The Risk of Developing Type 2 Diabetes Mellitus Associated With Psychotropic Drug Use in Children and Adolescents: A Retrospective Cohort Analysis

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ABSTRACT

Objective: Type 2 diabetes mellitus in children and adolescents has become an important public health concern, in parallel with the "epidemic" of overweight/obesity in this age group and a sharp increase in children being prescribed antidepressant or antipsychotic medications. In children and adolescents, the prevalence of being prescribed antidepressant or antipsychotic medications was examined as well as the association of these medications with developing type 2 diabetes mellitus.

Method: A retrospective cohort design evaluating South Carolina Medicaid medical and pharmacy claims between January 1, 1996, and December 31, 2006, was employed to identify 4,070 children and adolescents diagnosed initially with type 2 diabetes mellitus, 39% of whom were later reclassified as type 1 (using *ICD-9* criteria). The added risk of developing type 2 diabetes mellitus posed by the use of antidepressants or antipsychotics was investigated in this cohort, controlling for individual risk factors and comorbid cardiometabolic conditions.

Results: Use of antidepressants or antipsychotics alone, or the 2 in combination, conferred an increased risk (1.3 to 2 times greater) of having diagnosed type 2 diabetes mellitus and several comorbid cardiometabolic conditions (obesity, dyslipidemia, and hypertension). However, psychiatric illnesses generally developed and were treated after the initial development of diabetes.

Conclusions: Depression was diagnosed and treated in 10% to 20% of this cohort. While antidepressants and antipsychotics, alone or in combination, are associated with a diagnosis of type 2 diabetes mellitus and its cardiometabolic comorbidities by adolescence, they do not appear to be an explanatory factor in the early onset of type 2 diabetes mellitus in this age group and do not appear to cloud the initial, overlapping clinical picture between type 1 and type 2 diabetes mellitus.

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Historically associated with adulthood, type 2 diabetes mellitus has become a significant public health problem in childhood as well, with the American Diabetes Association declaring the escalating number of new cases as reaching "epidemic" proportions.[1,2] Factors associated with the relatively earlier development of type 2 diabetes mellitus in children include obesity,[3–5] family history, puberty, minority status,[2,5–8] poverty,[9] hypertension,[10] and dyslipidemia.[10–12] The prevalence of obesity and associated cardiometabolic complications (eg, diabetes mellitus, primary hypertension) in pediatric populations has also increased significantly during the past 2 decades,[13,14] and a growing body of research indicates that these cardiometabolic disorders may differentially affect African Americans.[15,16] The rapidly changing demographics and clinical manifestations of diabetes in children have produced an ambiguous clinical picture between type 1 and type 2 diabetes mellitus in the pediatric population, at times leading to misclassification and inappropriate clinical care.[17] The extent of this "misclassification" problem is difficult to quantify since pediatricians and endocrinologists require some time to allow the clinical picture to fully unfold, and there has been very limited discussion of this clinical issue in the literature.

During the past decade, there has also been a substantial increase in the use of predominantly atypical or second-generation antipsychotics (SGAs) in young persons treated in privately and publicly insured systems.[18] Second-generation antipsychotics have been associated with clinically significant weight gain and a propensity to metabolic derangements such as hyperglycemia and dyslipidemia in pediatric populations.[19–24] The morbidity associated with antipsychotic treatment may relate to comorbid medical conditions or to concomitant medication use. SGAs are being increasingly prescribed in combination with other psychotropic agents, ie, antidepressants, which further introduces the possibility of additive adverse effects.[25,26] Some studies suggest that the use of antidepressants might increase the risk of weight gain and associated metabolic disorders such as glucose intolerance, type 2 diabetes mellitus, and dyslipidemia.[27–29] The results of previous epidemiologic investigations indicate that females, adolescents, and individuals prescribed a combination of antipsychotic agents or treated concomitantly with an antidepressant and antipsychotic are at increased risk for metabolic disruption compared to untreated youth, especially over the long-term (24–36 months).[21,22,30]

