Metabolic and Cardiovascular Adverse Events Associated With Antipsychotic Treatment in Children and Adolescents

Roger S. McIntyre, MD, FRCPC; Jeanette M. Jerrell, PhD

Objective: To identify factors associated with incident cardiovascular events and metabolic disturbance in children and adolescents treated with antipsychotics.

Design: A retrospective cohort design evaluating Medicaid medical and pharmacy claims.

Setting: South Carolina’s Medicaid program covering outpatient and inpatient medical services and medication prescriptions from January 1, 1996, through December 31, 2005.

Participants: A treatment cohort of 4140 children and adolescents prescribed 1 of 5 atypical or 2 conventional antipsychotics, and a random sample of 4500 children not treated with psychotropic medications.

Main Exposure: Antipsychotics.

Main Outcome Measures: Incidence/prevalence rates for obesity, type 2 diabetes mellitus, dyslipidemia, cardiovascular events, cerebrovascular events, hypertension, and orthostatic hypotension.

Results: Compared with the control sample, the treated cohort had a higher prevalence of obesity (odds ratio [OR], 2.13), type 2 diabetes mellitus (OR, 3.23), cardiovascular conditions (OR, 2.70), and orthostatic hypotension (OR, 1.64). In the treated cohort, patients exposed to multiple antipsychotics were at significantly higher risk for incident obesity/weight gain (OR, 2.28), type 2 diabetes mellitus (OR, 2.36), and dyslipidemia (OR, 5.26). Incident cardiovascular events were more likely with the use of conventional (OR, 4.34) or multiple (OR, 1.57) antipsychotics and mood stabilizers (OR, 1.31). Incident orthostatic hypotension was more prevalent in those co-prescribed selective serotonin reuptake inhibitors (OR, 1.77) and mood stabilizers (OR, 1.35).

Conclusion: Antipsychotics are associated with several metabolic and cardiovascular-related adverse events in pediatric populations, especially when multiple antipsychotics or classes of psychotropic medications are co-prescribed, controlling for individual risk factors.

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During the past decade, there has been a substantial increase in the use of antipsychotics, predominantly atypical or second-generation antipsychotics (SGAs), in young persons treated in privately and publicly insured systems. However, a paucity of controlled studies provide a quantitative estimate of the relative risks associated with these agents in young populations. In clinical trials and case reports, the most frequently identified cardiovascular adverse effects of conventional antipsychotics and SGAs in children were orthostatic hypotension, tachycardia, QTc interval prolongation, and arrhythmias. Reports of electrocardiographic changes, myocarditis, and cerebrovascular events provide the impetus for questioning the cardiovascular safety of antipsychotics across all age groups.

Furthermore, a diverse array of metabolic tolerability and safety concerns attributable to SGAs has previously been documented in adult populations, and SGAs are associated with clinically significant weight gain and alterations in metabolic indexes (eg, type 2 diabetes mellitus and dyslipidemia) in children and adolescents. The morbidity associated with antipsychotic treatment may also relate to comorbid medical conditions and concomitant medication use. The prevalence of obesity and associated complications (eg, diabetes mellitus and primary hypertension) in these populations has increased significantly during the past 2 decades. A growing database indicates that cardiometabolic disorders may differentially affect African American patients. The increased rate of diabetes mellitus and associated dyslipidemia in pe-
diabetic populations portends a greater risk for cardiovascular disease, which is the most frequent cause of premature death in individuals with mood and psychotic disorders.\(^5\)\(^{14} \)\(^{-} \)\(^{17}\) Therefore, elucidating iatrogenic factors that contribute to this risk is a clinical research priority.\(^15\) Any investigation of the association between SGA use and incident metabolic disruption or cardiovascular conditions needs to adjust for preexisting medical comorbidities and salient individual risk factors.

