

Objective: To meta-analytically examine the trends and correlates of antipsychotic use in youth with mood disorders.

Methods: Systematic literature search without language restriction in PubMed/MEDLINE/PsycINFO from database inception through March 2015 using the following search terms: (*antipsychotic** OR *neuroleptic** OR "*dopamine blocker**" OR *antidopaminergic*) AND (*child** OR *adolescen** OR *pediatric* OR *youth*) AND (*prescription** OR *prescrib** OR *use* OR *utilization* OR *database* OR *pharmacoepidemiolog** OR *frequency* OR *rate* OR *rates*). Random effects meta-analysis and meta-regression analyses were conducted.

Study Selection: Included were studies reporting on the frequency of (1) mood disorders in antipsychotic-treated youth (≤ 19 years) and (2) antipsychotic use in youth with mood disorders.

Data Abstraction: Two independent investigators abstracted data on study, patient, and treatment characteristics.

Results: Forty-one studies were meta-analyzed (N = 518,919, mean ± SD age = 12.8 ± 1.8 years, males = 65.7%). Altogether, 24.2% of antipsychotic-treated youth had a mood disorder diagnosis (studies = 34, depression spectrum disorder = 10.9%, bipolar spectrum disorder = 13.6%). In longitudinal studies, the overall proportion increased significantly from 17.3% in 2000 (range, 1996–2009) to 24.5% in 2006 (range, 2004–2011) (odds ratio [OR] = 1.50; 95% confidence interval [CI], 1.26–1.79; $P < .0001$). This increase was driven entirely by bipolar spectrum diagnoses (2001 = 11.1%, 2006 = 16.3%, $P < .0001$), rather than depression spectrum diagnoses (2001 = 9.1%, 2007 = 9.2%, $P = .77$). Among youth with mood disorders (8 studies), 24.0% received antipsychotics (depression spectrum disorder = 4.6%; bipolar spectrum disorder = 44.0%).

Conclusions: The proportion of youth with mood disorder diagnoses increased significantly among antipsychotic-treated youth, driven entirely by an increase in youth with bipolar spectrum disorders. Progress in understanding the reasons for these trends and for an evaluation of the appropriateness of the observed antipsychotic prescribing requires more detailed information than is available in traditional pharmacoepidemiologic databases.

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Concern has been raised regarding the increasing use of psychotropic medications in children and adolescents.[1–3] The widespread use of antipsychotics plays a relevant role in the rise of psychopharmacologic treatments in the pediatric population,[4] mainly due to a significant increase in the frequency of second-generation antipsychotic (SGA) prescriptions in recent years.[1,4–9] This trend can partly be interpreted as a consequence of the growing data supporting the efficacy of antipsychotics in youth for the treatment of specific psychotic and nonpsychotic psychiatric conditions, including schizophrenia, bipolar mania, irritability and aggression associated with autistic disorders, and Tourette disorder.[10–17]

Despite the lack of regulatory approval and evidence for the efficacy of antipsychotic treatment for psychiatric conditions in youth other than the above-mentioned, the increased evidence-based use of antipsychotics has been paralleled by a corresponding rise in off-label prescriptions.[18–20] The risk for severe weight gain and metabolic, as well as potentially chronic neuromotor side effects of SGAs[21–26] plus the uncertainty over the long-term effects of antipsychotic exposure on the developing human brain[27–30] warrant a comprehensive analysis of this prescribing trend.

Although several studies have reported on the diagnostic correlates of antipsychotic prescriptions in youth, the available evidence is limited to individual studies. In order to provide a more comprehensive view of antipsychotic use in youth with mood disorders, we conducted a meta-analysis and meta-regression analyses focusing on the proportion of youth with mood disorders in antipsychotic-treated pediatric samples as well as on the proportion of antipsychotic use in youth with mood disorders. The latter diagnostic category represents a complex area for antipsychotic use, encompassing both an evidence-based indication, namely manic episodes of bipolar I disorder in children and adolescents aged 10–17 years,[31] and many

more off-label indications, such as bipolar II disorder, bipolar disorder not otherwise specified, and all depressive spectrum disorders, for which efficacy and safety data in children and adolescents are lacking.

METHODS

Data Sources

A systematic literature search was conducted in PubMed/MEDLINE/PsycINFO, from database inception through March 2015, without language restrictions, by 2 authors independently (C.C., S.Y.P.), using the following search terms: (*antipsychotic** OR *neuroleptic** OR "*dopamine blocker**" OR *antidopaminergic*) AND (*child** OR *adolescen** OR *pediatric* OR *youth*) AND (*prescription** OR *prescrib** OR *use* OR *utilization* OR *database* OR *pharmacoepidemiolog** OR *frequency* OR *rate* OR *rates*). The electronic search was supplemented by a manual review of reference lists from eligible publications and relevant reviews. Whenever necessary, authors were contacted to provide additional information.

Study Selection

Inclusion criteria were (1) ≥ 100 children and adolescents, (2) samples of youth aged ≤ 19 years, and (3) reporting data on the frequency of either (a) mood disorders in youth treated with antipsychotics or (b) antipsychotic use in youth with mood disorders (ie, bipolar spectrum disorders and depressive spectrum disorders, irrespective of presence of psychotic features). Whenever possible, studies that combined adult and pediatric populations were retained if separate data for the population aged ≤ 19 years were either reported or could be obtained from the authors.

