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Pharmacoepidemiology of Antipsychotic Use in Youth with ADHD: Trends and Clinical Implications

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Abstract

Although concern has been raised about antipsychotic prescribing to youth with attention-deficit/hyperactivity disorder (ADHD), the available database is limited to individual studies. Therefore, in order to provide a synthesis of prevalences and time trends, we conducted a systematic review

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Compliance with Ethics Guidelines

Conflict of Interest

Tobias Gerhard received an honorarium for a methodology lecture from Boeringer-Ingelheim.

John M. Kane has been a consultant and/or received honoraria from Amgen, Alkermes, Azur, Bristol-Myers Squibb, Forrest, Genentech, Intracellular Therapeutics, Janssen, Johnson & Johnson, Eli Lilly, Lundbeck, Merck, Novartis, Otsuka, Roche, and Sunovion. He is a shareholder of MedAvante. He has received grant support from NIMH.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

and pooled analysis of pharmaco-epidemiologic data on antipsychotic use in ADHD youth. Of 1806 hits, 21 studies (N) were retained that reported analyzable data for three separate populations: 1) antipsychotic-treated youth (N=15, n=341,586); 2) ADHD youth (N=9, n=6,192,368), and 3) general population youth (N=5, n=14,284,916). Altogether, 30.5±18.5% of antipsychotic-treated youth had ADHD. In longitudinal studies, this percentage increased over time (1998-2007) from 21.7±7.1% to 27.7±7.7%, ratio=1.3±0.4. Furthermore, 11.5±17.5% of ADHD youth received antipsychotics. In longitudinal studies, this percentage also increased (1998-2006) from 5.5±2.6% to 11.4±6.7%, ratio=2.1±0.6. Finally, 0.12±0.07% of youth in the general population were diagnosed with ADHD and received antipsychotics. Again, in longitudinal studies, this percentage increased over time (1993-2007): 0.13±0.09% to 0.44±0.49%, ratio=3.1±2.2.

Taken together, these data indicate that antipsychotics are used by a clinically relevant and increasing number of youth with ADHD. Reasons for and risk/benefit ratios of this practice with little evidence base require further investigation.

Keywords

Attention-deficit/hyperactivity disorder; ADHD; Antipsychotics; Prescribing; Trends; Correlates; Pharmacoepidemiology; Psychiatry

Introduction

Over the past two decades psychotropic medication prescriptions for children and adolescents in the United States have grown considerably (1,2). Although medication use has increased for all psychotropic medication classes, antipsychotic prescriptions have increased at the highest rate (3). For example, between 2002 and 2007, antipsychotic use increased by 62% in Medicaid enrolled children (3). Between 1993 and 2007, the number of office-visits with antipsychotic prescriptions increased from 0.24 to 1.84 per 100 children and from 0.78 to 3.76 per 100 adolescents (1).

The increase in prescribing of antipsychotic medication to children and adolescents has been attributed to several reasons. There is now greater recognition that severe psychiatric disorders in adults can begin in childhood and, especially, in adolescence (4,5). Moreover, in adults, antipsychotics have been used increasingly for non-psychotic disorders, including bipolar disorder and unipolar depression, and the evidence base as well as indications for antipsychotic use in youth have increased (6,7). Finally, second-generation antipsychotics, which have largely replaced first-generation antipsychotics, have significantly less acute and chronic extrapyramidal adverse effects, an antipsychotic adverse effect cluster, which children and adolescents were particularly sensitive to (8). Importantly, however, antipsychotic medication use in youth has increased not only for approved indications, such as schizophrenia, bipolar disorder and autistic disorder, but also for off-label use. Particularly, in youth antipsychotics are predominantly used for the treatment of impulsive aggression (1), which presents oftentimes concomitantly with ADHD. Despite the lack of empirical support and FDA approval, adjunctive antipsychotic use in youth with ADHD appears to be the fastest growing indication. Between 2001 and 2005, Pathak et al. (9) found

that the most common condition associated with antipsychotic use in Medicaid enrolled children was ADHD (61.3%). Furthermore, Zito et al. (10) demonstrated an increase in antipsychotic use in Medicaid enrolled youth with ADHD from 7.3% in 1997 to 20.2% in 2006.

The increasing use of antipsychotics in youth has stimulated concern, especially regarding the safety of antipsychotics in vulnerable children and adolescents (11). Antipsychotics are associated with a number of adverse effects that can lead to impairment of functioning and physical health. These include sedation, muscle stiffness, prolactin elevation with effects on sexual functioning and bone density, and especially, age-inappropriate weight gain and metabolic abnormalities (8,12-15). Although the risk of long-term adverse effects, such as tardive dyskinesia and diabetes mellitus, is much less clear in youth, due to mostly short-term data, there is concern that early exposure may predispose to an earlier onset of such long-term risks. Additionally, other potential long-term adverse consequences of antipsychotic exposure to the developing brain and body remain largely unknown.

Given the high prevalence of ADHD in youth and the increasing off-label adjunctive use of antipsychotic medications in this population, we aimed to summarize the extent, time trends and correlates of antipsychotic use in pediatric patients with ADHD.

Methods

Search and Inclusion Criteria

We conducted a systematic literature search in PubMed, from database inception through December 2012 without language restrictions, using the following search terms: (antipsychotic* OR neuroleptic* OR "dopamine blocker*" OR antidopaminergic) AND (child OR childhood OR children OR adolescen* OR pediatric) AND (prescription* OR prescrib* OR use OR utilization OR database OR pharmacoepidemiolog* OR rate OR rates).

Inclusion criteria were: 1) studies with information on either a) the frequency of antipsychotic use in youth diagnosed with ADHD or b) the frequency of an ADHD diagnosis in youth treated with antipsychotics; 2) study sample consisting of children or adolescents 19 years old. In addition to these frequency estimates, we extracted data on the study design, patient characteristics and cotreatments of youth with ADHD receiving antipsychotics. Whenever available, we also extracted reported correlates of antipsychotic use in youth with ADHD as well as data on antipsychotic use in youth with other diagnoses included in these same studies.

Statistical Analyses

Except for univariate analyses of correlates of antipsychotic use in ADHD, data were analyzed descriptively, presenting non-weighted means and standard deviations (SD). Due to large variations in study and sample characteristics and heterogeneous, as well as partially overlapping data sets, sometimes without mentioning of the exact number of patients that prevalence estimates were based on meta-analytic summary estimates were considered inappropriate. Data were analyzed for three distinct subsamples ("denominators") in which

data on antipsychotic use in ADHD youth were available: i) antipsychotic-treated youth; ii) ADHD youth; and iii) general pediatric populations. In each of these subsamples, antipsychotic use prevalences were calculated in three different ways: i) pooling data from cross-sectional studies with data from time 1 (the earliest time point) in longitudinal studies; ii) pooling data from time 1 (the earliest time point) in longitudinal studies; and iii) pooling data from time 2 (the latest time point) in longitudinal studies. Specification (i), which includes data from longitudinal and cross-sectional studies, was used to approximate overall estimates, while specifications (ii) and (iii) were used to examine time trends. Data from intermediary time points in longitudinal studies were not considered, as preliminary analyses showed that the amount of data was insufficient for each individual year to allow for meaningful pooling and comparison. Since, generally, studies included data from a time period spanning several years, we first calculated the median of each study period (rounding to the next higher full year in case the median fell in the middle between two discrete years), followed by averaging the medians of all study periods without providing standard deviations. All other values are expressed as simple means $\pm$ standard deviations.

