Original Investigation

Antipsychotics and the Risk of Type 2 Diabetes Mellitus in Children and Youth

William V. Bobo, MD, MPH; William O. Cooper, MD, MPH; C. Michael Stein, MB, ChB; Mark Olfson, MD, MPH; David Graham, MD, MPH; James Daugherty, MS; D. Catherine Fuchs, MD; Wayne A. Ray, PhD

IMPORTANCE The increased prescribing of antipsychotics for children and youth has heightened concerns that this practice increases the risk of type 2 diabetes mellitus.

OBJECTIVE To compare the risk of type 2 diabetes in children and youth 6 to 24 years of age for recent initiators of antipsychotic drugs vs propensity score-matched controls who had recently initiated another psychotropic medication.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of the Tennessee Medicaid program with 28,858 recent initiators of antipsychotic drugs and 14,429 matched controls. The cohort excluded patients who previously received a diagnosis of diabetes, schizophrenia, or some other condition for which antipsychotics are the only generally recognized therapy.

MAIN OUTCOMES AND MEASURES Newly diagnosed diabetes during follow-up, as identified from diagnoses and diabetes medication prescriptions.

RESULTS Users of antipsychotics had a 3-fold increased risk for type 2 diabetes (HR = 3.03 [95% CI = 1.73-5.32]), which was apparent within the first year of follow-up (HR = 2.49 [95% CI = 1.27-4.88]). The risk increased with cumulative dose during follow-up, with HRs of 2.13 (95% CI = 1.06-4.27), 3.42 (95% CI = 1.88-6.24), and 5.43 (95% CI = 2.34-12.6) for respective cumulative doses (gram equivalents of chlorpromazine) of more than 5 g, 5 to 99 g, and 100 g or more (P < .04). The risk remained elevated for up to 1 year following discontinuation of antipsychotic use (HR = 2.57 [95% CI = 1.34-4.91]). When the cohort was restricted to children 6 to 17 years of age, antipsychotic users had more than a 3-fold increased risk of type 2 diabetes (HR = 3.14 [95% CI = 1.50-6.56]), and the risk increased significantly with increasing cumulative dose (P < .03). The risk was increased for use restricted to atypical antipsychotics (HR = 2.89 [95% CI = 1.64-5.10]) or to risperidone (HR = 2.20 [95% CI = 1.14-4.26]).

CONCLUSIONS AND RELEVANCE Children and youth prescribed antipsychotics had an increased risk of type 2 diabetes that increased with cumulative dose.

CONFLICTS OF INTEREST None reported.


Increasing antipsychotic use among children and youth raises the concern that this practice increases the risk of type 2 diabetes mellitus in this vulnerable population.5-7 For adults, there is considerable evidence linking antipsychotic use to increased risk of type 2 diabetes. Several antipsychotics have metabolic effects, such as weight gain, increased glucose level, and insulin resistance, that are thought to be precursors to diabetes.9 Epidemiologic studies have confirmed an increased risk for type 2 diabetes for individuals using some types of antipsychotics, particularly the atypical antipsychotic drugs.9-11 However, the evidence for children and youth is less extensive. Although metabolic studies of children suggest that antipsychotic use might increase the risk of type 2 diabetes, epidemiologic data are more limited.5-7 Obstacles to studies of this population include the lower incidence of type 2 diabetes, the need to distinguish between type 1 and type 2 diabetes, and the identification of appropriate comparison groups.

Prior to the introduction of the atypical antipsychotic drugs, the primary indications for antipsychotics in pediatric or adolescent populations were schizophrenia and other psychotic disorders. Subsequently, use expanded to include bipolar disorders, affective disorders, and symptoms related to behavior and conduct, which now account for the majority of prescriptions.5-4,14 There are other well-recognized alternative medications for each of these conditions; indeed, antipsychotics are often a secondary or off-label therapeutic choice.14-17 Thus, an increased risk of diabetes conferred by an-
Antipsychotics and the Risk of Type 2 Diabetes

Methods

Sources of Data
Study data were obtained from the computerized files of the Tennessee Medicaid program, augmented with linkage to a statewide hospital discharge database and computerized birth certificates. Study files (enrollment, pharmacy, hospital, outpatient, nursing home, and linked death certificates) allowed for the identification of the study cohort, the classification of baseline comorbidity, the tracking of medication use, and the ascertainment of diabetes.