Antipsychotics are prescribed for disparate mental disorders, including psychotic, affective, impulse-control, externalizing behavioral, and tic disorders,\(^18\)\(^{-} \)\(^{19}\) increasingly in combination with other psychotropic agents, which further introduces the possibility for additive or multiplicative adverse events.\(^19\)\(^{-} \)\(^{20}\) Cardiovascular adverse events have been reported for several classes of psychotropic agents frequently prescribed in pediatric populations. For example, cardiac conduction delays, proarrhythmic effects, orthostatic hypotension, and metabolic disturbances are known adverse effects of tricyclic antidepressants and several selective serotonin reuptake inhibitors.\(^21\)\(^{-} \)\(^{24}\) In addition, therapeutic use of psychostimulants is associated with several cardiovascular-related events such as angina, sinus tachycardia, hypertension, hypotension, sudden death, and myocardial infarction.\(^25\)\(^{-} \)\(^{26}\) For complex mood disorder presentations (eg, bipolar disorder), mood stabilizers are frequently prescribed, some of which may have hazardous effects on cardiovascular function or the metabolic milieu.\(^7\)

There is a pressing need to characterize the adverse event profile associated with antipsychotic use in children and adolescents. Herein, we aim to compare the incidence/prevalence of metabolic, cardiovascular, and cerebrovascular events in an antipsychotic-treated cohort from the Medicaid system of a single state with those in a random sample of children served through Medicaid with no exposure to psychotropic medications, and to identify the risk factors associated with metabolic, cardiovascular, and cerebrovascular events, controlling for comorbid conditions, the coprescription of other psychotropic medications, and individual risk factors.

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**COHORT SELECTION**

Claims data for South Carolina’s Medicaid program were obtained through the state’s Office of Research and Statistics. Each Medicaid medical claim identifies a service encounter and gives the date of service and the diagnosis codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* related to that visit (visit file). Pharmacy claims identified the medication dispensed and the date the prescription was filled (pharmacy file). A separate data file regarding eligibility was used to summarize the demographics for each patient (person file). The databases are frequently updated before being made available for analysis. This study was approved by the University of South Carolina institutional review board as exempt from human subject research guidelines.\(^27\)

Medical and pharmacy claims for the calendar years from January 1, 1996, through December 31, 2005, were used to identify a cohort of children and adolescents (≤17 years of age) enrolled in and eligible for Medicaid for a minimum of 9 months in each calendar year included in this analysis, who had a service encounter, and who were prescribed 1 of 3 atypical antipsychotics (ie, aripiprazole, ziprasidone hydrochloride, quetiapine fumarate, risperidone, or olanzapine) or 2 conventional antipsychotics (haloperidol or fluphenazine hydrochloride) between January 1, 1998, and December 31, 2003. The date of the first prescription of an antipsyicotic in the Medicaid data set was defined as the selection encounter date.

From the same population and the same period, medical and pharmacy claims were also used to identify a randomly selected group of children and adolescents (≤17 years of age) eligible for Medicaid 9 of 12 months in all of the calendar years of the study and who had service encounters but no prescriptions in the database for any class of psychotropic medication (antipsychotics, antidepressants, mood stabilizers, or psychostimulants). This process resulted in the identification of 40,660 patients who met the criteria. From this group, a random sample of 4,500 patients was selected to use as a representative control group.

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**ADVERSE EVENT CODING**

Metabolic, cardiovascular, or cerebrovascular medical conditions that were detected in the 24 months before each patient’s selection encounter date were coded as preexisting for this study. If the patient developed a medical condition subsequent to the prescription of the antipsychotic medication, new variables were created for these incident events. In the control group, detection of any of the metabolic, cardiovascular, or cerebrovascular medical conditions in a service billing record was coded. The following categories of conditions and events were evaluated: obesity and excessive weight gain (ICD-9-CM codes 278, 278.00, 278.01, 783.1, and 783.2). dyslipidemia (codes 272, 272.0-272.9, 288.0, and 285.9), type 2 diabetes mellitus (codes 230 and 230.00-251.92 with the fifth digit 0 or 2), hypertension (codes 401-405), cardiovascular events (codes for myocardial infarction [410-412], ischemic/pulmonary heart disease [413-416 and 428-429], arrhythmias [426-427], and cardiomyopathy [425]), cerebrovascular events (codes for cerebrovascular disease [436-437], cerebrovascular accident [435], cerebrovascular hemorrhage [430-434], and peripheral vascular disease [440-448]), and orthostatic hypotension/syncope (codes 458 and 780.2). Comorbid conditions of congenital heart defects were assigned codes 747.0 through 747.9, and a substance-related disorder was assigned codes 304 and 305.