At the three mean of median time points (i.e., cross-sectional or time 1; time 1; and time 2), we descriptively compared the mean prevalence of antipsychotic use in youth with ADHD, youth with ADHD and comorbid diagnoses, and in youth with non-ADHD psychiatric diagnoses. We further descriptively compared time trends from time 1 to time 2 within each diagnostic group as well as across diagnostic groups, using the prevalence ratio (expressed as mean prevalence at time 2 divided by mean prevalence at time 1) observed in ADHD youth as the reference group. Since a ratio is a proportional number that depends on the magnitude of the percent values at each time point that are not subtracted from each other (as in calculating the difference), but rather divided by each other, it is possible that trends reverse when averaging proportions compared to averaging differences. For example, if prescribing increases by 5% from 5% to 10%, the ratio is 2, yet, if the same 5% increase is from 50% to 55%, the ratio is only 1.1. This possible trend reversal in antipsychotic prescribing from T1 to T2 - depending on whether differences or proportions were averaged - occurred in only two instances in antipsychotic-treated youth, i.e., the antipsychotic prescribing for PDD/MR ($\Delta = +1.4\%$, ratio=0.9) and mood disorders ($\Delta = -4.2\%$, ratio=1.5).

Results

Search Results and Study Characteristics

The search returned 1806 citations. Altogether, 1646 articles were excluded at the title/abstract level, as they did not contain pharmaco-epidemiological data, reported primarily on adult populations, did not describe the frequency of antipsychotic use, or did not contain ADHD populations. Of 160 full text articles (N), 138 were excluded for lacking frequency data on antipsychotics and ADHD (N=123), not describing ADHD as a distinct diagnostic entity (N=11), not providing epidemiologic data (N=5) and describing primarily adult samples (N=1) (Figure 1). Finally, 21 studies (1,3,9,10,16-32) reporting on a total of 20,249,592 youth (age range: 0-19 years, 66.5% male, 57.3% white), of which 6,192,368 were diagnosed with ADHD, were included in the pooled analyses (Table 1). Studies were

published between 1999 and 2013 and covered reporting periods from 1989-2010. The sample size with analyzable data ranged from 34 to 15,461,455. The majority of these studies (N=18, 85.7%) were conducted in the United States, 2 studies (9.5%) were conducted in Canada and 1 (4.7%) in the Netherlands. Eleven (52.4%) provided cross-sectional data and ten (47.6%) provided longitudinal data. Ten (47.6%) reported on both in- and outpatients, seven (33.3%) reported on outpatients alone and 4 (19.0%) did not specify this information. Thirteen (61.9%) studies provided data on Medicaid-eligible youth, 8 (38.1%) reported exclusively on Medicaid youth, and three (14.3%) reported exclusively on privately insured youth. Three studies (14.3%) reported on youth in foster care and 2 (9.5%) studies reported exclusively on youth in foster care (Table 1).

Demographic, Illness and Treatment Characteristics

Table 2 displays demographic, illness and treatment variables in three separate populations with data on antipsychotic exposure frequencies in youth with ADHD: antipsychotic-treated subgroup (N=15, total n=341,586, ADHD subjects=70, 421); ADHD subgroup (N=9, total n=6,192,368); and general population subgroup (N=5, n=14,284,916, ADHD subjects=836,994). Demographic information was extracted whenever available in all three populations on age, sex, race, insurance status, non-ADHD diagnoses and non-antipsychotic medication treatment (Table 2).

In the antipsychotic treated youth subgroup, we obtained data from 15 studies reporting data for at least one time point (mean age: 9.5 ± 4.5 years). The average median year of data collection for the cross-sectional or time one (T1) study period was 2003. Of these 15 studies, 7 (total n=750,423, ADHD subjects=124,740) provided longitudinal data (average median T1=1998, total n=278,446, ADHD subjects 43, 074; T2=2007, total n=471,977, ADHD subjects=81, 666) (Table 2).

In the ADHD youth subgroup, we obtained data from 9 studies reporting data for at least one time point (mean age: 9.2 years). The average median year of data the collection for the cross-sectional or T1 study period was 2004. Of these 9 studies, 4 (n=16,478,860) provided longitudinal data (average median T1=1998, n=6,088,372; T2=2006, n=10,390,488) (Table 2).

In the general youth population subgroup, we obtained data from 5 studies reporting data for at least one time point (mean age: not reported) (average median time=2003). Of these 5 studies, 3 provided longitudinal data (average median T1=2003, total n=14,256,115, ADHD subjects=346,686; T2=2007, total n=16,514,442, ADHD subjects=485,404) (Table 2).

Proportion of ADHD Diagnosed Youth among Antipsychotic Treated Youth

In total, $30.5 \pm 18.5\%$ of antipsychotic-treated youth had a diagnosis of ADHD (Table 3). This proportion was numerically larger than for all other diagnoses (range: $8.8 \pm 5.9\%$ for psychotic disorders to $24.0 \pm 27.3\%$), except for disruptive behavior disorders ($31.3 \pm 22.6\%$) which was slightly more prevalent than ADHD among antipsychotic treated youth. In studies with longitudinal data, ADHD youth accounted for a larger proportion of antipsychotic use than every other diagnostic group at T1 and T2. Furthermore, between a median time of 1998 and 2007, the proportion of youth diagnosed with ADHD increased

from $21.7 \pm 7.1\%$ to $27.7 \pm 7.7\%$. This increase (T1 to T2 ratio = 1.3 ± 0.4) was larger than for any other diagnosis, other than ADHD with co-morbid disruptive behavior disorder (ratio = 1.4 ± 0.8) and bipolar disorder (ratio = 1.3 ± 0.3). In addition to ADHD, ADHD plus co-morbid disruptive behavior disorders (DBD) and bipolar disorders, the prevalence of pervasive developmental disorder (PDD) or mental retardation (MR) also increased in antipsychotic youth cohorts, while there was a small decrease for youth with anxiety disorders and DBDs alone, as well as a more substantial decrease for psychotic disorders (Table 3).

Frequency of and Trends in Antipsychotic Use in Youth with a Diagnosis of ADHD

In total, $11.5 \pm 17.3\%$ of youth with ADHD were treated with antipsychotics (Table 4). This proportion was numerically higher than that for disruptive behavior disorders ($8.7 \pm 1.3\%$) and depression ($9.6 \pm 1.8\%$), but lower than bipolar disorder ($44.6 \pm 1.1\%$) and ADHD plus comorbid DBD ($15.0 \pm 7.1\%$), comorbid mood ($15.5 \pm 6.3\%$) and comorbid bipolar disorder (28%, based on only one study). However, in studies with longitudinal data, the proportion of antipsychotic use was lower in ADHD youth than in youth with any other diagnosis when concurrent time points were compared. Further, in the studies with longitudinal data, antipsychotic use for ADHD rose from $5.5 \pm 2.6\%$ in 1998 to $11.4 \pm 6.7\%$ in 2006 (ratio T1 to T2 = 2.1 ± 0.6). Although the antipsychotic use rates also rose across other diagnoses (T1 to T2 ratios: 1.4 ± 0.4 for bipolar disorder to 1.7 ± 0.8 for ADHD plus co-morbid disruptive behavior disorders, this increase was highest in youth with ADHD, except for the PDD/MR populations (ratio = 2.7), but this result was based on one study (Table 4).