Outcomes and Data Abstraction

The coprimary outcomes of our meta-analysis included period prevalence data in 2 distinct populations: (1) prevalence of mood disorders in general as well as of bipolar spectrum disorders and depressive spectrum disorders specifically among those treated with antipsychotics and (2) prevalence of antipsychotic use within youth with mood disorders in general and, more specifically, in youth with bipolar spectrum disorders and with depressive spectrum disorders. As a secondary outcome, we explored time trends of antipsychotic use in all longitudinal studies within the 2 subgroups using the data from the first reported time until the last reported time. In addition to these frequency data, information was abstracted on the study and sample characteristics. Data were extracted by 2 authors independently (C.C., S.Y.P.) using the following categories: author; year of study publication; country; year of data collection; setting of the study (inpatient vs outpatient vs mixed); number of patients; age (mean and range), sex, and race of the sample; and diagnosis (mood disorders vs bipolar spectrum disorders vs depressive spectrum disorders). Any inconsistencies were resolved by consensus or involvement of a third author (B.G., C.U.C.).

Clinical Points

- Antipsychotic prescriptions have been rising in youth, but comprehensive data are lacking in regard to the frequency and time trends of antipsychotic use in youth with mood spectrum disorders.
- Meta-analytic studies now show that the proportion of youth with mood spectrum disorders increased significantly among antipsychotic-treated youth, a trend driven entirely by youth with bipolar spectrum disorders.
- Altogether, 44% of youth with bipolar spectrum disorders received antipsychotics, indicating that studies are needed that examine the reasons for and appropriateness of the observed antipsychotic prescribing rates.

Statistical Analyses

We conducted a random effects meta-analysis of outcomes for which 3 or more studies contributed data, using Comprehensive Meta-Analysis V3 (https://www.meta-analysis.com). In the primary analyses, we calculated an aggregate event rate (prevalence) for all studies reporting percentage of (1) mood disorder diagnoses (mood disorders, bipolar spectrum disorders, depressive spectrum disorders) among antipsychotic-treated youth and (2) antipsychotic-treated individuals among youth with a mood disorder diagnosis (mood disorders, bipolar spectrum disorders, depressive spectrum disorders). To assess potential time trends, data were arranged into the following period intervals according to the year of data collection: 1996–2000; 2001–2005; 2006–2010; and 2011–2015. For studies in which the data collection spanned multiple years, the data were assigned to the median year of data collection. For longitudinal studies, odds ratios (ORs) were calculated to compare the time trends by pooling data from the first to the last time point or period for which data were reported. Furthermore, we performed a sensitivity analysis of longitudinal studies with nonoverlapping time periods. Moreover, mixed random effects meta-regression analyses of continuous variables were conducted to investigate moderators of antipsychotic use in youth with mood disorders. Whenever possible, we conducted exploratory subgroup analyses to investigate the prevalence of mood disorders in antipsychotic-treated youth using studies reporting data for (1) outpatients only, (2) children aged 0–12 years, or (3) studies conducted in the United States. All tests were 2-tailed with α set at .05, without adjustments for multiple comparisons.

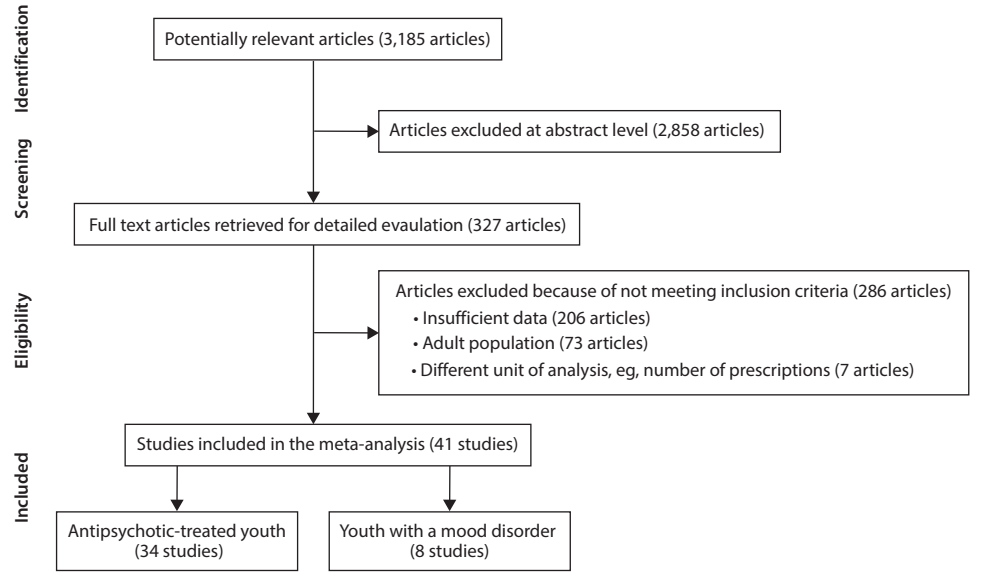
RESULTS

Search and Study Characteristics

The literature search identified 3,185 articles. Of these, 2,858 were excluded based on the title and abstract. Of 327 full-text articles, 206 were excluded for reporting insufficient data, 73 for reporting on adult populations, and 7 for using the number of prescriptions as unit of analysis (Figure 1). Thus, 41 studies were used for the final analysis, including 518,919 patients.

Thirty-four studies reported data on the frequency of mood disorder diagnoses among antipsychotic-treated

Figure 1. Study Flowchart



youth,[19,20,32–63] including a total of 315,300 antipsychotic-treated youth (Table 1). These studies were published between 2004 and 2015, covering prescription periods from 1996 to 2011. The sample sizes ranged from 103 to 223,009 patients (median = 1,792 patients). The majority of studies were conducted in the United States (22 studies), followed by Canada (6 studies), Europe (4 studies), New Zealand (1 study), and Taiwan (1 study). Twenty-two studies reported data from inpatients and outpatients, while 8 reported data on outpatients only, and 4 included inpatients only. Twenty-seven studies included mixed child and adolescent samples, whereas 5 reported on children only (0–12 years old), and 2 reported on adolescents only (11–18 years old).