Antipsychotics and other study medications were identified from Medicaid pharmacy files. These included the date that the prescription was dispensed, drug name, quantity, dose, and days of supply. Computerized pharmacy records are an excellent source of medication data because they are not subject to information bias and have a high level of concordance with patient self-reports of medication use. Residual misclassification should be limited and, if nondifferential, should bias toward the null.

Antipsychotic Users
The study population included children and youth 6 to 24 years of age enrolled in Medicaid for at least 1 year between January 1, 1996, and December 31, 2007. The lower age limit is the youngest age for which there are material numbers of case reports of type 2 diabetes; the upper age limit corresponds to the World Health Organization’s definition of youth. Cohort eligibility (eAppendix and eTables 1 and 2 in Supplement) required that, during the past year, there was adequate enrollment and health care utilization to ensure availability of data for study variables, no evidence of life-threatening illness or institutional residence, no evidence of diabetes, and no evidence of pregnancy (gestational diabetes might be misdiagnosed) or polycystic ovarian syndrome (treated with oral hypoglycemics). Cohort members could not have been in the hospital in the past month because changes in the medication regimen cannot be identified until up to 30 days following hospital discharge.

Cohort antipsychotic users had recently initiated antipsychotic therapy by filling an antipsychotic prescription on a day of cohort eligibility. The first such prescription during the study period was the qualifying prescription. They could have nonqualifying use of antipsychotics in the 90 days preceding the qualifying prescription (allowed inclusion of patients starting an antipsychotic shortly before meeting cohort eligibility criteria) but had to have a prior period of 365 days free of antipsychotic use. The cohort was restricted to recent users to include cases of diabetes that occurred early in therapy and to ensure that baseline covariates were unaffected by chronic antipsychotic effects.

We excluded patients with diagnosed conditions for which antipsychotics generally are the only recommended treatment. These included schizophrenia or related psychoses, organic psychoses, autism, mental retardation, Tourette syndrome, or other tic disorders. We also excluded patients prescribed clozapine or long-acting injectable preparations—usually indicators of schizophrenia or related psychoses—as well as those with parenterally administered drugs, typically given for transient agitation.

Controls
Potential controls were recent initiators of other psychotropic drugs, defined as for antipsychotics, with no antipsychotic use in the 365 days preceding the qualifying prescription. Control drugs included mood stabilizers (lithium or anticonvulsant mood stabilizers [absent evidence of a neurologic indication]), antidepressants with a psychiatric diagnosis, psychostimulants, a-agonists with diagnosed attention-deficit/hyperactivity disorder (ADHD) or other problems of behavior/conduct, and benzodiazepines with a psychiatric diagnosis (eAppendix and eTable 3 in Supplement).

From the pool of potential controls, we calculated the propensity scores, the conditional probability of being an antipsychotic user, given the study covariates. These were factors that might be directly or indirectly related to both antipsychotic use and the development of type 2 diabetes (eAppendix and eTable 4 in Supplement). The 115 covariates included demographic characteristics, psychiatric diagnoses and medications, metabolic disorders and related conditions (eg, diagnosed obesity), obstetric-gynecologic conditions (eg, absent/irregular menstruation), cardiovascular disease (eg, hypertension), respiratory disorders (eg, sleep apnea), musculoskeletal symptoms (eg, joint pain), other somatic conditions, and intensity of health care utilization (medical surveillance) for both psychiatric and somatic comorbidity. The estimation of the propensity scores was stratified according to the presence of a bipolar disorder (diagnosis or mood stabilizer prescription) because the propensity score coefficients differed for patients with this disorder.