Proportion of Antipsychotic treated Youth with ADHD Among General Youth Populations

In total, antipsychotic-treated youth with ADHD represented $0.12 \pm 0.07\%$ of youth in the general population (Table 5). This proportion was numerically greater than that for antipsychotic treated youth with all other represented diagnoses, including disruptive behavior disorder ($0.09 \pm 0.08\%$), bipolar disorder ($0.05 \pm 0.06\%$), depression ($0.05 \pm 0.07\%$) and PDD/MR ($0.03 \pm 0.02\%$). Moreover, in studies with longitudinal data, youth with ADHD also represented a larger proportion of antipsychotic use at T1 and T2 than every other diagnosis. Furthermore between 1993 and 2007, the proportion of youth diagnosed with ADHD increased substantially from 0.13 ± 0.09 to $0.44 \pm 0.49\%$. This increase (T1 to T2 ratio = 3.1 ± 2.2) was also larger than for any other diagnosis, except for depression (ratio = 4.4 ± 0.9) and bipolar (ratio = 3.0 ± 2.8) (Table 5).

Correlates of Antipsychotic Use in Cohorts of Youth with ADHD

Exploratory univariate analyses of demographic and payment source correlates yielded no significant associations with percent of ADHD youth receiving antipsychotics. The same was true for percent of ADHD youth treated with antipsychotics in the general youth population. However, percent of antipsychotic use in ADHD youth was associated with greater use of antidepressants ($p=0.002$) and of alpha 2 agonists ($p=0.011$).

Discussion

Aiming to characterize the frequency and time trends of antipsychotic use in ADHD treated youth, we identified 21 studies including a total of over 20 million youth aged 0-19 years old with pharmaco-epidemiological data on antipsychotic use and ADHD. Within identified studies we focused on treatment patterns in three distinct populations: 1) frequency of ADHD in antipsychotic treated youth 2) frequency of antipsychotic use in youth with ADHD and 3) frequency of antipsychotic treated ADHD youth in general population youth.

Across these studies and subgroups, ADHD was associated with a substantial proportion of antipsychotic medication prescriptions, at frequencies that were higher than for all other disorders, except for those that were comorbid with ADHD and for bipolar disorder and PDD/MR concurrently assessed in studies reporting on ADHD youth. From the early to the late 1990s until the mid to late 2000s, increases in antipsychotic use were larger for ADHD youth in all three populations than for youth with almost all other diagnoses. The only exceptions included similar increases in youth with bipolar disorder and greater increases in those with comorbid ADHD and DBD in the antipsychotic-treated population, and similar increases in youth with bipolar disorder as well as greater increases in those with depression in the general population cohort. Of note, when comparing time 1 with time 2, the frequency of antipsychotic use in youth increased over time for all other disorders in the ADHD and general youth populations, too. In the antipsychotic-treated cohort, also most disorders increased in frequency with the exception of stable antipsychotic use in depression and anxiety disorder, a slight decrease in DBDs and PDD/MR, as well as a more substantial relative decrease in psychotic disorders.

Both in the antipsychotic treated cohort and the general youth cohort, ADHD was the most common diagnosis associated with antipsychotic use with the exception of disruptive behavior disorder in the antipsychotic treated youth cohort. This finding is due to the frequent use of antipsychotics in youth diagnosed with ADHD combined with the high frequency of ADHD within these cohorts, as ADHD is one of the most common psychiatric disorders in children and adolescents, second only to social and specific phobias and oppositional defiant disorder (4,33).

By contrast, in youth diagnosed with ADHD, antipsychotic use was lower in those with ADHD alone than for bipolar disorders and PDD/MR, two condition associated with irritability and aggression, as well as all for other disorders that co-occurred with ADHD. The latter is a reflection of the fact that comorbidities generally increase the severity of both the psychiatric impairment and complexity of the related treatment approaches (34). Pointing to the same effect of comorbidity increasing antipsychotic use, we found in our exploratory correlational analyses that greater treatment with antidepressants and alpha2 agonists was associated with antipsychotic use in youth with ADHD. However, it is unclear from the database studies for which symptoms or coded (as well as uncoded) diagnoses antipsychotics and these comedications were used. For example, it is possible that antidepressants are used for depression, which was also the only diagnosis for which larger increases in antipsychotic use were observed over time than for ADHD in the general youth cohort. In this case, the higher use of antipsychotics in patients cotreated with

antidepressants may represent off-label use using antipsychotics as augmenting agents to treat depression that is unresponsive to antidepressant monotherapy, and indication for which efficacy has been demonstrated in adults (35). On the other hand, it is also possible that antipsychotics, rather than psychosocial interventions, are being used to treat aggression, irritability and oppositionality that may be related to depression or psychosocial stressors (21,36,37). The latter would be concerning, as several different psychosocial interventions have shown to be effective for rating-scale based aggression with moderate to large effect sizes (36), not too dissimilar to effect sizes for antipsychotics (37). Unfortunately, the published data were insufficient to allow for a pooled analysis of antipsychotic use frequency in relation to the use of psychotherapeutic interventions. Similarly, the higher use of antipsychotics in youth with more alpha2 agonist treatment may point to use of antipsychotics in more severe forms of ADHD and impulsivity, or to use for unresolved aggression and oppositionality, as alpha2 agonists have shown some efficacy for both symptom clusters (38,39).

Our results support findings from previous individual reports suggesting that antipsychotics are being prescribed increasingly to treat psychiatrically ill youth in the United States and particularly for youth with ADHD and DBDs, predominantly by non-psychiatrists for these indications (1,3). This clear trend is troubling for several reasons. Most importantly, antipsychotics are not approved for the treatment of symptoms of ADHD and limited, if any, evidence exists to suggest their utility for the core symptoms of inattention and hyperactivity. Although, aripiprazole and risperidone are approved for irritability and aggression associated with autistic disorder (age 5 or 6-17 years) (6), and data exist for their utility in disruptive behavior disorders and aggression (37,40), antipsychotics should be the last resort for the treatment of impulsivity, oppositionality and aggression (6,37,41). In fact, concern has been raised that antipsychotics are used instead of appropriate use of psychotherapies and family interventions (1,21,36). Moreover, guidelines recommend in patients with ADHD to first treat ADHD aggressively and comprehensively and only to address residual impulsivity, oppositionality and aggression that do not respond to appropriately dosed psychostimulant treatment alone (42). These recommendations are supported by a recent pooled analysis of randomized controlled trials of psychotropic medications for rating scale based aggression in youth. In these analyses, stimulant treatment had an effect size of 0.6 for aggression in youth with ADHD and/or disruptive behavior disorders (37). This moderate effect size is quite respectable and not too different from the pooled effect size of 0.7 for antipsychotics given for the same purpose (37). Importantly, Blader et al (43) found that an open lead-in stimulant optimization strategy in youth who reportedly had not responded to stimulant treatment in the community and who were referred for a trial with valproic acid for aggression led to a high response rate, making 49.3% of 65 enrolled children ineligible for the second, randomized controlled trial phase. These results suggest that ADHD treatments may be underutilized or not sufficiently optimized before antipsychotics are prescribed in clinical practice, something that needs to be assessed further. If this is true, then education programs for antipsychotic prescribers who treat ADHD youth may be necessary, especially for non-psychiatrists.