Altogether, 8 studies reported data on the frequency of antipsychotic prescriptions in youth with mood disorders.[19,64–70] These studies were published between 2004 and 2013, covering prescription periods from 1997 to 2007. The sample sizes ranged from 139 to 171,888 patients (median = 7,499 patients). The majority of studies were conducted in the United States (6 studies), 1 was conducted in Canada, and 1 was conducted in India. All studies had mixed child and adolescent samples, except for 1 study that reported on adolescents only.

Subject Characteristics

Table 2 displays study design and demographic, illness, and treatment characteristics in 2 separate populations: (1) antipsychotic-treated subgroup (34 studies, total patients = 315,300, mood disorder patients = 96,425) and (2) mood disorder subgroup (8 studies, total patients = 225,471, antipsychotic-treated patients = 34,205).

In the antipsychotic-treated study subgroup (34 studies), the mean ± SD patient age was 12.8 ± 1.8 years (14 studies), 66.9% ± 11.5% of patients were male (25 studies), and 50.9% ± 9.7% were white (14 studies). All except 1 of the studies that reported data on insurance coverage were conducted in the United States. Altogether, 97.3% ± 11.9% of the sample were Medicaid-insured (17 studies), while only 2.1% ± 13.5% were covered by private insurance (18 studies). Of note, 11 studies included Medicaid patients only (n = 240,678). Among the 18 studies reporting insurance status, no subject was uninsured. A diagnosis of attention-deficit/hyperactivity disorder (ADHD) was reported in 42.1% ± 12.3% of the antipsychotic-treated sample (27 studies). Disruptive behavior disorders accounted for 25.3% ± 14.6% of the antipsychotic-treated sample (24 studies), anxiety disorders for 9.6% ± 12.6% (23 studies), autism spectrum disorders or intellectual disability for 6.3% ± 3.6% (29 studies), and psychotic disorders for 4.6% ± 5.8% (33 studies). SGA prescriptions predominated (98.7% ± 3.6%, 17 studies). Specifically, risperidone was the most commonly prescribed antipsychotic (43.4% ± 8.7%, 15 studies), followed by aripiprazole (26.2% ± 4.7%, 9 studies), quetiapine (21.4% ± 5.6%, 12 studies), olanzapine (6.3% ± 4.4%, 11 studies), and ziprasidone (3.5% ± 0.8%, 8 studies). A mean of 4.6% ± 13.4% of patients had antipsychotic polypharmacy (7 studies).

In the mood disorder study subgroup (8 studies), the mean patient age was 13.1 years (1 study), and 52.8% ± 2.3% of patients were male (4 studies). There were no data regarding the sample's race or ethnicity. Approximately 1 of 4 patients had a comorbid diagnosis of ADHD (26.6% ± 2.7%, 3 studies), 15.1% ± 1.9% had a disruptive behavior disorder (3 studies), and 11.1% ± 4.8% had an anxiety disorder (3 studies).

Frequencies and Trends of Mood Disorder Diagnoses Among Antipsychotic-Treated Youth

Among antipsychotic-treated youth, the pooled prevalence of mood disorders was 24.2% ± 22.6% (including data

Table 1. Design and Population Characteristics of Studies Reporting Quantitative Data in Youth With Mood Disorders Receiving Antipsychotics