Furthermore, the presence of chronic conditions such as diabetes, hypertension, and obesity in children and adolescents is independently associated with an increased prevalence of psychiatric disorders. Psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder have been diagnosed with an increased frequency in young adults with both type 1 and type 2 diabetes mellitus.[31–34] In 2 studies with similar methodologies, 19.4% and 26.2% of children with type 2 diabetes mellitus in hospital-based clinics were found to have depression, ADHD, pervasive developmental disorders, schizophrenia, or bipolar disorder.[35,36] However, there have been very few studies of the prevalence of depression and other psychiatric disorders in large, population-based cohorts of children and adolescents with diabetes, especially those with type 2 diabetes mellitus.

Clinical Points

- In a heterogeneous cohort of children and adolescents diagnosed with diabetes mellitus, the prevalence of depression (< 10%) and psychosis (≤ 4%) and being prescribed antidepressant (20%) or antipsychotic medications (< 1%) was low.
- Use of antidepressants or antipsychotics alone, or the 2 in combination, was more likely to be associated with having diagnosed type 2 diabetes and its cardiometabolic comorbidities (obesity, hypertension, and dyslipidemia) by adolescence. However, the use of these psychotropic medications does not appear to contribute to the early onset of type 2 diabetes in this age group or to the initial, overlapping clinical picture between type 1 and type 2 diabetes mellitus in primary care settings.
- Since these dysmetabolic conditions are highly associated with the onset and worsening of depressive or "sickness" symptoms over time and vice versa, the primary care physician must diligently and consistently monitor changes in all conditions (glucose control, weight, blood pressure, lipid levels, activity level, and mood symptoms) to effectively treat and manage the care of these individuals.

There is an even greater paucity of literature on the use of antidepressants and atypical antipsychotics and their potential adverse effects among children and adolescents with diabetes. Therefore, elucidation of iatrogenic factors that contribute to a child's risk of developing type 2 diabetes mellitus and other cardiometabolic disorders as well as depression associated with diabetes over time is a clinical research priority.

In this investigation, we focus on examining the risk of developing type 2 diabetes mellitus with the use of antipsychotics and antidepressants in a population-based, routine clinical care cohort of children from very low-income families (eligible for Medicaid), controlling for individual risk factors (age, gender, race) and cardiometabolic conditions previously identified as significant correlates of type 2 diabetes mellitus or psychotropic medications.

METHOD

Data for this study were obtained from the South Carolina Medicaid claims database. Medical claims data included each service encounter with associated *ICD-9* codes (up to 5 for outpatient and 8 for inpatient visits), type of visit, and date of service. Pharmacy claims data included the prescribed drug and date dispensed. Demographic data included enrollment/eligibility for each year examined, age at enrollment, birth month and year, gender, and race/ethnicity. The retrospective study cohort included children and adolescent patients, 17 years of age and under, who were continuously enrolled in and eligible for Medicaid for a minimum of 9 months in each calendar year and had at least 1 initial service encounter with a diagnosis of type 2 diabetes mellitus (*ICD-9* codes: 250.00 and 250.02) in the years January 1, 1996, through December 31, 2006. The selection date in the cohort was the date of the first encounter with the diagnosis of type 2 diabetes mellitus, and each individual was followed over time until the end of the study period. All encounters with diabetes over the follow-up period of up to 11 years were used to define the 2 main exposure groups: (1) "type 2 diabetes mellitus"—included individuals who had more than 95% of diabetes visits over the follow-up period coded as type 2 (*ICD-9* codes: 250.00 and 250.02) and (2) "reclassified type 1 diabetes mellitus"—included individuals who after at least 2 initial encounters with a diagnosis code of type 2 diabetes mellitus were later reclassified as type 1 (*ICD-9* codes: 250.01 and 250.03) and overall had more than 20% of all diabetes encounters coded as type 1.