Another concern regarding the potentially too frequent use of antipsychotics in ADHD youth is their adverse effect potential that can interfere with psychiatric and physical well-

being. Potentially problematic adverse effects include extra-pyramidal effects, sedation, prolactin changes and sexual/reproductive system effects, interference with normal sleep, activity and eating patterns, as well as age-inappropriate weight gain and metabolic abnormalities that are associated with future risk for diabetes as well as cardiovascular morbidity and mortality (11-15,44). In this context, the low and inappropriate rates of cardiometabolic monitoring in youth (45,46) are highly concerning. Additionally, beyond short-term and even less medium-term data, there is a limited understanding of the longer-term effects of antipsychotics on the developing brain and body.

There are several important limitations to our study. Most importantly, despite availability of some very large studies, the number of individual studies and specific data in each respective population/subgroup was still relatively small. Moreover, all but two studies originated in the US and data characterizing the populations or describing potential correlates of antipsychotic use were scarce, limiting our ability to conduct meaningful correlational analyses. In addition, due to the pharmacoepidemiologic nature of the data, no information was available on the treatment targets, efficacy and side effects of antipsychotic use in youth with ADHD. Furthermore, although we primarily included claims based studies, the resultant data are based on heterogeneous populations, including widely varying sampling methods, age ranges, insurance status, sample sizes, and settings (inpatient, outpatient or both, and foster care). Additionally, the majority of data were extrapolated from reports using various administrative records, which could impact diagnostic accuracy, including underreporting of more severe diagnoses than ADHD that may have motivated antipsychotic use. Medicaid claims, for example, may be incomplete and not fully capture diagnostic comorbidities or behaviors, such as aggression that may be difficult to code on claims. Further, while some papers attempted to differentiate ADHD alone from ADHD with comorbidities, most did not. Despite these limitations, this is the first study on antipsychotic use in ADHD use that pooled data according to the population that antipsychotic use was based on and that examined time trends and correlates across multiple studies and time periods.

Conclusion

In summary, this analysis contributes to the growing body of literature highlighting the persistent growth in antipsychotic use among children and adolescents over the past decade. Youth with ADHD represent a significant proportion of antipsychotic users and generally appear to represent the largest and fastest increasing cohort over time. This is of concern, as approved and highly effective treatments for ADHD exist and as data suggest that simply treating ADHD with psychostimulants will reduce associated symptoms of impulsivity and aggression in a significant proportion of youth (42,43). Thus, clinicians should follow guidelines and use primary treatments for the core symptoms of ADHD (37,41,42), optimizing this treatment approach and combining ADHD medications with psychosocial interventions (36) before considering the addition of an antipsychotic for the treatment of residual and impairing impulsivity, oppositionality and aggression. Moreover, monitoring of efficacy and side effects of antipsychotics should routinely be implemented (8,13,15). Since antipsychotic use appears to be increasing across a range of diagnoses in youth well beyond approved indications, more studies are required to better understand why antipsychotic

agents are being used at such high rates and why prescribers are choosing non approved treatments when other, possibly less harmful interventions exist. Additionally carefully controlled comparative effectiveness trials are required to better understand the short-term and long-term effects of antipsychotic medications on impulsivity and aggression in relation to lower-risk interventions, and to investigate their long-term safety.

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References

Recently published papers of particular interest have been highlighted as:

* Of importance

** Of major importance

- 1**. Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry*. Dec 1; 2012 69(12):1247–56. This article demonstrates the significant increase in antipsychotic prescriptions in youth in the US in both youth and adults and explores the various characteristics associated with antipsychotic prescriptions. [PubMed: 22868273]
2. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf*. Feb; 2011 20(2):177–84. [PubMed: 21254289]
- 3**. Matone M, Localio R, Huang YS, dosReis S, Feudtner C, Rubin D. The relationship between mental health diagnosis and treatment with second-generation antipsychotics over time: a national study of U.S. Medicaid-enrolled children. *Health Serv Res*. Oct; 2012 47(5):1836–60. This article highlights the growing trend towards antipsychotic prescription in US youth, in particular for non-approved indications. [PubMed: 22946905]
4. Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, He JP, Koretz D, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Arch Gen Psychiatry*. Apr; 2012a 69(4):372–80. [PubMed: 22147808]
5. Costello EJ, Copeland W, Angold A. Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? *J Child Psychol Psychiatry*. Oct; 2011 52(10):1015–25. [PubMed: 21815892]
6. Correll CU, Kratochvil CJ, March JS. Developments in pediatric psychopharmacology: focus on stimulants, antidepressants, and antipsychotics. *J Clin Psychiatry*. May; 2011 72(5):655–70. [PubMed: 21658348]
7. Schimmelmann BG, Schmidt SJ, Carbon M, Correll CU. A Rational, Evidence Informed Approach to Psychopharmacology for Adolescents with Early Onset, First Episode Psychoses. *Curr Opin Psychiatry*. Mar; 2013 26(2):219–30. [PubMed: 23364281]
8. Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry*. Jan; 2008 47(1):9–20. [PubMed: 18174821]
9. Pathak P, West D, Martin BC, Helm ME, Henderson C. Evidence-based use of second-generation antipsychotics in a state Medicaid pediatric population, 2001-2005. *Psychiatr Serv*. Feb; 2010 61(2):123–9. [PubMed: 20123816]