The final control group included 1 control for every 2 antipsychotic users, frequency-matched with the antipsychotic users according to propensity score to ensure baseline comparability with regard to study covariates. Because we sought a control group highly comparable to the antipsychotic users, we required that the controls be matched within centiles (1%) of the antipsychotic propensity score distribution. The 1:2 matching ratio was established by a preliminary analysis of the potential control pool, indicating that there were too few controls to permit such close 1 to 1 matching (eAppendix and eTable 5 in Supplement).
Follow-up
Follow-up began on \( t_0 \), the day following the filling of the qualifying prescription for the antipsychotic or control drug, which permitted exclusion of participants based on medical care on the prescription fill date (eg, schizophrenia diagnosis). Follow-up ceased (eAppendix and eTable 6 in Supplement) with the end of the study, owing to a failure of the participant to meet study inclusion/exclusion criteria, a diagnosis of diabetes, or the death of the participant or 365 days following the last day of antipsychotic/control drug use. Follow-up for controls also ended with an antipsychotic prescription. Antipsychotic users or controls who left the cohort could reenter if they subsequently met the study eligibility criteria, unless follow-up terminated because of diabetes.

Antipsychotic Exposure Variables
The primary exposure variable was antipsychotic use status (user or control) on \( t_0 \), the first day of follow-up. Because baseline exposure status did not change during follow-up, the analysis provided a conservative assessment of antipsychotic effects. At baseline, antipsychotic users were also classified according to daily dose on \( t_0 \), expressed as chlorpromazine equivalents (eAppendix and eTable 7 in Supplement).

We defined time-dependent antipsychotic exposure variables in order to study antipsychotic cumulative dose and cessation of use. Cumulative dose on a given follow-up day was the sum of all previously dispensed antipsychotic doses (chlorpromazine equivalents). A follow-up day was considered “recent use” if the prescription days of supply indicated use on that day or within the preceding 90 days. The “former use” of antipsychotics was defined as more than 90 days without use of an antipsychotic.

Diabetes
Newly diagnosed cases of diabetes during study follow-up were identified from medical care encounters using an algorithm that was validated in a sample of the study cohort. A primary discharge diagnosis of diabetes met the case definition. Otherwise, we required both a diagnosis of diabetes and a prescription for an antidiabetic medication within a 120-day period. We required confirmation because single outpatient diabetes-related medical care encounters often were false positives. Outpatient diagnoses of diabetes in the absence of an antidiabetic medication prescription frequently indicated subthreshold hyperglycemia, whereas prescriptions for oral hypoglycemics in the absence of a diagnosis of diabetes were often considered the treatment of choice for polycystic ovarian syndrome. The presumed date of the diagnosis was that of the earliest diabetes-related medical encounter. Type 1 diabetes was indicated by exclusive treatment with insulin; other cases were considered type 2 diabetes.

In the validation study, 84% of cases identified by our computer algorithm as having type 2 diabetes were confirmed as being true cases, 10% had subthreshold hyperglycemia, 3% had type 1 diabetes, and 3% had polycystic ovarian syndrome. The positive predictive value for type 2 diabetes did not differ materially between antipsychotic users (82%) and controls (85%).

Analysis
The statistical analysis compared the adjusted incidences of diabetes according to antipsychotic exposure status. Relative risk was estimated with the hazard ratio (HR), calculated from Cox regression models with a robust sandwich estimation of variance to account for persons reentering the cohort. There was no evidence of interaction between time and antipsychotic use status (HR for interaction, 1.00; \( P < .30 \)), indicating that the proportional hazards assumption was satisfied. Regression models included the baseline propensity score (deciles), to adjust for residual confounding, as well as age and calendar year during follow-up. Other time-dependent covariates were not included in the primary analysis because these might be on the causal pathway for development of diabetes (eg, new diagnosis of obesity).

For the analyses of antipsychotic dose, the propensity score may not control for confounding, given that the distribution of study covariates could vary according to dose. Thus, models for these analyses included a disease risk score (the probability of type 2 diabetes, conditional on no antipsychotic use), expressed as deciles. Tests for the dose-response relationship used a single degree of freedom orthogonal polynomial contrast for linear trend.

An a priori subgroup analysis was performed for children 6 to 17 years of age, with follow-up ending on the day before their 18th birthdays. Subgroup analyses also were performed according to sex, the presence of a bipolar disorder (the most common labeled indication for antipsychotics in the cohort), use of psychostimulants (which can possibly limit weight gain), and a diagnosis of ADHD or conduct disorder.

Given that since 2004 guidelines have recommended routine glucose monitoring for antipsychotic users, we performed several analyses to assess the potential effect of differential screening during follow-up. Thus, follow-up time was classified according to the presence of a metabolic panel with glucose or other screening test in the past year. The screening variable was lagged 90 days to exclude the tests associated with the diagnosis of diabetes in the cases. We also performed an analysis that excluded person-time subsequent to 2004, which should be little affected by screening recommendations.