Author/Citation Year/ Country	Design	Time	Cohort	% on Antipsychotics With Mood Disorders/BD/DEP T1 (T2)	T1 (T2), N	Age, y		% Male T1 (T2)	% White
						Range	Mean ± SD		
Youth Receiving Antipsychotics									
Alessi-Severini et al[32] 2012, Canada	LT	1999–2008	Manitoba Population Health Research Data Repository	8.3 (16.9)/NR/NR	594 (2240)	0–18	NR	NR	NR
Baeza et al[33] 2014, Spain	LT	2005–2007	Pediatric psychiatry department inpatient and outpatient charts	NR/14.3/12.8	265	4–17	14.4 ± 2.9	54.7	NR
Maršanić et al[34] 2012, Croatia	CR	2009	Pediatric psychiatry department outpatient charts	NR/NR/5.7	106	0–18	13.9 ± 2.9	77.4	NR
Christian et al[35] 2013, USA	CR	2011	A+KIDS registry data and Medicaid prescription claims	35.6/NR/NR	5,532	< 12	NR	73.0	59.0
Connolly et al[36] 2015, USA[a]	CR	2005–2011	Nationwide commercial United Healthcare insurance claims database; new SGA users	NR/46.9/22.6	42,328	5–18	NR	NR	NR
Constantine et al[37] 2010, USA	LT	2002–2007	Florida's Medicaid claims data	10.3/5.6 BD I/4.8	23,183	6–17	NR	68.5	45.9
Constantine et al[38] 2011, USA	CR	2003–2004	Florida's Medicaid claims data; new antipsychotic users	NR/5.3/NR	528	0–5	NR	73.3	34.9
Cooper et al[39] 2004, USA[a]	LT	1996; 2001	TennCare; new antipsychotic users	NR/14.2/7.2	6,022	2–18	11.5 ± 4.2	64.4	NR
Crystal et al[40] 2009, USA	CR	1996–2006	Medicaid Analytic eXtracts; Thomson MarketScan data	NR/14.2 (18.7)/NR; NR/11.5 (25.2)/NR[b]	51,442 (105,619)	6–17	NR	69.2	NR
Deurell et al[41] 2008, Denmark	CR	2002	National survey of inpatients and outpatients	4.1/NR/NR	244	4–18	14.5 ± 3.1	63.0	NR
DosReis et al[42] 2011, USA	CR	2003	Mid-Atlantic Medicaid database	NR/20.8/33.8	16,969	0–19	NR	69.8	67.3
Findling et al[43] 2011, USA	LT	2005–2008	Children prescribed antipsychotics in the Longitudinal Assessment of Manic Symptoms cohort	NR/42.0/11.5	157	6–12	9.4 ± 1.9	73.0	81.0
Fullerton et al[44] 2012, USA	CR	1996–2005	Administrative data from Florida's Medicaid program; children diagnosed with ADHD	NR/28.2 (51.4)/11.2 (20.6)	1,377 (4,817)	3–17	NR	NR	NR
Ghate et al[45] 2012, USA	LT	2004–2009	General Electric Centricity electronic medical record database; adolescents on SGA monotherapy	NR/11.9/3.9	3,038	12–19	15.5 ± 2.2	54.2	34.0
Halloran et al[46] 2010, USA	CR	2002–2005	Administrative data from a private insurance company in a Midwestern state	65.0/NR/NR	2,194	2–18	12.6 ± 3.8	64.0	NR
Harrison-Woolrych et al[47] 2007, New Zealand	CR	2003	Data from the Intensive Medicines Monitoring Program	5.0/NR/NR	265	2–15	NR	NR	NR
Hong and Bishop[48] 2010, USA[a]	CR	2005–2008	Chart review from a Midwest academic medical center; youth newly prescribed antipsychotics	NR/43.4/17.1	152	5–18	14.5 ± 2.4	49.3	18.4
Hsu et al[49] 2013, Taiwan	CR	1997–2005	Taiwan's National Health Insurance database; youth prescribed SGAs	NR/10.9/9.5	211	0–17	NR	73.9	NR
Linton et al[50] 2013, Canada	CR	2008–2009	Department of Pharmacy's inpatient computer database, British Columbia Children's Hospital	NR/8.6/13.7	139	< 18	12.9 ± 3.0	63.0	NR
Matone et al[19] 2012, USA	LT	2002–2007	Medicaid Analytic eXtract; inpatients and outpatients treated with SGAs	Results vary depending on age group	126,106 (223,009)	3–18	NR	NR	NR
Nielsen et al[51] 2014, Denmark	LT	1999–2010	Danish Psychiatric Central Research Register, Danish Prescription Database	15.6/NR/NR	7,253	< 18	NR	58.3	NR
Olfson et al[52] 2010, USA	LT	1999–2007	MarketScan Research Databases	NR/10.5 (8.7)/1.3 (3.4)	269 (1,202)	2–5	NR	81.9 (77.9)	NR
Panagiotopoulos et al[53] 2009, Canada	CR	2005–2007	Retrospective chart review of psychiatric emergency admissions (CAPE Unit) at British Columbia Children's Hospital; adolescents prescribed SGAs	25.0/NR/NR	163	11–16	13.7	62.0	NR
Patel et al[54] 2006, USA	LT	1998–2001	Texas Medicaid Vendor Drug database and Texas Department of Mental Health and Mental Retardation Client Assignment and Registration System	NR/15.8 (20.3)/28.7 (25.3)	2,355 (2,506)	0–19	NR	70.8	46.0

(continued)

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Table 1 (continued). Design and Population Characteristics of Studies Reporting Quantitative Data in Youth With Mood Disorders Receiving Antipsychotics