- 10*. Zito JM, Burcu M, Ibe A, Safer DJ, Magder LS. Antipsychotic use by Medicaid-insured youths: impact of eligibility and psychiatric diagnosis across a decade. *Psychiatr Serv.* Mar 1; 2013 64(3):223–9. This article demonstrates the significant increase in antipsychotic use for Medicaid enrolled youth with ADHD between 1997 and 2006. It highlights the different prescription patterns for youth based on socio-economic factors as opposed to diagnostic characteristics. [PubMed: 23242390]
11. Vitiello B, Correll C, van Zwieten-Boot B, Zuddas A, Parellada M, Arango C. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. *Eur Neuropsychopharmacol.* Sep; 2009 19(9):629–35. [PubMed: 19467582]
12. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA.* Oct 28; 2009 302(16):1765–73. [PubMed: 19861668]
13. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol.* Oct 18; 2011 8(2):114–26. [PubMed: 22009159]
14. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry.* Apr; 2011 26(3):144–58. [PubMed: 21295450]
15. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacol.* Dec; 2011 21(6):517–35. [PubMed: 22166172]
16. Alessi-Severini S, Biscontri RG, Collins DM, Sareen J, Enns MW. Ten years of antipsychotic prescribing to children: a Canadian population-based study. *Can J Psychiatry.* Jan; 2012 57(1):52–8. [PubMed: 22296959]
17. Classi PM, Le TK, Ward S, Johnston J. Patient characteristics, comorbidities, and medication use for children with ADHD with and without a co-occurring reading disorder: A retrospective cohort study. *Child Adolesc Psychiatry Ment Health.* Dec 6.2011 5:38. [PubMed: 22145783]
18. Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. *Clin Ther.* May; 2010 32(5):949–59. [PubMed: 20685503]
- 19*. Constantine RJ, Jentz S, Bengtson M, McPherson M, Anel R, Jones MB. Exposure to antipsychotic medications over a 4-year period among children who initiated antipsychotic treatment before their sixth birthday. *Pharmacoepidemiol Drug Saf.* Feb; 2012 21(2):152–60. This article highlights the concerning trend towards antipsychotic medication use in very young children and the urgent need to better understand their long-term effects. [PubMed: 21793097]
20. Cooper WO, Hickson GB, Fuchs C, Arbogast PG, Ray WA. New users of antipsychotic medications among children enrolled in TennCare. *Arch Pediatr Adolesc Med.* Aug; 2004 158(8):753–9. [PubMed: 15289247]
21. Crystal S, Olfson M, Huang C, Pincus H, Gerhard T. Broadened use of atypical antipsychotics: safety, effectiveness, and policy challenges. *Health Aff (Millwood).* Sep-Oct;2009 28(5):w770–81. [PubMed: 19622537]
22. Dosreis S, Yoon Y, Rubin DM, Riddle MA, Noll E, Rothbard A. Antipsychotic treatment among youth in foster care. *Pediatrics.* Dec; 2011 128(6):e1459–66. [PubMed: 22106072]
23. Fullerton CA, Epstein AM, Frank RG, Normand SL, Fu CX, McGuire TG. Medication use and spending trends among children with ADHD in Florida's Medicaid program, 1996-2005. *Psychiatr Serv.* Feb 1; 2012 63(2):115–21. [PubMed: 22302327]
- 24*. Garfield CF, Dorsey ER, Zhu S, Huskamp HA, Conti R, Dusetzina SB, Higashi A, Perrin JM, Kornfield R, Alexander GC. Trends in attention deficit hyperactivity disorder ambulatory diagnosis and medical treatment in the United States, 2000-2010. *Acad Pediatr.* Mar; 2012 12(2):110–6. This article demonstrated the large increase in ADHD diagnosis in the US between 2000 and 2010 as well as the provider shift from pediatricians to psychiatrists. [PubMed: 22326727]
25. Goodwin R, Gould MS, Blanco C, Olfson M. Prescription of psychotropic medications to youths in office-based practice. *Psychiatr Serv.* Aug; 2001 52(8):1081–7. [PubMed: 11474055]

26. Halloran DR, Swindle J, Takemoto SK, Schnitzler MA. Multiple psychiatric diagnoses common in privately insured children on atypical antipsychotics. *Clin Pediatr (Phila)*. May; 2010 49(5):485–90. [PubMed: 20118088]
27. Hodgkins P, Sasané R, Meijer WM. Pharmacologic treatment of attention-deficit/hyperactivity disorder in children: incidence, prevalence, and treatment patterns in the Netherlands. *Clin Ther*. Feb; 2011 33(2):188–203. [PubMed: 21497704]
- 28*. Olfson M, Crystal S, Huang C, Gerhard T. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolesc Psychiatry*. Jan; 2010 49(1):13–23. This article highlights the concerning trend towards antipsychotic medication use in very young children and the urgent need to better understand factors explaining this trend. [PubMed: 20215922]
29. Patel NC, Crismon ML, Shafer A. Diagnoses and antipsychotic treatment among youths in a public mental health system. *Ann Pharmacother*. Feb; 2006 40(2):205–11. [PubMed: 16434563]
30. Pringsheim T, Lam D, Patten SB. The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005–2009. *J Child Adolesc Psychopharmacol*. Dec; 2011 21(6):537–43. [PubMed: 22136092]
31. Zito JM, Safer DJ, dosReis S, Magder LS, Gardner JF, Zarin DA. Psychotherapeutic medication patterns for youths with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. Dec; 1999 153(12):1257–63. [PubMed: 10591302]
32. Zito JM, Safer DJ, Sai D, Gardner JF, Thomas D, Coombes P, Dubowski M, Mendez-Lewis M. Psychotropic medication patterns among youth in foster care. *Pediatrics*. Jan; 2008 121(1):e157–63. [PubMed: 18166534]
33. Visser SN, Lesesne CA, Perou R. National estimates and factors associated with medication treatment for childhood attention-deficit/hyperactivity disorder. *Pediatrics*. Feb; 2007 119(Suppl 1):S99–106. [PubMed: 17272592]
34. Kessler RC, Avenevoli S, Costello J, Green JG, Gruber MJ, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR. Severity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Arch Gen Psychiatry*. Apr; 2012b 69(4):381–9. [PubMed: 22474106]
35. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. Sep; 2009 166(9):980–91. [PubMed: 19687129]
- 36**. Knapp P, Chait A, Pappadopulos E, Crystal S, Jensen PS. Treatment of Maladaptive Aggression in Youth: CERT Guidelines I. Engagement, Assessment, and Management. *Pediatrics*. Jun; 2012 129(6):e1562–e1576. [PubMed: 22641762]
- 37**. Scotto Rosato N, Correll CU, Pappadopulos E, Chait A, Crystal S, Jensen PS. Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management. *Pediatrics*. Jun; 2012 129(6):e1577–e1586. This is the first of a two-set article series on the management of maladaptive aggression in youth, focusing on the evidence-based engagement, assessment and non-pharmacologic management of pediatric aggression that is a frequently cited reason for antipsychotic use in youth with ADHD. This is the second of a two-set article series on the management of maladaptive aggression in youth, focusing on the evidence-based psychotherapeutic and psychopharmacologic management of pediatric aggression that is a frequently cited reason for antipsychotic use in youth with ADHD. [PubMed: 22641763]
38. Turgay A. Psychopharmacological treatment of oppositional defiant disorder. *CNS Drugs*. 2009; 23(1):1–17. [PubMed: 19062772]
39. Nevels RM, Dehon EE, Alexander K, Gontkovsky ST. Psychopharmacology of aggression in children and adolescents with primary neuropsychiatric disorders: a review of current and potentially promising treatment options. *Exp Clin Psychopharmacol*. Apr; 2010 18(2):184–201. [PubMed: 20384430]
40. Jensen PS, Buitelaar J, Pandina GJ, Binder C, Haas M. Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials. *Eur Child Adolesc Psychiatry*. Mar; 2007 16(2):104–20. [PubMed: 17075688]