Compilation of these data files for the proposed analyses was approved by the University of South Carolina Institutional Review Board (Columbia, South Carolina) and the Research Committee of the South Carolina Department of Health and Human Services as research not involving human subjects (45 Code of Federal Regulations part 46). We also evaluated the *ICD-9* codes for depression, ADHD, and psychosis using these data, as well as the comorbid conditions most frequently associated with diabetes: obesity, dyslipidemia, and hypertension. We compiled data from the pharmacy file on those patients who were prescribed any of 5 atypical antipsychotics (ie, aripiprazole, ziprasidone, quetiapine, risperidone, or olanzapine) or any of 22 antidepressants (ie, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desipramine, doxapram, doxepin, imipramine, isocarboxazid, amitriptyline, nortriptyline, protriptyline, trimipramine, clomipramine, duloxetine hydrochloride, mirtazapine, bupropion hydrochloride, venlafaxine hydrochloride, trazodone, or nefazodone).

Preliminary descriptive analyses were performed to determine data distribution and to assess univariate association of covariates with the type 2 or the reclassified type 1 diabetes mellitus groups. Crude prevalence rates of depression and other psychiatric disorders and rates of use of antipsychotics and antidepressants for the 2 groups were also calculated. Statistical differences were assessed by χ^2 test for categorical variables and Mann-Whitney test for continuous variables. Multivariable logistic regression analyses were then used to examine the association between the use of antipsychotic or antidepressant medications and the cumulative prevalence of cardiometabolic disorders (obesity, hypertension, and dyslipidemia) among the 2 groups and the association with the development of type 2 diabetes mellitus in our cohort. The covariates in multivariable analyses included individual risk factors (age at diabetes diagnosis, gender, ethnicity) and other confounding comorbid conditions. The initial full multivariable models were reduced by using a backward elimination procedure to

Table 1. Individual Risk Factors and Prevalence of Complications in Pediatric Patients Diagnosed With Type 1 or Type 2 Diabetes Mellitus

Independent Variable	Type 2 Diabetes Mellitus Group[a]	"Reclassified" Type 1 Diabetes Mellitus Group[b]
Ethnicity, n (%)		
Other, nonwhite	176 (7.1)	112 (7.1)
African American	1,376 (55.3)	903 (57.1)
White	937 (37.7)	566 (35.8)
Gender, n (%)		
Male	1,106 (44.4)	625 (39.5)
Female	1,383 (55.6)	956 (60.5)
Age at diabetes mellitus diagnosis, mean (SD), y	10.0 (5.40)	11.5 (4.33)**
Duration of diabetes mellitus, mean (SD), y	3.5 (2.23)	4.5 (2.44)
Insulin treatment, n (%)	148 (6.0)	1,290 (81.6)**
Age at antidepressant prescribed, mean (SD), y	11.7 (3.39)	13.1 (3.02)**
Age at antipsychotic prescribed, mean (SD), y	11.3 (3.50)	12.6 (3.18)*
Age at psychostimulant prescribed, mean (SD), y	9.2 (3.35)	10.3 (3.30)*
Unadjusted prevalence rates for comorbid conditions and medications, n (%)		
Weight gain/obesity	764 (30.7)	482 (30.5)
Dyslipidemia	192 (7.7)	176 (11.1)*
Hypertension	499 (20.1)	386 (24.4)*
Attention-deficit/hyperactivity disorder	482 (19.4)	199 (12.6)**
Depression	161 (6.5)	135 (8.5)*
Psychosis	68 (2.7)	59 (4.0)*
Taking antidepressants only	541 (21.7)	316 (20.0)
Taking antipsychotics only	18 (0.7)	12 (0.8)
Taking both antidepressants and antipsychotics	174 (7.0)	100 (6.3)

[a]n = 2,489; 61.2%.
[b]n = 1,581; 38.8%.
*Significant at $P < .01$.
**Significant at $P < .0001$.

achieve parsimonious models. P values < .05 were considered statistically significant, and all statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