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**METHODS**

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**STATISTICAL ANALYSIS**

To address research questions regarding differences in the incidence/prevalence of the metabolic, cardiovascular, and cerebrovascular conditions and events in the treated vs control groups, 6 multiple logistic regression equations were constructed to assess the relative odds associated with developing each adverse event, using the control group as the primary comparator, and controlling for the 3 dichotomously coded individual risk factors of sex (male or female), ethnicity (African American or other), and age (≤12 years or ≥13 years). Then, to identify factors associated with the metabolic, cardiovascular, and cerebrovascular events in the treated cohort of pediatric patients prescribed antipsychotics, we constructed 7 separate multiple logistic regression equations to assess the relative odds associated with developing each adverse event under scrutiny, using the antipsychotic medication groupings as the main covariates, with olanzapine as the comparator, and controlling for the 3 dichotomously coded individual risk factors. Risperidone was the antipsychotic most frequently prescribed in the database as monotherapy and in combination with other...
pharmacological agents; therefore, olanzapine, the next most frequently used agent, was chosen as the primary comparator to avoid comparing risperidone with itself.

To address research questions regarding the role of comorbid medical conditions and concomitant psychotropic medications on the development of metabolic or cardiovascular conditions in the cohort treated with antipsychotics, the following 3 separate logistic regressions were constructed: (1) independent covariates coded for preexisting obesity and hypertension, preexisting type 2 diabetes mellitus and dyslipidemia, and incident type 2 diabetes mellitus and dyslipidemia using cardiovascular events as the dependent variable; (2) covariates controlling for the concomitant use of antidepressants, mood stabilizers, and psychostimulants and for comorbid congenital heart defects and substance-related disorders in regression equations using cardiovascular events as the dependent variable; and (3) 2 independent covariates coded for prescribed antidepressants likely to cause weight gain and for prescribed mood stabilizers were added to the logistic regression equation predicting development of obesity/excessive weight gain.

Antidepressants categorized as selective serotonin reuptake inhibitors included citalopram, escitalopram, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine, sertraline hydrochloride, and olanzapine and fluoxetine. Those categorized as tricyclic antidepressants included desipramine hydrochloride, doxepin hydrochloride, doxepin hydrochloride, imipramine hydrochloride, amitriptyline hydrochloride, nortriptyline hydrochloride, protriptyline hydrochloride, trimipramine maleate, and clomipramine hydrochloride. The antidepressants coded as likely to cause weight gain were amitriptyline, nortriptyline, mirtazapine, and paroxetine. Mood stabilizers coded in the regression equations included divalproex sodium, lithium carbonate, and carbamazepine. Psychostimulants coded in the analyses included methylphenidate hydrochloride, dextroamphetamine sulfate, and amphetamine salts.

Using Kaplan-Meier survival analysis, we assessed the time elapsed from the prescription of an antipsychotic to the first diagnosis of 1 of the 7 primary metabolic or cardiovascular conditions. We then used a Cox proportional hazards model regression (SAS PROC PHREG; SAS Institute Inc, Cary, North Carolina) to determine whether there were differences in the time elapsed to the adverse event, using the individual antipsychotics as the main covariates and controlling for the 3 individual risk factors.

**RESULTS**

The demographics and diagnostic information on psychiatric and comorbid medical conditions for the cohort are presented in Table 1. Dosages in the risperidone group ranged from 0.25 to 4.0 (mode, 0.5 or 1.0) mg/d, and girls were likely to be prescribed higher doses. In the olanzapine group, dosages ranged from 2.5 to 20.0 (mode, 2.5 or 5.0) mg/d. For quetiapine fumarate, the dosages ranged from 25 to 300 (mode, 25 or 100) mg/d, and a higher percentage of girls were prescribed the medication at every dosage. Aripiprazole dosages ranged from 5 to 30 (mode, 5 or 10) mg/d, and a slightly higher percentage of boys were consistently prescribed the higher dosages. Ziprasidone dosages ranged from 20 to 80 (mode, 20 or 40) mg/d, and a consistently higher percentage of girls were prescribed each dosage.

An additional medication group was created because of the large percentage of individuals receiving combination antipsychotic pharmacotherapy (ie, 1756 patients [42.4%] were prescribed >1 SGA). The numbers of patients in each of the monotherapy medication groups were 38 for aripiprazole, 87 for ziprasidone, 266 for quetiapine, 1634 for risperidone, and 326 for olanzapine. Thirty-two patients were prescribed haloperidol (conventional). These low rates of use may reflect the differential introduction of SGAs into the American marketplace and their subsequent approval for Medicaid reimbursement, that is, risperidone in 1993, olanzapine in 1996, quetiapine in 1997, ziprasidone in 2000, and aripiprazole in 2002.