41. Pappadopulos E, Rosato NS, Correll CU, Findling RL, Lucas J, Crystal S, Jensen PS. Experts' recommendations for treating maladaptive aggression in youth. *J Child Adolesc Psychopharmacol*. Dec; 2011 21(6):505–15. [PubMed: 22196314]
42. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M. Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. Jun; 2006 45(6):642–57. [PubMed: 16721314]
43. Blader JC, Pliszka SR, Jensen PS, Schooler NR, Kafantaris V. Stimulant-responsive and stimulant-refractory aggressive behavior among children with ADHD. *Pediatrics*. Oct; 2010 126(4):e796–806. [PubMed: 20837589]
44. Roke Y, van Harten PN, Boot AM, Buitelaar JK. Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. *J Child Adolesc Psychopharmacol*. Aug; 2009 19(4):403–14. [PubMed: 19702492]
45. Morrato EH, Nicol GE, Maahs D, Druss BG, Hartung DM, Valuck RJ, Campagna E, Newcomer JW. Metabolic screening in children receiving antipsychotic drug treatment. *Arch Pediatr Adolesc Med*. Apr; 2010 164(4):344–51. [PubMed: 20368487]
46. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline Concordant Monitoring of Metabolic Risk in People with Mental Ill Health: Systematic Review and Meta-Analysis of Screening Practices. *Psychol Med*. Jan; 2012 42(1):125–47. [PubMed: 21846426]

Figure 1.
Search Results

Table 1

Study Design and Sample Characteristics of Pharmacoepidemiologic and Cohort Studies Reporting on Antipsychotic Use in ADHD Samples

Study/Country/ Design	Data Base/ Time Period	Aims	Overall Population	Youth Cohort	N	Age (years)	% Male T1 (T2)	% White T1 (T2)
Alessi-Severini 2012 (16) /Canada/ Longitudinal	Administrative health databases of Manitoba Health and the Statistics Canada census/ 1999-2008	Report AP prescribing to Manitoba youth he during the course of a decade	OP youth in Manitoba receiving 1 AP	AP- Treated	NR	0-18	NR	NR
				All Youth	NR	0-18	NR	NR
Classi 2011 (17) /USA/ Cross-sectional	U.S. Thomson Reuter Marketscan® Databases/2005-2007	Examine differences between children with ADHD and those with ADHD plus co- occurring reading disorder	IP and OP youth with ADHD or ADHD + reading disorder	ADHD	97,968	0-18	70	NR
Constantine 2010 (18)/USA/ Cross-sectional	Florida's Medicaid fee- for- service program/ 2002-2007	Examine AP polypharmacy use among youth aged 6-12 and 13-17 years	OP youth receiving AP on Medicaid	AP- Treated	23,183	6-17	68.5	76
Constantine 2012 (19) /USA/ Cross-sectional	Florida's fee for service Medicaid program/ 2003- 2004	Identify variable associated with risk of AP treatment	IP and OP children on Medicaid starting AP	AP- Treated	528	0-5	73.3	35
Cooper 2004 (20) /USA/ Longitudinal (only cross sectional data available)	Tennessee's managed care program for Medicaid enrollees and the uninsured (TennCare)/ 1996-2001	Identify population-based new use of APs among youth	IP and OP youth new AP users on Medicaid or uninsured.	AP- Treated	6,803	2-18	64.4	77
Crystal 2009 (21) /USA/ Longitudinal	Medicaid Analytic Extracts and Thomson MarketScan data/ 1996-2006	Describe AP use in youth with Medicaid vs private insurance	Youth receiving AP on Medicaid or private insurance	AP- Treated	T1:55,154 T2:104, 288	6-17	71 (69)	47 (49)
DosReis 2011 (22) /USA/ Cross-sectional	Medicaid fee-for- service and managed care claims data from 1 Mid-Atlantic state/2003	Compare AP use among Medicaid- enrolled youth in foster care with disabled or low-income Medicaid youth	IP and OP youth enrolled in a Mid- Atlantic state Medicaid program	AP- Treated	16,969	0-19	70	67
Fullerton 2012 (23) /USA/ Longitudinal	Florida Medicaid claims/1996-2005	Assess trends and cost in use of pharmaceuticals among youth with ADHD	IP and OP youth with ADHD on Medicaid	ADHD	T1:16,794 T2: 27,369	3-17	78 (73)	50 (40)

Study/Country/ Design	Data Base/ Time Period	Aims	Overall Population	Youth Cohort	N	Age (years)	% Male T1 (T2)	% White T1 (T2)
Garfield 2012 (24) /USA/ Longitudinal	IMS Health National Disease and Therapeutic Index/2000-2010	Quantify changes in the diagnosis of ADHD and its pharmacologic treatment	OP youth with ADHD	ADHD	T1:5,725,000 T2:9,878,000	0-18	77 (74)	NR
Goodwin 2001 (25) /USA/ Cross-sectional	National Ambulatory Medical Care Survey/ 1992- 1996	Determine sociodemographic characteristics of treatment of youth for whom psychotropic medications are prescribed	OP youth receiving psychotropic prescription	AP- Treated	34	0-19	47	64.5
				ADHD	155	0-19	NR	NR
Halloran 2010 (26) /USA/ Cross-sectional	Inpatient and outpatient administrative claims records/ 2002-2005	Evaluate the prevalence of atypical AP use and associated diagnoses in privately insured youth	IP and OP youth in the Midwest on private insurance	AP- Treated	2,194	2-18	64	NR
Hodgkins 2011 (27) / Netherlands/ Cross- sectional	PHARMO medical record/2000-2007	Estimate the incidence and prevalence of youth receiving initial pharmacotherapy for ADHD	Youth newly prescribed ADHD medication in the Netherlands	ADHD	4,909	6-17	82	NR
Matone 2012 (3) /USA/ Longitudinal	Medicaid Analytic Extract (MAX) files for 50 states and the District of Columbia/2002 to 2007.	Describe the relationship between mental health diagnosis and treatment with APs among U.S. Medicaid- enrolled youth	IP and OP youth on for Medicaid	AP- Treated	T1:218,763 T2:354,425	3-18	NR	NR
				ADHD	T1:346,290 T2:482128	3-18	NR	NR
				ALL Youth	T1:13,696,748 T2:15,461,455	3-18	51	40
Olfson 2012 (1) /USA/ Longitudinal (only cross-sectional data available)	National Ambulatory Medical Care Surveys/ 1993- 2009	Compare national trends and patterns in AP treatment of adults and youths	OP children, teens and adults receiving APs	AP- Treated	527	0-19	70	74
				All Youth	28,801	0-19	50.3	62
Olfson 2010 (28) /USA/ Longitudinal	MarketScan Research Databases of privately insured/1999 and 2007	Describe recent trends and patterns in AP treatment of privately insured children	OP children privately insured	AP- Treated	T1: 314 T2: 1202	2-5	82	NR
				All Youth	T1:400,196 T2:755,793	2-5	51.2 (51.0)	
Patel 2006 (29) /USA/ Longitudinal	Texas Medicaid Vendor Drug database/ 1998-2001	Evaluate trends in psychiatric diagnoses of youth in a public mental health system who were prescribed APs	IP and OP youth in public mental health facilities prescribed AP on Medicaid	AP- Treated	T1:2355 T2:2506	0-19	72 (71)	44 (43)
Pathak 2010 (9) /USA/ Cross-sectional	Medicaid claims database/ 2001 and 2005	Identify children in a state Medicaid population who were	IP and OP youth newly started on AP both on	AP- Treated	11,700	0-18	34	61