Additional analyses modeled possible clustering effects introduced by the frequency matching, restricted the cohort to new users of antipsychotics and control medications, did not allow antipsychotic users to reenter the cohort, and utilized an alternative definition of type 2 diabetes. All analyses were performed with SAS version 9.2 (SAS Institute Inc). All \( P \) values are 2-sided. The institutional review board at Vanderbilt University and the Tennessee Bureau of TennCare and the Department of Health approved our study, which was funded by grants from federal agencies with no role in study conduct or reporting.

Results
Cohort Characteristics at Baseline
The cohort included 28,858 children and youth who had recently initiated antipsychotic therapy (eAppendix and eTable
those of the antipsychotic users (characteristics of the controls were entirely comparable to tial controls. By virtue of the matching, the baseline chotropic drug and who were selected from 122 738 potent-ial propensity score–matched controls who had recently initiated a control psy-

Hyperglycemia, insulin resistance, acanthosis nigricans, and hyperlipidemia.

b None of the differences are statistically significant except for “Psychiatric inpatient stay” (P = .03).

HYPERGLYCEMIA, INSULIN RESISTANCE, ACANTHOSIS NIGRICANS, AND HYPERLIPIDEMIA.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chiatric diagnoses in past year, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>18.4 18.3</td>
</tr>
<tr>
<td>Depression</td>
<td>19.5 19.3</td>
</tr>
<tr>
<td>Other mood disorder</td>
<td>32.5 33.3</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
<td>38.3 38.9</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>24.9 25.3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19.9 20.6</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3.3 3.1</td>
</tr>
<tr>
<td>Other substance abuse</td>
<td>9.3 8.9</td>
</tr>
<tr>
<td>Psychiatric inpatient stay</td>
<td>13.8 14.5</td>
</tr>
<tr>
<td>Lithium</td>
<td>4.1 4.2</td>
</tr>
<tr>
<td>Valproate</td>
<td>9.3 9.5</td>
</tr>
<tr>
<td>Lamotrigine, carbamazepine, oxcarbazepine</td>
<td>9.0 8.8</td>
</tr>
<tr>
<td>Other mood stabilizer</td>
<td>1.8 1.8</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor</td>
<td>46.6 47.0</td>
</tr>
<tr>
<td>Heterocyclic antidepressant</td>
<td>14.3 14.9</td>
</tr>
<tr>
<td>Psychostimulant</td>
<td>33.7 34.1</td>
</tr>
<tr>
<td>α-Agonist</td>
<td>14.2 14.6</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>12.6 12.4</td>
</tr>
<tr>
<td>Conditions associated with metabolic disorders in past year, %</td>
<td></td>
</tr>
<tr>
<td>Menstruation absent or infrequent</td>
<td>3.7 3.8</td>
</tr>
<tr>
<td>Menstruation disorder, other</td>
<td>5.0 4.9</td>
</tr>
<tr>
<td>Diagnosed obesity</td>
<td>3.9 3.8</td>
</tr>
<tr>
<td>Metabolic disorder*</td>
<td>2.1 2.1</td>
</tr>
<tr>
<td>Blood chemistry panel with glucose</td>
<td>22.5 22.9</td>
</tr>
<tr>
<td>Diabetes-screening procedures</td>
<td>5.9 5.5</td>
</tr>
<tr>
<td>Hyperlipidemia-screening procedures</td>
<td>8.4 8.5</td>
</tr>
<tr>
<td>Cardiovascular conditions in past year, %</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.5 2.6</td>
</tr>
<tr>
<td>Other diagnosed cardiovascular disease</td>
<td>4.2 4.5</td>
</tr>
</tbody>
</table>

* Unless otherwise noted, all demographic characteristics are as of the first day of follow-up (t0).

None of the differences are statistically significant except for “Psychiatric inpatient stay” (P = .03).

Hyperlipidemia, hypertriglyceridemia, and hyperglycemia.

1 in Supplement). There were 14 429 propensity score-matched controls who had recently initiated a control psychotropic drug and who were selected from 122 738 potential controls. By virtue of the matching, the baseline characteristics of the controls were entirely comparable to those of the antipsychotic users (Table 1). Both antipsy-choptic users and controls had initiated use of the study psychotropic drug within a mean of fewer than 6 days prior to cohort entry.