**COMPARISON OF THE TREATED COHORT AND UNTREATED CONTROL SAMPLE**

The incidence/prevalence rates for the 3 metabolic and 4 cerebrovascular- and cardiovascular-related conditions are presented in Table 2. The prevalence rates of these conditions in the untreated control sample are also presented in Table 2. Table 3 presents statistical comparisons of the treated cohort and untreated control sample, controlling for differences in the 3 individual risk factors. The cohort treated with antipsychotics was more likely to have been diagnosed as having obesity (odds ratio [OR], 2.13), type 2 diabetes (OR, 3.23), cardiovascular conditions (OR, 2.70), and orthostatic

### Table 1. Descriptive Analysis of the Cohort of 4140 Youths Prescribed Antipsychotics

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male: 2825 (68.2); Female: 1315 (31.8)</td>
</tr>
<tr>
<td>Race</td>
<td>White: 1722 (41.6); African American: 1680 (40.6); Hispanic: 13 (0.3); Asian: 6 (0.1); Unknown, mixed: 719 (17.4)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>10.4 (3.6)</td>
</tr>
<tr>
<td>Psychiatric diagnoses</td>
<td>Schizophrenia: 358 (8.6); Major affective disorders: 2261 (54.6); Other psychotic disorders: 1149 (27.8); Conduct disorder or oppositional-defiant disorder: 2970 (71.7); Attention-deficit/hyperactivity disorder: 3258 (78.7)</td>
</tr>
<tr>
<td>Comorbid disorders</td>
<td>Convulsions: 954 (23.0); Central nervous system disorders: 919 (22.2); Organic brain syndrome or severe mental retardation: 704 (17.0); Congenital heart defects: 146 (3.5); Substance-related disorder: 490 (11.8)</td>
</tr>
<tr>
<td>Concomitant psychotropic medications</td>
<td>TCAs: 716 (17.3); SSRIs: 2367 (57.2); Psychostimulants: 3170 (76.6); Mood stabilizers: 1898 (45.8); Weight-inducing antidepressants: 3292 (79.5)</td>
</tr>
</tbody>
</table>

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

aUnless otherwise indicated, data are expressed as number (percentage) of patients.
hypotension (OR, 1.64), whereas the untreated control sample was more likely to have been diagnosed as having dyslipidemia (OR, 3.01) or hypertension (OR, 2.35).

### OBESITY/WEIGHT GAIN

The odds of incident obesity/excessive weight gain were higher for girls (OR, 1.75; 95% CI, 1.43-2.17), adolescents 13 years or older (1.34; 1.09-1.66), and those exposed to multiple antipsychotics (2.28; 1.43-3.65), high-risk antidepressants (1.66; 1.22-2.26), and mood-stabilizing medications (1.78; 1.44-2.20). African American patients had a lower risk for incident obesity/weight gain (0.69; 0.56-0.85). The mean (SD) age at the time of the initiation of antipsychotic therapy was 11.0 (3.6) years, and the mean (SD) age at onset of obesity/excessive weight gain was 13.3 (3.7) years.

### TYPE 2 DIABETES MELLITUS

The odds of developing type 2 diabetes mellitus were higher for girls (OR, 1.79; 95% CI, 1.28-2.50), adolescents aged 13 years or older (1.52; 1.08-2.13), and those exposed to multiple antipsychotics (2.36; 1.13-4.92). The mean (SD) age at the time of the initiation of antipsychotic therapy was 11.4 (3.4) years, whereas the mean (SD) age at onset for incident type 2 diabetes mellitus was 13.8 (3.8) years. There was a significant difference in time elapsed, that is, a longer time from the initiation of therapy with the antipsychotic agent aripiprazole to an incident diagnosis of type 2 diabetes mellitus (hazard ratio [HR], 35.92; 95% CI, 3.45-373.80).
DYSLIPIDEMIA

The odds of incident dyslipidemia were higher for girls (OR, 2.08; 95% CI, 1.41-3.03), adolescents 13 years or older (2.08; 1.41-3.03), and those exposed to multiple antipsychotics (5.26; 1.64-16.82). The mean (SD) age at the initiation of antipsychotic therapy was 11.8 (3.6) years, whereas the mean (SD) age at onset of dyslipidemia was 14.3 (3.9) years. There was a marginally significant difference in the time elapsed across the individual risk factors or medication groups to incident dyslipidemia, with a shorter time from the initiation of therapy with multiple agents to dyslipidemia (HR, 0.44; 95% CI, 0.22-0.89). After being exposed to antipsychotics, the risk of patients with preexisting obesity and hypertension developing type 2 diabetes or dyslipidemia was 4.5 times greater than that of patients without the preexisting conditions (OR, 4.46; 95% CI, 3.03-6.57).