Of the total cohort of 4,070 children and adolescents initially diagnosed with type 2 diabetes mellitus, 38.8% were later reclassified as type 1 and the remainder continued to be classified as type 2. Median follow-up duration for the cohort was 7 years (interquartile range [IQR]: 4–9 years). There was no significant gender or racial difference between the 2 cohorts. As depicted in Table 1, those in the reclassified type 1 diabetes mellitus group were more likely to be diagnosed initially at an older age (11.5 vs 10.0 years, $P < .0001$), had been in our cohort for a longer time (4.5 vs 3.5 years, $P < .0001$), and were more likely to be treated with insulin (81.6% vs 6%, $P < .0001$). Almost 50% of the reclassified group had a diabetic ketoacidosis event. From this clinical profile, we are relatively certain that the reclassified type 1 and type 2 diabetes mellitus groups have been correctly classified in our analyses. The reclassified type 1 diabetes mellitus group was used as the comparison condition in the logistic regression analyses performed for this study. Antidepressants were later prescribed to about 20% of the type 1 diabetes mellitus group at a mean age of 13.1 years and to the type 2 diabetes mellitus group at a mean age of 11.6 years.

As shown in Table 2, obesity, hypertension, and dyslipidemia were significantly associated with each other, but only obesity/overweight was positively associated with a diagnosis of type 2 diabetes mellitus in this cohort (nonsignificant). All 3 categories of psychotropic medication use (taking antidepressants or antipsychotics alone or taking the 2 in combination) conferred an increased risk (1.3 to 2 times greater) of being diagnosed with each of the cardiometabolic conditions (obesity, hypertension, and dyslipidemia), as well as being diagnosed with type 2 diabetes mellitus. Conversely, these results suggest that the use of antidepressants and antipsychotic treatment, individually or in combination, is *not* associated with an increased risk of initial misclassification of type 1 diabetes mellitus as type 2. Unfortunately, the small numbers of children being treated with only antipsychotic medications yield nonsignificant odds ratio results in all regression models due to a lack of power.

We did not attempt to further delineate the antidepressant agents by subclass (eg, selective serotonin reuptake inhibitors) to examine associated cardiometabolic disturbances due to very small subgroup sizes. Other subgroup differences that might be informative, however, were that males had a lower risk of developing obesity ($P < .0001$) but a higher risk of developing hypertension ($P < .01$), older children/adolescents were at increased risk of developing all of the cardiometabolic conditions except type 2 diabetes mellitus, and nonwhites had a significantly increased risk of developing obesity and hypertension ($P < .0001$).

DISCUSSION

Our findings confirm the association of certain factors with the diagnosis of type 2 diabetes mellitus in children, including age, minority (nonwhite) ethnic/racial status,[2,5–8] poverty,[9] and obesity,[3–5,37] but not with the dysmetabolic conditions of hypertension[10] and dyslipidemia.[10–12] Our analysis also confirmed that the use of antidepressants alone, antipsychotics alone, and antidepressants combined with SGAs is associated with an increased risk of a type 2 diabetes mellitus diagnosis and clinically significant weight gain and alterations in cardiometabolic indices (eg, dyslipidemia, hypertension) in pediatric populations.[19–25,37]

In this cohort, the initial clinical diagnosis of type 2 diabetes mellitus was significantly associated with comorbid overweight/obesity.[38] In contrast, the onset of dyslipidemia and hypertension was diagnosed at varying times thereafter. The psychiatric illnesses, predominantly ADHD and depression, also developed and were treated after the initial development/diagnosis of diabetes. Between the ages of 6 and

Table 2. Predictors of Comorbid Cardio-Metabolic Conditions in Children With Diabetes Mellitus[a]