Cohort members had a mean age of 14.5 years, and 56% were male participants (Table 1). The most frequently recorded psychiatric diagnoses were mood disorders (including bipolar disorder), ADHD, and conduct disorder. Metabolic disorders and other factors potentially associated with diabetes were relatively infrequent, although 23% of cohort members had had a diagnostic test that included glucose measurement administered in the year preceding t0.

The median starting dose for cohort antipsychotic users was 67 mg (interquartile range, 33-100 mg) of chlorpromazine equivalents. Of antipsychotic users, 87% were prescribed an atypical agent (eAppendix and eTable 8 in Supplement); use of typical antipsychotics was largely restricted to the earlier study years. The most frequently prescribed individual antipsychotic was risperidone (n = 10 718; 37% of antipsychotic users), followed by quetiapine fumarate (n = 5807; 20% of antipsychotic users) and olanzapine (n = 5671; 20% of antipsychotic users). Risperidone users were younger, more likely to be male, had greater prevalence of diagnosed ADHD, and were started at lower doses than were users of other atypical antipsychotics.

Antipsychotics and the Risk of Diabetes

The cohort had 55 984 person-years of follow-up, during which there were 21 cases of type 1 diabetes (3.8 cases per 10 000 person-years). These cases consisted of persons who had a mean age of 13 years, 62% were male, and 29% had Medicaid enrollment related to disability (Table 2). Antipsychotic users had no significantly increased risk for type 1 diabetes (HR = 1.13 [95% CI = 0.43-3.00]).

There were 106 incident cases of type 2 diabetes (18.9 cases per 10 000 person-years) during cohort follow-up. The mean age of the persons was 16.7 years, 37% were male, and 34% had Medicaid enrollment related to disability (Table 2).

Antipsychotic users had a 3-fold increased risk for type 2 diabetes (Figure 1 and Table 3; HR = 3.03 [95% CI = 1.73-5.22]). The increased risk was apparent within the first year of follow-up (HR = 2.49 [95% CI = 1.27-4.88]). Risk did not vary significantly according to baseline dose but did increase with cumulative dose during follow-up (Table 2). The HR for co-hort members with a cumulative dose of 100 g or greater of chlorpromazine equivalents was 5.43 [95% CI = 2.34-12.61],
whereas the HR for those with a cumulative dose of less than 5 g of chlorpromazine equivalents was 2.13 (95% CI = 1.06-4.27) ($P = .04$). The risk remained elevated for up to 1 year following the discontinuation of antipsychotic use (HR = 2.57 [95% CI = 1.34-4.91]). Although this was less than that for cohort members who continued to use antipsychotics (HR = 3.19 [95% CI = 1.77-5.74]), the difference was not statistically significant.

When the cohort was restricted to children 6 to 17 years of age, antipsychotic users had more than a 3-fold increased risk of type 2 diabetes (Figure 2; HR = 3.14 [95% CI = 1.50-6.56]). For these children, the incidence increased with increasing cumulative dose (Figure 2), from an HR of 2.00 (95% CI = 0.76-5.30) for cumulative doses of less than 5 g to an HR of 7.05 (95% CI = 2.63-18.89) for cumulative doses of 100 g or more ($P = .03$).

We examined the risk for atypical antipsychotics, which were used by 87% of cohort users, and for individual atypical drugs. The risk for type 2 diabetes increased with the cumulative dose of all atypical antipsychotics, including risperidone, which drug was used by approximately 40% of the cohort antipsychotic users (eAppendix and eTable 9 in Supplement). Significantly increased HRs were present for other atypical antipsychotics; the difference between HRs for risperidone and HRs for aripiprazole was statistically significant ($P < .001$).

We examined several subgroups defined by baseline cohort characteristics (Figure 3), including age, sex, presence of a bipolar disorder, psychostimulant use, and a diagnosis of either ADHD or conduct disorder. For each of these subgroups, the risk of type 2 diabetes was significantly increased for antipsychotic users, and the estimates for the subgroups defined by the individual factors did not differ statistically.