HYPERTENSION

The odds of developing incident hypertension were significantly higher for adolescents 13 years or older (OR, 2.78; 95% CI, 1.69-4.55) but were unrelated to which antipsychotics were received. The mean (SD) age at the time of the initiation of antipsychotic therapy was 12.2 (3.6) years; the mean (SD) age at onset of hypertension was 15.0 (3.8) years.

CARDIOVASCULAR EVENTS

The regression equation modeling the risk of developing incident cardiovascular events (predominantly ischemic/pulmonary heart disease [n = 77] and arrhythmias [n = 126], ie, cardiomegaly, heart disease not otherwise specified [NOS], tachycardia, and arrhythmia NOS) in relation to comorbid conditions was significant. As presented in Table 4, the odds of developing cardiovascular events were higher for those receiving conventional antipsychotics and those exposed to multiple antipsychotics. The odds of developing a cardiovascular event were 1.9 times greater in patients with preexisting type 2 diabetes mellitus and dyslipidemia. Those with incident type 2 diabetes mellitus and dyslipidemia (after exposure to antipsychotics) had 2.1 higher odds of subsequently developing a cardiovascular event. The odds of developing cardiovascular events were significantly higher for those prescribed conventional or multiple antipsychotics, those prescribed a mood stabilizer, those with congenital heart defects, and those with substance-related disorders (Table 5). The mean (SD) age at the initiation of antipsychotic therapy was 10.2 (3.6) years; the mean (SD) age at onset of incident cardiovascular events was 12.4 (4.0) years.

CEREBROVASCULAR EVENTS

Findings of the regression equation for cerebrovascular events were nonsignificant. The mean (SD) age at the initiation of antipsychotic therapy was 10.9 (3.8) years; the mean (SD) age at onset of cerebrovascular events was 13.8 (4.2) years.

ORTHOSTATIC HYPOTENSION

The odds of developing orthostatic hypotension/syncope were significantly higher for girls (OR, 1.47; 95% CI, 1.11-1.92), those receiving selective serotonin reuptake inhibitors (1.77; 1.31-2.39) and mood stabilizers (1.35; 1.03-1.77), and individuals not receiving psychostimulants (0.65; 0.48-0.88). The mean (SD) age at the initiation of antipsychotic therapy was 11.6 (3.3) years;
The results of this investigation indicate that, compared with untreated youth, girls, adolescents, and individuals prescribed combination antipsychotic therapy or concomitant treatment with antidepressants or mood stabilizers (ie, exposed to weight-inducing treatments), especially during the long term (24-36 months), are at increased risk for metabolic disruption. The use of antipsychotics was also associated with cardiovascular adverse events, notably cardiomegaly, heart disease NOS, tachycardia, and arrhythmia NOS, and with orthostatic hypotension/syncope, as has been previously noted in clinical trials and case reports. Individuals receiving conventional antipsychotics, multiple antipsychotics, and mood stabilizers and individuals with congenital heart defects, comorbid substance abuse, and comorbid type 2 diabetes mellitus and dyslipidemia were at higher risk of developing cardiovascular-related events. We can speculate that the antipsychotic treatment may have predisposed or exacerbated metabolic changes subsequently leading to cardiovascular events. Other hypothetical mechanisms could be electrocardiographic changes (eg, QTc interval prolongation), procoagulation effects, or direct effects on blood pressure via adrenoreceptor antagonism.

These findings also confirm the results of a few previous investigations in adults. However, they do not ostensibly comport with age-adjusted general population studies in which African American patients are at higher risk of having hypertension, obesity (especially female patients), and diabetes. One explanation is that the treated cohort analyses controlled for preexisting obesity and hypertension and for dyslipidemia and type 2 diabetes mellitus, which are more prevalent in African American youth, thereby adjusting the incidence rates for hypertension and cardiovascular events. The inability to detect an association between antipsychotic use and hypertension in our analysis is in accordance with other studies that have failed to find a definitive relationship between SGAs and hypertension.