Study/Country/ Design	Data Base/ Time Period	Aims	Overall Population	Youth Cohort	N	Age (years)	% Male T1 (T2)	% White T1 (T2)
		newly treated with second- generation APs	Medicaid					
Pringsheim 2011 (30) /Canada/ Longitudinal	IMS Brogan databases/ 2005-2009	Describe the frequency and trends of AP use in Canadian children and adolescents	Canadian youth	AP- Treated	NR	0-18	NR	NR
Zito '99 (31) /USA/ Cross-sectional	Annual Ambulatory medical care survey/1989-1996	Describe findings and trends for US youth treated for ADHD	OP youth treated for ADHD	ADHD	781	5-14	79.6	87.2
Zito 2008 (32) /USA/ Cross-sectional	Medicaid data/July 2004	Describe and quantify patterns of treatment in a sample of youth in foster care	Medicated youth in foster care from the Southwestern USA on Medicaid	ADHD	183	0-19	NR	NR
Zito 2013 (10) /USA/ Longitudinal	Medicaid administrative claims data/1997-2006	Evaluated the impact of Medicaid eligibility on the increased use of APs by Medicaid-insured youths across a decade	IP and OP youth continuously enrolled in Medicaid in a mid- Atlantic state	AP- Treated	T1: 1860 T2:9556	2-17	71 (68)	48 (47)
				ADHD	T1: 288 T2: 2991	2-17	NR	NR
				All Youth	T1: 159,171 T2: 297,144	2-17	50	27
Total: 21Studies	Longitudinal data: N=11 Cross-sectional data: N=10	Description of youth receiving antipsychotics (N=11) or psychotropics (N=2), youth with ADHD (N=5), or all youth (N=3)	Outpatients (N=7) Medicaid (N=13) Private (N=3)	AP- treated N=15; ADHD N=9; All Youth N=5	Cross- sectional or T1: n=20,249,592; ADHD: n=6,192,368	Range: 0-19	65.5%	57.3%

ADHD: attention-deficit / hyperactivity disorder; AP: antipsychotic; IP: inpatient; NR: not reported; OP: outpatient

Table 2

Demographic Illness and Treatment Variables in Three Antipsychotic Treated Pediatric Cohorts Containing Youth with ADHD

Variable	Antipsychotic Treated Youth				ADHD Youth Treated With Antipsychotics				General Population Youth Cohorts			
	N	X-sectional + Time 1	N	Time 1	Time 2	N	X-sectional + Time 1	N	Time 1	Time 2	N	X-sectional + Time 1
Time *	15	2003	7	1998	2007	9	2004	4	1998	2006	5	2003
N Total Cohort	15	341,586	7	750,423	471,977	-	-	-	-	-	5	14,284,916
				278,446	471,977							30,770,507
N ADHD Subjects	15	70,421	7	124,740		9	6,192,368	4	16,478,860		2	836,994
				43,074	81,666				6,088,372	10,390,488		346,686
N ADHD on antipsychotics	-	-	-	-	-	9	159,048	4	496,062		4	27,290
									142,886	353,176		79,563
Mean Age (yrs)	3	9.5±4.5	-	-	-	1	9.2	-	-	-	-	-
Age groups (%)												
0-5 years	12	23.0±37.0	6	22.9±38.6		6	3.7±4.1	3	5.1±4.6		3	45.6±47.2
5-9 years	5	22.3±13.6	3	22.0±19.0		3	43.3±6.4	1	36.0		1	35.0
6-12 years	8	33.8±23.3	4	33.9±24.9		3	56.3±7.5	2	60.0±5.6		1	38.0
10-14 years	5	30.0±18.9	3	25.0±24.0		3	48.3±3.2	1	46.0		1	27.0
13-18 years	8	36.7±23.5	4	38.8±27.3		3	36.3±8.6	2	32.5±7.8	1		38.0
15-19 years	5	19.2±14.1	3	10.0±8.6		3	7.3±7.5	1	15.0		1	23.0
Male (%)	12	65.6±12.9	4	74.0±5.3	71.5±4.5	5	77.3±4.5	2	77.5±0.7	73.5±0.7	3	50.6±0.57
White (%)	10	59.3±14.9	3	46.3±2.1	46.3±3.0	2	68.6±26.3	1	50.0	40.0	2	33.5±9.2
US Studies (N, %)	15	13 (86.7)	7	5 (71.4)		10	8 (88.8)	4	4 (100.0)		4	4 (75.0)
Insurance (%)												
Private	13	24.1±37.6	5	24.8±43.3		6	36.3±42.5	3	18.6±32.3		2	0.0±0.0
Medicaid	13	67.6±43.2	5	77.2±43.5		6	59.8±45.4	3	78.3±37.5		2	100±0.0
Uninsured	12	9.4±28.7	5	0.0±0.0		5	0.0±0.0	2	0.0±0.0		2	0.0±0.0
Foster Care (%)	2	66.0±48.1	1	32.0	25.0	1	100.0	-	-	-	-	-
Diagnoses (%)												

Variable	Antipsychotic Treated Youth				ADHD Youth Treated With Antipsychotics				General Population Youth Cohorts			
	N	X-sectional + Time 1	N	Time 1	Time 2	N	X-sectional + Time 1	N	Time 1	Time 2	N	X-sectional + Time 1
ADHD	-	-	-	-	-	-	-	-	-	-	2	1.56±1.25
Bipolar D/o	-	-	-	-	-	2	4.3±2.9	1	2.2	6.7	2	0.04±0.03
DBDs	-	-	-	-	-	3	10.5±3.7	1	14.0	26.0	2	0.49±0.17
Depression	-	-	-	-	-	3	6.1±3.5	1	5.5	4.5	2	0.32±0.34
PDD/MR	-	-	-	-	-	-	-	-	-	-	2	0.31±0.12
Anxiety D/o's	-	-	-	-	-	1	1.3	-	-	-	2	0.25±0.03
Psychotic D/o	-	-	-	-	-	-	-	-	-	-	2	0.01±0.002
Non-AP Rx (%)	-	-	-	-	-	-	-	-	-	-	-	-
Stimulants	-	-	-	-	-	7	74.9±20.0	2	78.5±24.7	75.0±16.9	-	-
Antidepressants	-	-	-	-	-	5	19.7±17.8	1	15.5	10.5	-	-
Clonidine	-	-	-	-	-	5	13.5±8.6	2	11.2±3.1	13.1±0.1	-	-

ADHD: attention-deficit/hyperactivity disorder; AP: antipsychotic; DBD: disruptive behavior disorder; D/o: disorder; MR: mental retardation; PDD: pervasive developmental disorder; Rx: treatment

* Time of the study is the total mean of medians from individual study periods; all other values are means ± standard deviations

Table 3

Antipsychotic Treated Youth: Prevalence and Trends for Youth with ADHD and those with Other Diagnoses