We also assessed the risk of type 2 diabetes according to screening for elevated glucose levels in either the year preceding $t_0$ or during follow-up (Figure 3). For the controls, 28% of the follow-up person-time had such screening, as did 33% of the person-time for the antipsychotic users. Both expo-

<table>
<thead>
<tr>
<th>Status</th>
<th>Person-Years</th>
<th>Cases</th>
<th>Rate per 10^4 Person-Years</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antipsychotic use in nonuser control group</td>
<td>17 963</td>
<td>14</td>
<td>7.8</td>
<td>1 [Reference]^a</td>
</tr>
<tr>
<td>Antipsychotic use at baseline for all antipsychotic users</td>
<td>38 022</td>
<td>92</td>
<td>24.2</td>
<td>3.03 (1.73-5.32)</td>
</tr>
<tr>
<td>Antipsychotic users, according to baseline daily dose of antipsychotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 mg</td>
<td>12 777</td>
<td>22</td>
<td>17.2</td>
<td>2.65 (1.69-5.77)</td>
</tr>
<tr>
<td>50-99 mg</td>
<td>11 991</td>
<td>30</td>
<td>25.0</td>
<td>3.07 (1.63-5.78)</td>
</tr>
<tr>
<td>≥100 mg</td>
<td>13 254</td>
<td>40</td>
<td>30.2</td>
<td>3.13 (1.33-5.30)</td>
</tr>
<tr>
<td>Antipsychotic users, according to cumulative dose of antipsychotic during follow-up^b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 g</td>
<td>13 634</td>
<td>27</td>
<td>19.8</td>
<td>2.13 (1.06-4.27)</td>
</tr>
<tr>
<td>5-99 g</td>
<td>21 734</td>
<td>56</td>
<td>25.8</td>
<td>3.42 (1.88-6.24)</td>
</tr>
<tr>
<td>≥100 g</td>
<td>2654</td>
<td>9</td>
<td>33.9</td>
<td>5.43 (2.34-12.61)</td>
</tr>
<tr>
<td>Antipsychotic users, according to continuity of use during follow-up^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former (use ceased for &gt;90 d)</td>
<td>11 388</td>
<td>26</td>
<td>22.8</td>
<td>2.57 (1.34-4.91)</td>
</tr>
<tr>
<td>Recent (use within past 90 d)</td>
<td>26 634</td>
<td>66</td>
<td>24.8</td>
<td>3.19 (1.77-5.74)</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio (adjusted).

^a Reference for all comparisons is the nonuser control group.

^b $P < .04$ (test for dose-response relationship).

^c Follow-up persisted for 365 days following last dispensed day of antipsychotic medication.
sure groups had increased HRs for type 2 diabetes, and these
did not differ significantly according to screening status. Simi-
lar results were present in an analysis according to the pre-
escence of a screening test during follow-up (there was a mean
number of 0.35 tests during follow-up for the controls and of
0.51 tests for the antipsychotic users). An analysis that ex-
cluded person-time subsequent to 2004 (the year of the first
publication of guidelines recommending screening of antipsy-
chotic users30) also demonstrated increased risk for antipsy-
chotic users (HR = 2.73 [95% CI = 1.35-5.53]).

The increased risk of type 2 diabetes among antipsy-
chotic users persisted in several sensitivity analyses that as-
shed study assumptions (eAppendix and eTable 10 in Supple-
ment). These analyses included control for possible clustering
induced by the frequency matching (HR = 3.07 [95% CI = 1.74-
5.39]), restriction of the cohort to new users of antipsychotics
and control psychotropic medications (HR = 3.05 [95% 
CI = 1.70-5.46]), not permitting antipsychotic users who left
the cohort to reenter (HR = 2.86 [95% CI = 1.55-5.26]), and use
of an alternative definition for type 2 diabetes that required a pre-
Antipsychotics and the Risk of Type 2 Diabetes

In this cohort of children and youth who had recently initiated use of an antipsychotic or a control psychotropic drug, antipsychotic users had a risk of newly diagnosed type 2 diabetes 3 times greater than that for propensity score–matched controls. The excess risk occurred within the first year of antipsychotic use, increased with cumulative antipsychotic dose, and was present for children 6 to 17 years of age. The increased risk persisted for up to 1 year following cessation of antipsychotic use.