Author/Citation Year/ Country	Design	Time	Cohort	% on Antipsychotics With Mood Disorders/BD/DEP T1 (T2)	T1 (T2), N	Age, y		% Male T1 (T2)	% White
						Range	Mean ± SD		
Pathak et al[55] 2010, USA	CR	2001–2005	Medicaid administrative claims database; outpatients receiving new treatment with SGAs	NR/NR/45.1	11,700	0–18	NR	34.0	44.9
Procyshyn et al[56] 2014, Canada	LT	2008–2009	Department of Pharmacy's inpatient computer database, British Columbia Children's Hospital	6.8 (11.0)/8.7 (17.9)	103 (173)	5–18	NR	63.0	NR
Rettew et al[57] 2015, USA	CR	2012	Medicaid-insured children in Vermont survey	37.2 /11.5/NR	647	3–18	13.2 ± 3.1	70.2	NR
Robst et al[58] 2012, USA	CR	2003–2006	Florida's Medicaid claims, return to out-of-home treatment in statewide psychiatric inpatient programs, therapeutic foster/group care	33.4/NR/NR	1,158	6–17	NR	60.5	NR
Ronsley et al[59] 2012, Canada	LT	2007–2010	Retrospective chart review from the Child and Youth Mental Health Team, Vancouver	NR/16.9 (17.3)/15.1 (25.9)	172 (81)	5–18	14.5 ± 3.7	61.6 (51.9)	49.9
Ronsley et al[60] 2013, Canada	LT	1996–2011	PharmaNet database	NR/NR/12.8	641 (1,471)	0–18	NR	NR	NR
Saldaña et al[61] 2014, USA	CR	2010–2011	Chart review from the psychiatric service at a large urban children's hospital	65.4/NR/NR	840	9–17	NR	NR	NR
Sohn et al[62] 2015, USA	CR	2007–2009	Retrospective chart review from a health insurance plan in the United States		6,236	4–18	NR	61.0	NR
Wonodi et al[63] 2007, USA	CR	2003–2006	Charts from the Children's Side Effects Clinic, Baltimore; inpatients, outpatients, and patients treated in residential facilities	NR/NR/88.0	118	6–18	11.9 ± 2.8	77.1	NR
Zito et al[20] 2013, USA	LT	1997–2006	Medicaid administrative claims data from a Midatlantic state	NR/9.6 (14.8)/10.5 (11.5)	1,860 (9,556)	2–17	NR	69.0	44.0
Subtotal N = 34	CR = 20 LT = 14				315,300 (349,472)	0–19	12.8 ± 1.8	66.9	47.2
Youth With a Mood Disorder Diagnosis									
Bhowmik et al[64] 2013, USA	LT	2003–2007	Medicaid Analytic eXtract files	49.1/49.1/NR	6,869	6–18	NR	NR	NR
Castilla-Puentes[65] 2008, USA	LT	2000–2003	Integrated Healthcare Information Services	46.1/46.1/NR	8,129	0–18	NR	53.7	NR
Dusetzina et al[66] 2012, USA	LT	2005–2007	Thomson Reuters MarketScan Commercial Claims and Encounters database	33.2 (34.5)/33.2 (34.5)/NR	10,565 (11,219)	0–17	NR	55.6	NR
Libby et al[67] 2007, USA	CR	1998–2005	PharMetrics Patient-Centric Database	0.8–1.5/NR/0.8–1.5	65,349	5–18	NR	NR	NR
Matone et al [19] 2012, USA	LT	2002–2007	Medicaid Analytic eXtract Medicaid enrollees	Results vary depending on age group	131,068 (171,888)	3–18	NR	NR	NR
Olfson et al[68] 2009, USA	CR	2004–2005	MarketScan Research Databases	23.8/23.8/NR	2,907	0–17	NR	49.9	NR
Rajeev et al[69] 2004, India	CR	1997–2001	Chart review of the Child and Adolescent Psychiatry Services of the National Institute of Mental Health and Neurosciences, Bangalore	68.0/68.0/NR	139	5–15	13.1 ± 2.5	60.0	NR
Sewitch et al[70] 2009, Canada	CR	2000–2001	Quebec Health Insurance Board	6.7/NR/6.7	445	12–16	NR	NR	NR
Subtotal N = 8	CR = 4 LT = 4				225,471 (248,456)	0–18	13.1 ± 2.5	52.8	NR
Total: 41 studies[c]	CR = 24 LT = 17		Description of youth receiving antipsychotics (N = 34), youth with mood disorder diagnoses (BD/depression) (N = 8)		518,919	Age range 0–19	12.8 ± 1.8	65.7%	

[a]New users. [b]The 2 entries refer to the 2 different data sets used in the study, namely Medicaid Analytic eXtracts and Thompson MarketScan data. [c]The total number of studies was 41. One study (Matone et al[19]) was used twice as it provided data on antipsychotic use in youth with mood disorders and on mood disorders in antipsychotic-treated youth.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, CR = cross-sectional study, DEP = depressive disorder, LT = longitudinal study, NR = not reported, RC = retrospective cohort study, SGA = second-generation antipsychotic, TennCare = Tennessee's managed care program for Medicaid enrollees and the uninsured, T1 = first reported time, T2 = last reported time.

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Table 2. Demographic, Clinical, and Treatment Characteristics of Antipsychotic-Treated Cohorts of Youth With Mood Disorders

	Antipsychotic-Treated Youth					Youth With Mood Disorders/BD/DE			
Variable	No. of Studies	Cross-Sectional +T1	No. of Studies	T1	T2	No. of Studies	Cross-Sectional +T1	No. of Studies	T1
Time[a]	34	2,003	9	2,000	2,006	8	2,001	4	2,001
Total cohort, N	34	315,300	9	184,650	349,472	8	225,471	4	206,982
Subjects with a mood disorder, n	34	96,425	9	38,249	78,729	8	225,471	4	206,982
Subjects with a mood disorder on antipsychotics, n	34	96,425	9	38,249	78,729	8	34,205	4	26,267
Age, y	14	12.8 ± 1.8	1	…		1	13.1	0	…
Male, %	25	66.9 ± 11.5	5	72.2 ± 0.7	68.7 ± 1.3	4	52.8 ± 2.3	0	…
White, %	14	50.9 ± 9.7	3	46.1 ± 0.8	48.8 ± 1.1	0	…	0	…
US studies, no. (%)		22 (61.8)		5 (55.6)			6 (75.0)		4 (100.0)
Insurance, %									
Private	18	2.1 ± 13.5	5	0.2 ± 4.7	5.1 ± 23.5	4	8.9 ± 31.8	2	7.5 ± 32.2
Medicaid	17	97.3 ± 11.9	5	99.8 ± 4.66	94.9 ± 23.5	4	91.1 ± 31.8	2	92.5 ± 32.2
Foster care	4	27.5 ± 2.1	2	32.2 ± 2.4	25.3 ± 1.9	0	…	0	…
Uninsured	18	0.0 ± 0.0	5	0.0 ± 0.0		4	0.0 ± 0.0	2	0.0 ± 0.0
Other diagnoses, %									
ADHD	27	42.1 ± 12.3	8	42.7 ± 12.7	44.1 ± 13.3	3	26.6 ± 2.7	1	25.5
DBDs	24	25.3 ± 14.6	8	23.6 ± 3.3	20.6 ± 5.0	3	15.1 ± 1.9	1	14.2
ASD/ID	29	6.3 ± 3.6	8	5.4 ± 1.6	5.3 ± 2.1	0	…	0	…
Anxiety disorders	23	9.6 ± 12.6	5	1.4 ± 2.4	1.4 ± 1.5	3	11.1 ± 4.8	0	…
Psychotic disorders	33	4.6 ± 5.8	8	2.0 ± 2.2	1.5 ± 1.7	1	25.4	0	…
Antipsychotic prescriptions, %									
FGA	17	7.0 ± 7.4	4	9.6 ± 7.8	3.4 ± 0.2	1	50.4	0	…
SGA	17	98.7 ± 3.6	5	98.6 ± 3.8	99.6 ± 0.6	3	11.4 ± 16.5	2	11.4 ± 17.5
Risperidone	15	43.4 ± 8.7	3	75.1 ± 10.3	67.2 ± 4.5	1	20.14	0	…
Aripiprazole	9	26.2 ± 4.7	1	0	1.2	0	…	0	…
Quetiapine	12	21.4 ± 5.6	3	9.2 ± 6.7	20.6 ± 8.6	0	…	0	…
Olanzapine	11	6.3 ± 4.4	3	24.0 ± 7.3	26.1 ± 7.3	1	2.16	0	…
Ziprasidone	8	3.5 ± 0.8	1	0	2.9	0	…	0	…
Combinations	7	4.6 ± 13.4	2	5.0 ± 2.6	9.8	2	37.3 ± 17.7	0	…

