Risk of Diabetes in Children and Adolescents Exposed to Antipsychotics: A Nationwide 12-Year Case-Control Study

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Objective: Antipsychotics are associated with weight gain and diabetes. The risk and rate of diabetes in children and adolescents treated with antipsychotics is unclear. **Method:** A longitudinal register linkage case-control study of diabetes in all psychiatric patients aged <18 years in Denmark was performed from January 1999 through the end of June 2010. Patients with and without antipsychotic exposure were compared regarding the occurrence of type 2 diabetes, defined as the prescription of oral antidiabetic medication. Regression analyses with type 2 diabetes as the dependent variable were conducted with sex, age, and diagnoses as covariates. **Results:** We compared the risk of diabetes in 48,299 psychiatrically ill youth. Of 7,253 youth exposed to antipsychotics, 52 (0.72%; 95% CI = 0.52% - 0.91%) developed type 2 diabetes. Of 41,046 youth without exposure to antipsychotics, 111 (0.27%; 95% CI = 0.22% - 0.32%) developed type 2 diabetes. In a 25,033 + 16,013 logistic regression analysis, type 2 diabetes development was associated with antipsychotic drug exposure (odds ratio [OR] = 1.60; 95% CI = 1.08 - 2.36, $p < .05$) female sex, (OR = 4.48; 95% CI = 2.90 - 6.91, $p < 0.001$) and older age at first psychiatric diagnosis (OR = 1.19; 95% CI = 1.12 - 1.27, $p < 0.001$), but not with psychiatric diagnosis. In a Cox-regression analysis, shorter time to type 2 diabetes onset was associated with female sex (Hazard Ratio (HR) = 4.83; 95% CI = 3.05–7.66, $p = 0.001$), and older age at first psychiatric diagnosis (HR = 1.19; 95% CI = 1.12-1.28, $p = 0.001$), while antipsychotic exposure (HR) = 1.41; 95% CI = 0.92-2.16, $p = 0.11$) trended towards increasing the rate of diabetes. **Conclusion:** Antipsychotic treatment, female sex, and older age at psychiatric diagnosis were associated with a significantly more frequent type 2 diabetes onset in children and adolescents. Strict indications for antipsychotic treatment and routine cardiometabolic monitoring are crucial. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(9):971–979. **Key Words:** Antipsychotics, diabetes, risk factors

The use of second-generation antipsychotics (SGAs) for psychiatric disorders in children and adolescents has increased significantly in recent years.[1,2] Children and adolescents diagnosed with psychotic disorders are often treated with antipsychotics, and current evidence has shown efficacy in this population, as well as in bipolar mania and irritability associated with autism spectrum disorder.[3-6] In addition, Tourette syndrome and disruptive behavior disorders are also often treated with antipsychotics, although most antipsychotics are not formally indicated for these disorders.[6,7] Off-label use of antipsychotics has been increasing, particularly in the United States, and particularly for the treatment of aggression and disruptive behavior disorders, as well as for augmentation in patients with depression and anxiety disorders.[8,9]

The increased use of antipsychotics might be caused by the better tolerability of SGAs

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compared to first-generation antipsychotics (FGAs), especially regarding extrapyramidal side effects, including tardive dyskinesia.[10,11] However, antipsychotics in general and many SGAs are also associated with significant weight gain and metabolic adverse effects.[5,12-14] Weight gain and metabolic side effects of antipsychotics seem to emerge even after short-term use and at low dosages,[12,13,15,16] and up to 80% of all children and adolescents treated with SGAs experience significant weight gain,[17-19] which is more pronounced and rapid in this population compared to adults.[10,15,18]

The association between antipsychotic treatment and an increased risk of weight gain, as well as an increased risk of diabetes, is well established in adults.[20-22] To date, research on the association between diabetes and antipsychotics in children and adolescents has been scarce. Andrade *et al.*[23] published a large study suggesting that there is indeed a heightened risk for diabetes in children and adolescents treated with SGAs. The authors found a potentially 4-fold increase in diabetes in children exposed to SGAs compared to children not treated with psychotropic medications. However, the diabetes risk with SGAs was not increased compared to that in patients treated with antidepressants,[23] and data were restricted to 3 health care plans. Nevertheless, the mean follow-up period was less than 1 year, thus pointing to a close link between SGA initiation and the emergence of diabetes.

In this study, we aimed to investigate the effects of exposure to antipsychotic drug treatment, as well as psychiatric diagnosis, on the risk and rate of developing type 2 diabetes, defined as prescription of an oral antidiabetic drug, in a large nationwide child and adolescent population in Denmark.

METHOD

We conducted a longitudinal register linkage case control study of type 2 diabetes in all child and adolescent hospital-based psychiatric patients diagnosed in Denmark from January 1, 1999 through June 30, 2010, a period chosen to allow full data retrieval from all registers used. The Danish Data Protection Agency, National Board of Health, and Statistics Denmark approved the use of the data for these study purposes.

Sample

The sample consisted of all children and adolescents diagnosed with a psychiatric *ICD-10* diagnosis before the age of 18 years, excluding only F50.x (eating disorders).[24] Eating disorder patients were excluded a priori to avoid introducing heterogeneity into the sample, because patients with eating disorders have a lower average weight, decreasing the risk of type 2 diabetes, and lack of significant weight gain on antipsychotic treatment, as shown in a recent meta-analysis,[25] which makes these patients categorically different from the remaining antipsychotic-treated population.[12-15]

Data on psychiatric diagnoses were retrieved from the Danish Psychiatric Central Research Register (DPCRR), which contains diagnostic data on all psychiatric inpatient and outpatient treatments in Denmark.[26] Data on medication variables were retrieved from the Danish Prescription Database, containing all prescription-based medications picked up from pharmacies since 1997. Data from medication usage during hospitalization is not registered in this database and was not available.[27]

Definition of Diabetes Status

Type 2 diabetes onset was defined by filling at least 1 prescription for an oral antidiabetic (Anatomical Therapeutic Chemical [ATC] Classification code A10B). Prescription of insulin was not used in the definition of diabetes onset in this study because of the risk of including subjects with type I diabetes. Furthermore, insulin is rarely used as the first or only antidiabetic agent for type 2 diabetes.

Type 2 diabetes is diagnosed by family doctors as well as hospital-based doctors. The family doctors do not submit data on diagnosis or treatment to any national register, which all hospital-based doctors do. As a result, we chose to use oral antidiabetic treatment as a proxy measure of type 2 diabetes, as all prescriptions are registered in the Danish Prescription Database, thereby ensuring full inclusion of all patients treated by both family doctors and hospital-based doctors.

Medication

Exposure was defined as filling 1 or more prescriptions for an antipsychotic during the study period. Antipsychotic drugs were defined as chlorpromazine, chlorprothixen, flupenthixol, fluphenazine, haloperidol, levomepromazine, periciazine, perphenazine, pimozide, pipamperone, prochlorperazin, and zuclopenthixol (all FGAs), and amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride, and ziprasidone (all SGAs).

Average cumulative antipsychotic dosage was calculated as the number of World Health Organization (WHO) Daily Defined Dosages (DDD)[28] collected from the pharmacy within the period from antipsychotic exposure to diabetes onset or end of study, whichever came first.

Benzodiazepines were defined as ATC code N05BA, N05CD, N05CF, and N03AE. Antidepressants were defined as ATC code N06AB, N06AX18, N06AX16, N06AX21, N06AX03, N06AX11, N06AA02, N06AA04, N06AA09, N06AA09, N06AA12, N06AA16,