Study cases of type 2 diabetes were identified from diagnoses from clinical practitioners and prescriptions for antidiabetic drugs. Thus, there was the potential for false positives. However, a validation study conducted in a cohort sample found that the case definition had a positive predictive value of 84% and that this did not differ materially according to antipsychotic use status. These data suggest that the errors made by clinical practitioners in the diagnosis of diabetes are unlikely to explain the study findings.

Another type of misclassification that may have affected our findings was the incomplete identification of type 2 diabetes in the cohort. In routine practice, many children and youth may not undergo the testing necessary for this diagnosis. This could introduce bias if the diagnostic scrutiny of the antipsychotic group was greater than that for controls. To minimize this potential bias, we sought to ensure comparability of medical surveillance for both groups. Thus, antipsychotic users and controls had recently initiated psychotropic drug therapy and were closely matched at baseline according to glucose or diabetes screening tests, as well as recent medical care utilization, which is an indicator of diagnostic scrutiny.

However, guidelines published in 2004 recommending routine glucose monitoring for antipsychotic users could have led to differential surveillance during follow-up. Thus, we performed several analyses to assess this possibility. When data were analyzed according to the presence of a screening test, either at any time or only during follow-up, the increased risk was present for both those who were and those who were not screened. This analysis should be conservative, given that screening could be triggered by antipsychotic-related weight gain. Furthermore, in an analysis that excluded person-time subsequent to the year of guideline publication, the magnitude of the increased risk for antipsychotic users was little changed.

We could not directly control for obesity, which is closely linked to the development of type 2 diabetes. However, a material difference in body mass index between antipsychotic users and controls seems unlikely, given that controls were very closely matched according to 115 study covariates, many of which either are plausibly associated with increased body mass or might mediate an association between obesity and antipsychotic use. These included diagnosed obesity, disorders or diagnostic testing linked to excess weight, psychiatric diagnoses, psychotropic drug use, and demographic characteristics. The observed dose–response relationship is further evidence that the study findings were not due to confounding by obesity.

For adults, the risk of type 2 diabetes conferred by antipsychotics is most pronounced for atypical antipsychotics and may vary according to specific drug. In the study cohort, 87% of antipsychotic users received atypical drugs. Study findings were largely unchanged when the cohort was restricted to this group or to risperidone, the most frequently prescribed individual drug. Olanzapine, quetiapine, ziprasidone, and aripiprazole were used less frequently, but each had a significantly elevated HR. However, this post hoc finding must be interpreted cautiously. There was marked variation in the baseline characteristics of users of specific antipsychotics. Our study was not designed to study the comparative risk of individual drugs, given that sample size did not permit a propensity score match for specific antipsychotics. Furthermore, it is possible that high-risk patients may have been recommended a drug perceived to have greater metabolic safety.

Both the pathophysiology and the epidemiology of type 2 diabetes indicate that its development is a chronic process. Although the risk of type 2 diabetes did increase with cumulative dose of antipsychotics, which is consistent with a chronic process, we also found that a significantly increased risk was present during the first year of therapy. Cases of early-onset antipsychotic-associated diabetes have been reported for adults. In one series, the majority of cases occurred within 6 months of drug initiation. Although there are fewer case reports in the literature for children, early-onset cases also have been described. Further study of the pathophysiology of antipsychotic-associated diabetes is needed.

In the study cohort, there were an estimated 15.8 additional cases of type 2 diabetes per 10,000 person-years of antipsychotic exposure, or a number needed to harm of 633. However, this number should be applied cautiously in clinical practice because the baseline risk for a child or youth will vary substantially according to age and body mass index. Furthermore, the study cohort consisted of Tennessee Medicaid enrollees (approximately 40% of the state’s children), which also limits the generalizability of study findings, given that the incidence of type 2 diabetes in children covered by Medicaid may be elevated owing to economic and social factors, as well as to a greater prevalence of behavioral risk factors, disability, and chronic illness.

In conclusion, in the study cohort of children and youth between 6 and 24 years of age, those recently initiating an antipsychotic medication had a 3-fold greater risk of newly diagnosed type 2 diabetes than did propensity score–matched controls. Risk was elevated during the first year of antipsychotic use, increased with increasing cumulative dose, and was present for children younger than 18 years of age.
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REFERENCES