Dependent Variable	Obesity	Dyslipidemia	Hypertension	Type 2 Diabetes Mellitus Group
Type 2 diabetes mellitus	1.16 (1.00–1.35)	0.88 (0.69–1.11)	0.99 (0.84–1.18)	NA
Male gender	0.50 (0.43–0.58)**	0.85 (0.67–1.08)	1.30 (1.10–1.53)*	1.00 (0.87–1.15)
Nonwhite race	1.81 (1.55–2.12)**	0.84 (0.66–1.08)	1.89 (1.58–2.07)**	1.03 (0.89–1.18)
Older age at diabetes mellitus onset	1.12 (1.04–1.20)*	1.36 (1.20–1.54)*	1.45 (1.33–1.57)**	0.62 (0.58–0.66)**
Longer duration of diabetes mellitus	0.96 (0.93–0.99)*	1.11 (1.06–1.16)**	1.08 (1.04–1.11)*	0.82 (0.80–0.85)**
Taking only antipsychotics	1.82 (0.85–3.91)	2.32 (0.90–5.99)	1.76 (0.77–4.03)	1.34 (0.60–2.98)
Taking only antidepressants	1.52 (1.27–1.82)**	1.56 (1.20–2.03)*	1.27 (1.04–1.55)*	1.41 (1.19–1.68)**
Taking both antidepressants and antipsychotics	2.10 (1.59–2.76)**	1.91 (1.32–2.77)*	1.39 (1.03–1.87)*	1.37 (1.05–1.80)**
Weight gain/obesity	NA	2.02 (1.60–2.55)**	2.71 (2.30–3.20)**	1.12 (0.96–1.30)
Dyslipidemia	1.98 (1.57–2.51)**	NA	2.38 (1.88–3.02)**	0.86 (0.67–1.07)
Hypertension	2.68 (2.27–3.16)**	2.35 (1.85–2.99)**	NA	0.95 (0.81–1.13)

[a]Data presented as odds ratio (95% CI).
*Significant at $P < .01$.
**Significant at $P < .0001$.
Abbreviation: NA = not applicable.

12 years, approximately 25% of these children were diagnosed with several components of the metabolic syndrome (type 2 diabetes mellitus, overweight/obesity, insulin resistance, lipodystrophies, or hypertension) and began to be diagnosed and treated for mood or other mental disorders.

This comorbidity pattern is similar to the estimated prevalence of major depressive disorder among adult patients with diabetes (2–4 times higher than in the general population) as well as the higher prevalence of the dysmetabolic syndrome in individuals with major depressive disorder.[37] Insulin resistance, the cardinal feature of metabolic syndrome and a commonly encountered biological abnormality in individuals with major mood disorders, may play a critical role in the development of affective or "sickness" symptoms and the worsening of metabolic syndrome components with age and as a mediator in the cognitive-signaling pathways of antidepressant and mood-stabilizing medications, including antipsychotic agents.[37]

The results of our data converge with an amply documented association between mood and metabolic disorders and extend our knowledge further by reporting on younger populations. The association between mood and metabolic disorders may be mediated/moderated by several mechanisms. First, from a systems perspective, both mood and metabolic disorders are associated with economic disadvantage, low education attainment, and insufficient access to both primary and preventative health services. Iatrogenic artifact is also a contributing issue insofar as insulin resistance and glucose dysregulation may be consequential to age-inappropriate weight gain and abnormal fat distribution. During the past decade, replicated evidence has suggested a neurobiological nexus between mood and metabolic disorders. For example, alterations in the proinflammatory/counterinflammatory milieu, dysregulated activity in the hypothalamic-pituitary-adrenal axis, or oxidative stress alone or collectively may increase the risk for metabolic abnormalities in those with mood disorders and vice versa.[37,39–42] Preliminary evidence also supports possible genetic associations (eg, the fat mass and obesity-associated *FTO* gene) between metabolic abnormalities (eg, obesity) and mood disorders.[43]