Variable	N*	X-sectional + Time 1 Median: 2003 (mean % $\pm$ SD)	N*	Time 1 Median: 1998 (mean % $\pm$ SD)	Time 2 Median: 2007 (mean % $\pm$ SD)	Ratio (mean $\pm$ SD)
ADHD	15	30.5 $\pm$ 18.5 N=70,421	7	21.7 $\pm$ 7.1 N=43,074	27.7 $\pm$ 7.7 N=81,666	1.3 $\pm$ 0.4
ADHD+DBD	2	6.9 $\pm$ 5.0 N=17,057	2	6.9 $\pm$ 5.0 N=17,057	7.7 $\pm$ 1.8 N=31,170	1.4 $\pm$ 0.8
PDD/MR	9	10.9 $\pm$ 9.8 N=14,146	5	6.9 $\pm$ 6.7 N=8,553	8.3 $\pm$ 11.3 N=15,030	0.9 $\pm$ 0.4 [†]
Mood Disorder	5	24.0 $\pm$ 27.3 N=1462	3	16.3 $\pm$ 20.0 (N=n/a)	12.1 $\pm$ 10.3 (N=n/a)	1.5 $\pm$ 1.2 [†]
Depression	10	15.3 $\pm$ 13.8 N=25,859	4	10.1 $\pm$ 5.7 N=12,464	10.2 $\pm$ 6.5 N=17,588	1.0 $\pm$ 0.2
Bipolar D/o	11	11.4 $\pm$ 5.8 N=21,099	5	9.0 $\pm$ 4.3 N=13,326	11.9 $\pm$ 5.9 N=33,300	1.3 $\pm$ 0.3
Anxiety D/o	10	10.3 $\pm$ 12.6 N=13,167	4	3.6 $\pm$ 3.5 N=6,968	3.1 $\pm$ 3.0 N=13,070	1.0 $\pm$ 0.4
DBD	14	31.3 $\pm$ 22.6 N=37,170	7	18.7 $\pm$ 10.5 N=18,074	18.0 $\pm$ 10.9 N=26,310	0.9 $\pm$ 0.1
Psychotic D/o	15	8.8 $\pm$ 5.9 N=11,164	7	6.4 $\pm$ 5.0 N=3,558	5.0 $\pm$ 6.7 N=4,369	0.6 $\pm$ 0.4

ADHD: attention-deficit/hyperactivity disorder; AP: antipsychotic; DBD: disruptive behavior disorder; D/o: disorder; MR: mental retardation; n/a: not available; PDD: pervasive developmental disorder; Rx: treatment

* not all studies provided information on the number of patients for all or any of the diagnostic subgroups

[†] the observed trend reversal between mean ratio and mean difference is due to the fact that the ratio is a proportional number that depends on the absolute percent values at each time point that are divided by each other, while the difference depends only on the delta between the value at each time point

Table 4

Cohorts of Youth with ADHD: Prevalence and Trends of Antipsychotic Use in Youth with ADHD as well as those with Other Diagnoses Reported on in the Same Studies

Variable	N*	X-sectional + Time 1 Median: 2004 (mean % $\pm$ SD)	N*	Time 1 Median: 1998 (mean % $\pm$ SD)	Time 2 Median: 2006 (mean % $\pm$ SD)	Ratio (mean $\pm$ SD)
ADHD	9	11.5 $\pm$ 17.3 N=159,048	4	5.5 $\pm$ 2.6 N=142, 886	11.4 $\pm$ 6.7 N=353,176	2.1 $\pm$ 0.6
ADHD + DBD	2	15.0 $\pm$ 7.1 N=13,362	2	15.0 $\pm$ 7.1 N=11,551	23.5 $\pm$ 0.7 N=22,724	1.7 $\pm$ 0.8
ADHD+Bipolar D/o	1	28.0 N=8,055	1	28 (N=n/a)	51 (N=n/a)	1.8
ADHD+Mood D/o	2	15.5 $\pm$ 6.3 N=9,259	2	15.5 $\pm$ 6.4 N=3,046	20.6 $\pm$ 0.9 N=4,421	1.4 $\pm$ 0.5
ADHD+Anxiety D/o	1	12.5 N=463	1	12.5 N=381	15.8 N=991	1.3
DBD	2	8.7 $\pm$ 1.3 N=10,702	2	8.7 $\pm$ 1.3 N=10,731	15.0 $\pm$ 9.9 N=15,195	1.6 $\pm$ 0.9
Bipolar Disorder	2	44.6 $\pm$ 1.1 N=4,591	2	44.6 $\pm$ 1.1 N=4,667	61.6 $\pm$ 14.8 N=12,289	1.4 $\pm$ 0.4
Depression	2	9.6 $\pm$ 1.8 N=6,706	2	9.5 $\pm$ 1.7 N=6,732	15.0 $\pm$ 9.2 N=8,067	1.5 $\pm$ 0.7
PDD/MR	1	14.2 N=5,204	1	14.2 N=5,233	38.6 N=9,270	2.7

ADHD: attention-deficit/hyperactivity disorder; AP: antipsychotic; DBD: disruptive behavior disorder; D/o: disorder; MR: mental retardation; n/a: not available; PDD: pervasive developmental disorder; Rx: treatment

* not all studies provided information on the number of patients for all or any of the diagnostic subgroups;

Table 5

Cohorts of Youth in the General Population: Prevalence and Trends of Antipsychotic Use in Youth with ADHD and Compared to Youth with Other Diagnoses

Variable	N*	X-sectional + Time 1 Median: 2003 (mean % $\pm$ SD)	N*	Time 1 Median: 1993 (mean % $\pm$ SD)	Time 2 Median: 2007 (mean % $\pm$ SD)	Ratio (mean $\pm$ SD)
ADHD	5	0.12 $\pm$ 0.07 N=27,630	3	0.13 $\pm$ 0.09 N=26,610	0.44 $\pm$ 0.49 N=51,978	3.1 $\pm$ 2.2
ADHD + DBD	1	0.08 N=11,578	1	0.08 N=11,579	0.14 N=22,790	1.75
ADHD + PDD/MR	1	0.02 N=3,333	1	0.02 N=2,580	0.02 N=4,380	1.40
DBDs	3	0.09 $\pm$ 0.08 N=11,320	3	0.09 $\pm$ 0.08 N=11,065	0.22 $\pm$ 0.25 N=16,508	2.2 $\pm$ 0.5
Bipolar Disorder	2	0.05 $\pm$ 0.06 N=4,840	2	0.05 $\pm$ 0.06 N=4,734	0.25 $\pm$ 0.35 N=12,609	3.0 $\pm$ 2.8
Depression	2	0.05 $\pm$ 0.07 N=6,976	2	0.05 $\pm$ 0.07 N=6,933	0.18 $\pm$ 0.25 N=8,937	4.4 $\pm$ 0.9
PDD/MR	2	0.03 $\pm$ 0.02 N=5,475	2	0.03 $\pm$ 0.02 N=5,429	0.05 $\pm$ 0.01 N=9,812	2.6 $\pm$ 1.9

ADHD: attention-deficit/hyperactivity disorder; AP: antipsychotic; DBD: disruptive behavior disorder; D/o: disorder; MR: mental retardation; PDD: pervasive developmental disorder; Rx: treatment

* not all studies provided information on the number of patients for all or any of the diagnostic subgroups