[a]Time of the study is the total mean of medians from individual study periods; all other values are weighted means ± SDs.
Symbol: … = not applicable.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, BD = bipolar disorder, DBD = disruptive behavior disorder, DEP = depressive disorder, FGA = first-generation antipsychotic, ID = intellectual deficiency (study conducted in India), SGA = second-generation antipsychotic, T1 = first reported time, T2 = last reported time.

Table 3. Percentage of Youth Diagnosed With Mood Disorders Among Youth Treated With Antipsychotic Medications

	Antipsychotic-Treated Youth						
	T1 + Cross-Sectional Data	Longitudinal Data		Longitudinal + Cross-Sectional Data			
Diagnosis		T1	T2	1996–2000	2001–2005	2006–2010	2011–2015
Mood disorders							
Mean % ± SD	24.2 ± 22.6	17.3 ± 13.7	24.5 ± 14.4	20.3 ± 14.8	25.4 ± 20.8	24.6 ± 23.5	29.6 ± 18.4
No. of studies	34	9		7	15	16	3
OR (95% CI)		1.5 (1.2–1.7)*					
Bipolar spectrum disorders							
Mean % ± SD	13.6 ± 6.2	11.1 ± 5.6	16.3 ± 8.7	15.8 ± 6.3	14.5 ± 9.6	14.7 ± 8.0	NR
No. of studies	19	7		5	7	11	
OR (95% CI)		1.6 (1.4–1.7)*					
Depressive spectrum disorders							
Mean % ± SD	10.9 ± 11.1	9.1 ± 12.0	9.2 ± 11.1	12.4 ± 11.8	11.6 ± 12.7	7.5 ± 10.6	NR
No. of studies	18	7		5	7	9	
OR (95% CI)		1.0 (0.8–1.2)					

*$P \leq .05$.
Abbreviations: CI = confidence interval, NR = not reported due to insufficient number of studies, OR = odds ratio, T1 = first reported time, T2 = last reported time.

reported for combined mood disorders, bipolar spectrum disorders, or depression spectrum disorders) (Table 3).

In studies reporting disorder-specific data, 13.6% ± 6.2% of antipsychotic-treated youth were diagnosed with a bipolar spectrum disorder (18 studies) and 10.9% ± 11.1%, with a depression spectrum disorder (17 studies, $P = .34$). In studies with longitudinal data, there was a statistically significant increase in the proportion of mood disorder diagnoses among antipsychotic-treated youth from 17.3% in 2000 (range, 1996–2009) to 24.5% in 2006 (range, 2004–2011) (OR = 1.50; 95% confidence interval [CI], 1.26–1.79; $P < .0001$). In studies with longitudinal data for bipolar

spectrum disorders specifically, there was a statistically significant increase in the proportion of bipolar spectrum diagnoses among antipsychotic-treated youth from 11.1% in 2001 (range, 1996–2009) to 16.3% in 2006 (range, 2001–2010) (OR = 1.57; 95% CI, 1.42–1.74; $P < .0001$), whereas this trend was not observed for depression spectrum diagnoses (from 9.1% ± 12.0% in 2001 to 9.2% ± 11.1% in 2007; OR = 0.96; 95% CI, 0.76–1.22; $P = .77$). When reanalyzing the data, removing 3 studies with overlapping time periods (ie, 6 studies with T1 range, 1996–2002 vs T2 range, 2004–2011), the results remained virtually identical (mood disorders: OR = 1.53; 95% CI, 1.26–1.90; $P < .0001$; bipolar spectrum disorder subgroup: OR = 1.62; 95% CI, 1.45–1.81; $P < .0001$; depressive spectrum disorder subgroup: OR = 0.86; 95% CI, 0.65–1.14; $P = .32$). Numerically, the prevalence of mood disorders grew steadily among antipsychotic-treated youth in studies reporting cross-sectional data from the late 1990s (1996–2000: 20.3% ± 14.8%) to the 2000s, except for a slight decrease observed between the periods 2001–2005 to 2006–2010 (2001–2005: 25.4% ± 20.8%; 2006–2010: 24.6% ± 23.5%; 2011–2015: 29.6% ± 18.4%). The same trend was not apparent in cross-sectional studies specifically reporting on the prevalence of either bipolar spectrum disorders or depressive spectrum diagnoses.