Cardiovascular toxic effects are usually associated with the use of tricyclic antidepressants and selective serotonin reuptake inhibitors. However, we did not detect a consistent association, which may be attributable to the fact that previous studies did not take into account the relative impact of concomitant medications such as mood stabilizers and the type or number of antipsychotics, or of comorbid conditions such as substance abuse or congenital heart defects, on the development of cardiovascular adverse events. Pragmatic and randomized controlled efficacy studies with antipsychotic monotherapy, or in combination with other psychotropic agents, are needed to provide a more refined estimate of the cardiovascular risk attributable to antipsychotics vs certain coprescribed antidepressants or mood stabilizers.

Of major public health concern is that, by the end of the study period, 25% of the sample had 1 to 3 comorbid chronic medical conditions (metabolic and cardiovascular), in addition to their psychiatric disorder. This rate of medical comorbidity parallels age-adjusted rates of medical disorders in the adult and child populations, where more than 20% of children have 2 or more risk factors for cardiovascular disease (obesity, metabolic disorders, and hypertension). The increased prevalence of cardiometabolic disorders in this cohort may be partially mediated by the use of psychotropic agents that disrupt the metabolic milieu. Psychiatric and primary care practitioners need to familiarize themselves with the potential for cardiometabolic toxic effects associated with antipsychotics in pediatric populations and use them sparingly in children displaying early-onset risk factors.

The perspective provided by the longitudinal database has several strengths. First, the cohort represents a large, heterogeneous group of children and adolescents with varying periods of SGA exposure ranging from brief to long-term treatment. Second, there is sufficient power in the treated cohort and untreated sample sizes to detect somewhat low-incidence conditions and to combine these conditions into related groupings. Third, previous studies have found that, although Medicaid databases provide much less detailed information on individuals than would a structured research interview, the physician diagnoses and utilization data are more reliable than client or family self-reports. Finally, the outcomes of disparate metabolic and cardiovascular events related to antipsychotic and concomitant medication use are clinically relevant and of substantial public health importance.

These results also need to be interpreted with several limitations in mind. For example, the data were not controlled and, instead, we used secondary administrative data and observational techniques in a retrospective cohort design. Second, some of the medication exposure groups included less than 5% of the cohort (ie, conventional antipsychotics, aripiprazole, and ziprasidone), and there may not have been sufficient power to determine the extent to which each adverse event is meaningfully associated with the use of antipsychotics. We have chosen to leave these groups in the logistic regression equations as controls, although they are very small and could skew the results. Third, we did not use structured research and clinical interviews to confirm any of the assigned medical disorders. Fourth, the reporting of adverse events was based on spontaneous reporting to a physician and, consequently, is likely to be an underestimate. Fifth, these results report associations and, as a result, directions of causality cannot be inferred. Sixth, key risk factors such as family history of obesity, metabolic disorders, and cardiovascular disorders were not available in the database and are not modeled in these analyses. Seventh, the truncated availability of ziprasidone and aripiprazole during the study period might limit the incidence of adverse events attributable to them, such that our conclusions may not accurately portray complications from either agent. Finally, there is no way to estimate how representative this Medicaid cohort is in relation to those in other states and service systems.
The encompassing aim of this analysis was to draw further attention to the safety profile of antipsychotics in young populations and the need for an empirical foundation to guide decision support. The results herein indicate that antipsychotics are associated with metabolic and cardiovascular adverse events in usual-care settings and are germane to the overall appraisal of the benefits and risks of this class of agents. When evaluating the overall benefit-risk ratio of antipsychotics in children and adolescents, the practitioner needs to give careful consideration to possible metabolic disruptions or cardiovascular toxic effects, especially in individuals with comorbid metabolic conditions and those receiving concomitant psychotropic medications.

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Author Contributions: Dr Jerrell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McIntyre and Jerrell. Acquisition of data: Jerrell. Analysis and interpretation of data: Jerrell. Drafting of the manuscript: McIntyre and Jerrell. Critical revision of the manuscript for important intellectual content: Jerrell and McIntyre. Statistical analysis: Jerrell. Obtained funding: Jerrell. Administrative, technical, and material support: McIntyre and Jerrell. Study supervision: Jerrell.

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REFERENCES