The direct effects of psychotropic agents on insulin action (eg, insulin receptors) are also implicated by available data, but the mechanism of induction of medication-associated diabetes has not been fully explained. In adults experiencing diabetes secondary to SGA use, suggestions of subacute and fulminant deterioration of β cell function with resultant relative insulin deficiency that has sometimes led to extreme hyperglycemia, diabetic ketoacidosis, and death have been made.[44,45] Expected β cell compensation for the degree of insulin resistance induced by weight gain can be reduced or eliminated by these agents.[46] Increased proinflammatory markers and β cell toxicity have also been implicated.[47] Whether similar factors working through a stunting of pancreatic islet cell response to worsening insulin resistance and increased insulin demand are operative in antidepressant and SGA-treated children is difficult to speculate but worth further investigation. Since inflammatory processes contribute to depression (and vice versa), and exposure to inflammatory mediators produce a constellation of "sickness" behaviors that are present in a variety of mood and psychotic disorders, the effects of the disease and the agents used to treat the diseases (depression or diabetes) would have to be teased out.[37]

The underlying dynamics for the disparity in the diagnoses of type 1 and type 2 diabetes mellitus in relation to the other metabolic disorders are uncertain, but the presence or lack thereof of the comorbid dysmetabolic conditions may form a basis for their initial differential clinical development in pediatric populations, while their overlap may become much more pronounced as dysmetabolic syndrome progresses into adulthood. Age, racial factors, and the hormonal changes of puberty may also impact the clinical manifestation of hyperglycemia, glucose intolerance, and diabetes in a disproportionate manner. The presence of a mood disorder might be expected to disrupt metabolic parameters in individuals as a function of duration of illness.[37]

The perspective provided by this longitudinal database analysis has several strengths: (1) the cohort represents a large, heterogeneous group of children and adolescents with diabetes, comorbid cardiometabolic conditions, and varying periods of antidepressant and SGA exposure; (2) previous studies have found that although Medicaid databases provide much less detailed information on individuals than a structured research interview, the physician diagnoses and utilization data are more reliable than client or family self-

reports[48,49]; (3) Medicaid relies on the treating physician to code these conditions and treatments and submit them accurately for each visit, which may be more accurate for type 1 than type 2 diabetes mellitus except when overweight/obesity is present[50]; and (4) the outcomes of disparate metabolic and cardiovascular events related to antipsychotic and concomitant medication use are clinically relevant and of substantial public health importance.

However, these results also need to be interpreted with several limitations in mind: (1) the data were not controlled and, instead, we used secondary administrative data and observational techniques in a retrospective cohort design; (2) structured research and clinical interviews were not employed to confirm any of the medical diagnoses assigned by the treating clinicians; (3) these results report associations and, as a result, directions of causality cannot be inferred; (4) 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; (5) children who were periodically ineligible for Medicaid are not represented in this data set and their results might be different; and (6) there is no way to estimate how representative this Medicaid cohort is in relation to those in other states and service systems.

In conclusion, metabolic disorders such as obesity, hypertension, hyperlipidemia, and diabetes, which are well-established risk factors for cardiovascular disease, are increasing in epidemic proportions in younger populations, along with contemporaneous use of several classes of psychotropic agents associated with metabolic disruption. The results of our analysis indicate that these risk factors exist in about 20% to 30% of the pediatric diabetes cohort and that the use of both antidepressants and antipsychotics, separately as well as in combination, is also associated with an increased risk of being diagnosed with obesity, hypertension, and dyslipidemia. We cannot determine causal associations from this data set. However, since these dysmetabolic conditions are highly associated with the onset and worsening of depressive or "sickness" symptoms over time and vice versa, the primary care physician must diligently and consistently monitor changes in all conditions (glucose control, weight, blood pressure, lipid levels, activity level, and mood symptoms) to effectively treat and manage the care of these individuals. Primary care physicians are encouraged to consider psychosocial treatment strategies to manage clinically significant depressive symptoms and also to judiciously use psychotropic agents with a preference for those agents that do not hazardously affect metabolic function. All children identified to have mood disorders, regardless of treatment modality assignment, should receive routine surveillance of metabolic parameters.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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