Moderators of Mood Disorder Diagnoses Among Antipsychotic-Treated Youth

There was a near-significant positive association between larger proportions of patients with mood disorder diagnoses among antipsychotic-treated youth and more recent year of prescription ($r^2 = 0.20$, $P = .051$). In exploratory subgroup analyses, a larger proportion of patients with mood disorder diagnoses among antipsychotic-treated youth was moderated by more recent year of data collection in youth aged 0–12 years ($r^2 = 0.43$, $P = .032$), in outpatient populations in the United States ($r^2 = 0.09$, $P = .0096$), and in female patients ($r^2 = 0.41$, $P = .014$). When the moderator analyses were replicated for the subgroups of bipolar spectrum and depression spectrum disorders separately, none of the results were statistically significant.

Antipsychotic Prescribing Patterns Among Youth With Mood Disorders

The mean prevalence of antipsychotic prescriptions among youth diagnosed with a mood disorder was 24.0% ± 30.0%. The mean antipsychotic prevalence was significantly higher in bipolar spectrum populations than in depressive spectrum samples (44.0% ± 9.9% vs 4.6% ± 13.5%, respectively, $P < .001$). Due to lack of data, we were not able to examine time trends.

Moderators of Antipsychotic Prescribing Patterns Among Youth With Mood Disorders

Higher antipsychotic treatment among youth diagnosed with mood disorders was moderated by smaller study sample sizes ($r^2 = 0.46$, $P = .0105$). No other variables were significantly correlated with antipsychotic prescription frequency.

DISCUSSION

The main findings of this first meta-analysis of frequencies and time trends of mood disorder diagnoses among antipsychotic-treated youth and of antipsychotic use in youth diagnosed with mood disorders are: (1) about one-quarter of antipsychotic-treated youth had a mood disorder diagnosis (depression spectrum disorder = 11%; bipolar spectrum disorder = 14%); (2) the proportion of antipsychotic-treated youth with a mood disorder diagnosis increased significantly from 17% in 2000 to 25% in 2006; (3) this increase was driven entirely by bipolar spectrum diagnoses (11% in 2001 to 16% in 2006), while the proportion of antipsychotic-treated youth with depression spectrum diagnoses remained virtually unchanged (9% in both 2001 and 2007); (4) the increase in the proportion of antipsychotic-treated youth with a mood disorder diagnosis was generalized across studies from the United States and other areas of the world; (5) no significant moderators were identified for the proportion of youth with mood disorder diagnoses among antipsychotic-treated youth in the overall sample; and (6) among youth with mood disorders, 24% received antipsychotics (depression spectrum disorder = 5%; bipolar spectrum disorder = 44%).

Mood disorders, encompassing both depression and bipolar spectrum disorders with the respective wide range of clinical severity and functional impairment,[71] are linked to a significant share of antipsychotic prescriptions in youth. The growing attention directed at bipolar disorder in children and adolescents in the past 2 decades, regulatory approval of 5 SGAs for the treatment of bipolar mania in children and adolescents aged 10–17 years in the United States in the last decade,[10] and the increasing number of bipolar spectrum disorder diagnoses reported in the pediatric population[72,73] might help explain the rise of mood diagnoses among antipsychotic-treated youth. The acknowledgment of an increase in the ratio of visits for pediatric bipolar disorder by as much as 40-fold from 1994 to 2003[74] contributed to the debate whether bipolar disorder is being overdiagnosed or whether this trend represents the result of previous underrecognition. The introduction of the diagnosis of disruptive mood dysregulation disorder in the *DSM-5* should help to identify children with mood instability who do not fulfill criteria for a diagnosis of bipolar disorder, thus offering some insight into this question.[75] In this controversial framework, the identification of an increasing share of youth with mood disorders treated with antipsychotics stresses the importance of determining the clinical appropriateness of the diagnosis. Alarmingly, in a study on very young privately insured children, the majority of those prescribed antipsychotics had received neither a psychiatric visit nor any mental health assessment during the year in which the medication was prescribed.[52] Within the same cohort, children diagnosed with bipolar disorder had the highest rate of antipsychotic treatment. A recent study[76] confirmed that only a minority of antipsychotic-treated children and adolescents received their prescription from a child and adolescent psychiatrist.

Although the proportion of antipsychotic-treated youth with depressive spectrum disorders is not increasing, almost 1 of 10 young patients treated with antipsychotics has a diagnosis of unipolar depression. This use lacks evidence-based support in youth[77] warranting further research into the factors underlying this prescribing practice that may be related to approval of SGAs for augmentation of antidepressants in adults with treatment-resistant depression.

No significant association was found between the increasing proportion of mood disorder diagnoses among antipsychotic-treated youth and year of data collection/publication, country, setting, sample size, patient age, sex, or race. The same was true when analyzing the results separately for bipolar spectrum and depression spectrum disorders. This finding suggests that other variables, such as, among others, symptom severity, prescriber specialty, and socioeconomic status, could represent significant underlying reasons for this prescribing behavior.[78] More detailed investigations are needed to obtain a better understanding of the moderators driving the rise in antipsychotic use in youth with mood disorders.

Furthermore, 1 of 4 young patients diagnosed with a mood disorder received treatment with an antipsychotic. This number is largely accounted for by the subsample diagnosed with bipolar spectrum disorders. Regardless of the evidence for the efficacy of antipsychotics in the treatment of bipolar disorder in older children and adolescents based not only on case-series and open-label trials,[79] but also on randomized, double-blind, placebo-controlled trials,[10–17,80] significant gaps remain. For instance, antipsychotic prescriptions commonly occur outside evidence-based indications, such as in children below age 10 years with bipolar disorder diagnoses and youth with unipolar depression. A reason for this prescribing choice might be represented by the scarcity of effective alternative psychopharmacologic options. The use of antipsychotics in depressed youth may reflect a downward extrapolation of research results obtained from adults.[29,81] With the exception of lithium and lamotrigine, lack of evidence for the efficacy of mood stabilizers for bipolar depression might lead prescribers to opt for what they view as more manageable or faster treatment with SGAs. However, the demonstrated metabolic and neuromotor side effects of SGAs in youth must not be overlooked.[21–26] Rigorous therapeutic monitoring is required in this vulnerable population.[22,25] Furthermore, potential long-term adverse effects of antipsychotic exposure on the developing human brain are uncertain,[29,30,82] warranting additional caution when using antipsychotics in youth.

Although psychopharmacologic treatments represent the cornerstone of the therapeutic approach to bipolar disorder, psychosocial interventions also play a critical role.[83] Recognition of the limited accessibility to nonpharmacologic interventions has given rise to the assumption that antipsychotic treatment might serve as a practical alternative to more costly and time-consuming or little accessible psychosocial interventions,[4,84] particularly in lower income populations.[40,85] This hypothesis raises deep concern, as a comprehensive multimodal treatment approach, consisting of psychopharmacology and adjunctive psychosocial therapies, is almost always indicated for early-onset bipolar disorder.[86]

Several limitations must be considered when interpreting the results of this study. First, the limited number of studies, particularly in the subgroup of youth diagnosed with mood disorders, restricted our ability to investigate time trends and subpopulation effects, including the potential moderator effect of the proportion of youth with mood disorders and psychotic features. Second, the patients' diagnoses were based on clinical judgment only. Recent studies have shown poor agreement between clinical and research-based diagnoses,[87,88] suggesting a lack of accuracy of chart diagnoses. For this reason, in our sample, we cannot exclude that a subgroup of patients with disruptive behavior disorders or ADHD and impulsivity or aggression might have been misclassified as patients diagnosed with a mood disorder diagnosis, particularly bipolar spectrum diagnosis. In a small inpatient study[89] of adolescents with mania, most youth who were clinically diagnosed with mania did not meet *DSM* criteria for a manic episode, yet all of those with clinically diagnosed, but not *DSM* criteria–based mania, were treated with lithium or another mood stabilizer. Similarly, a Finnish study[90] of patients with first-episode psychosis and affective disorders reported that diagnostic concordance between clinical and research interviews was moderate ($\kappa = 0.51$), with a tendency to miss affective symptoms in psychotic patients and to overdiagnose psychotic symptoms in patients with affective disorders. Thus, variations in this observed diagnostic imprecision could affect antipsychotic prescribing rates. Nevertheless, findings from the included studies do reflect real-world prescribing of antipsychotics to youth with a clinically assigned mood disorder diagnosis guiding therapeutic action. Third, the fact that the pharmacoepidemiologic studies reported few patient and treatment characteristics precluded a more detailed assessment of moderators and mediators of antipsychotic prescription trends in youth with mood disorders. For example, most studies did not report information on clinical reasons for treatment selection or treatment targets, including psychiatric comorbidities, nor on the efficacy and safety of antipsychotic use. The lack of information concerning prior treatment effects, including different treatment modalities and efficacy or safety outcomes, precluded an assessment of the appropriateness of antipsychotic prescribing. Fourth, our finding of a proportional increase of youth with mood disorder diagnoses, particularly, bipolar spectrum disorders, among antipsychotic-treated youth cannot be taken as proof that the absolute number of patients with bipolar spectrum disorders receiving antipsychotics has increased. However, data from multiple sources have demonstrated that the overall use of antipsychotics in youth has increased,[1,4,7,52,76] which suggests that there is a parallel increase in the number of youth with bipolar spectrum disorders who are prescribed antipsychotics. Fifth, all studies using administrative records defined antipsychotic use by the presence of ≥ 1 antipsychotic prescription. Therefore, short-term use and chronic exposure to antipsychotics are mixed together,

complicating the interpretation of the results. Future studies should include information on the mean duration of antipsychotic treatment and display results for groups receiving antipsychotics only for a short time and those being persistently treated with antipsychotics. Sixth, as is always an issue in pooling data in meta-analyses, studies varied greatly in their design and patient population and treatment characteristics, introducing heterogeneity into the observed results. However, a key strength of meta-analyses is the ability to provide an overall picture of prescribing practices and trends, and we examined subgroups and moderators to reduce the observed heterogeneity to the extent possible. Nevertheless, despite these limitations, this is the first pooled analysis to examine frequencies and time trends of mood disorder diagnoses among antipsychotic-treated youth and of antipsychotic use in youth diagnosed with mood disorders, thereby providing comprehensive data on this issue.

In summary, this first meta-analysis of frequencies and time trends of mood disorder diagnoses among antipsychotic-treated youth and of antipsychotic use in youth diagnosed with mood disorders suggests that approximately one-quarter of antipsychotic-treated youth has a mood disorder diagnosis and that 1 of 4 patients with a diagnosis of mood disorders receives antipsychotic medications. Furthermore, patients with bipolar spectrum disorders represent a significantly expanding population among youth treated with antipsychotics, while the proportion of antipsychotic-treated youth with depression spectrum diagnoses has remained stable. Finally, the lack of informative significant moderator findings indicates that pharmacoepidemiologic studies with limited data are insufficient to capture the underlying reasons for the observed prescribing behavior, warranting more detailed investigations into the reasons for antipsychotic prescribing trends in this vulnerable population.

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Drug names: aripiprazole (Abilify), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.