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► **To cite this version:**

Jimmi Nielsen, Søren Skadhede, Christoph U Correll. ANTIPSYCHOTICS ASSOCIATED WITH THE DEVELOPMENT OF TYPE II DIABETES IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS. *Neuropsychopharmacology*, 2010, 10.1038/npp.2010.78 . hal-00542221

HAL Id: hal-00542221

<https://hal.science/hal-00542221>

Submitted on 2 Dec 2010

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ANTIPSYCHOTICS ASSOCIATED WITH THE DEVELOPMENT OF TYPE II DIABETES IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS

Running title: Type II diabetes and schizophrenia

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Abstract

Diabetes mellitus occurs in schizophrenia patients at higher rates than in the general population. Reasons for this elevated risk are poorly understood and have not been examined prospectively in antipsychotic-naïve, first episode patients. This study aims to determine which antipsychotics are associated with diabetes development in antipsychotic-naïve schizophrenia patients. All antipsychotic-naïve patients diagnosed with schizophrenia in Denmark between 01.01.1997 and 31.12.2004, followed until 31.12.2007, allowing for ≥ 3 years follow-up, unless death or diabetes onset occurred. Risk factors for the time to diabetes onset were assessed, including antipsychotics taken for at least 180 defined daily doses in the first year after first antipsychotic prescription (“initial treatment”). Risk factors for diabetes incidence were assessed, including antipsychotic use within three months before diabetes onset or study end (“current treatment”). Of 7,139 patients, followed for 6.6 years (47,297 patient years), 307 developed diabetes (annual incidence rate: 0.65%). Time to diabetes onset was significantly shorter in patients with higher age (HR:1.03, CI:1.02-1.03) and those with “initial” treatment of olanzapine (HR:1.41, CI:1.09-1.83), mid-potency first-generation antipsychotics (FGAs) (HR:1.60, CI:1.07-2.39), antihypertensive (HR:1.87, CI:1.13-3.09) or lipid lowering drugs (HR:4.67, CI:2.19-10.00). Significant factors associated with diabetes within three month of its development included treatment with low-potency FGAs (OR:1.52, CI: 1.14-2.02), olanzapine (OR:1.44, CI:1.98-1.91) and clozapine (OR:1.67, CI:1.14-2.46), while aripiprazole was associated with lower diabetes risk (OR:0.51, CI:0.33-0.80). In addition to general diabetes risk factors, like age, hypertension and dyslipidemia, diabetes is promoted in schizophrenia patients by initial and current treatment with olanzapine and mid potency first-generation antipsychotics, as well as by current treatment with or low potency first generation antipsychotics and clozapine, whereas current aripiprazole

treatment reduced diabetes risk. Patients discontinuing olanzapine or mid-potency FGA had no increased risk of diabetes compared to patient not treated with the drugs at anytime.

Keywords: schizophrenia, first-episode, antipsychotic-naïve, diabetes, risk factors, olanzapine, clozapine, first-generation antipsychotics

Introduction

Patients with schizophrenia have a reduced lifespan of more than 20 years, with cardiovascular disorders being the main cause of death (Colton and Manderscheid, 2006; Tiihonen *et al*, 2009). Reasons for the premature cardiovascular death are related to higher rates of cardiovascular risk factors in patients with severe mental disorders, including obesity, arterial hypertension, the metabolic syndrome and type II diabetes (Newcomer, 2005). Reasons for the increased prevalence of cardiovascular risk factors are complex and include sedentary lifestyle, (Koopman *et al*, 2005), treatments that increase body weight and worsen metabolic parameters (Newcomer, 2005) and, possibly, illness related or genetic factors (Fleischhacker *et al*, 2008).

Diabetes mellitus is a particularly strong risk factor for cardiovascular morbidity, being a risk equivalent of myocardial infarction (Haffner *et al*, 1998). Despite their widespread use, second-generation antipsychotics (SGAs), especially olanzapine and clozapine, have been associated with metabolic syndrome and the development of type II diabetes (Cohen and Correll, 2009; Meyer and Stahl, 2009; Yood *et al*, 2009) . However, the risk of metabolic complications differs within the class of first-generation antipsychotics (FGAs) and SGAs, with high-potency FGAs and more recent SGAs, such as aripiprazole and ziprasidone, having smaller metabolic burden compared to the rest of the antipsychotic drugs (Meyer *et al*, 2008).

Antipsychotic induced weight gain is considered an indirect pathway to the development of diabetes via decreasing peripheral insulin resistance due to decreased insulin sensitivity. Of note, in addition to indirect pathways to diabetes development, at least, studies with olanzapine and clozapine have suggested a possible, direct adverse effect on glucose homeostasis (Henderson *et al*, 2006; Houseknecht *et al*, 2007; Kinon *et al*, 2008; Newcomer *et al*, 2002). Moreover, in a

recent study of antipsychotic-naïve youth treated with olanzapine, the adverse metabolic effects on glucose and lipid metabolism appeared to be dose related, whereas increases in body composition parameters were not dose related (Correll *et al*, 2009). This opens the possibility that a direct diabetogenic effect of olanzapine may accelerate the development of diabetes in susceptible individuals even more when occurring early in the treatment course, leading to a stronger signal compared to other antipsychotics than when given later in the illness course, when weight gain associated with other medications is added to the pathophysiology of diabetes development.

Since diabetes development in the severely mentally ill is an increasing issue of high public health importance, we aimed to identify antipsychotics associated with increased risk for the development of diabetes in patients with first episode schizophrenia. This information is relevant to develop strategies that decrease the risk of metabolic complications in severely mentally ill patients. To date, diabetes development has not been studied as an outcome in first episode cohorts due to the small numbers and relatively brief follow-up periods. Therefore, we utilized a cohort study design, using a large and representative data set. We focused on patients with first episode schizophrenia in order to decrease the confounding effect of unknown prior treatments and to examine if the early use of antipsychotics with more pronounced cardiometabolic effects is associated with an acceleration of diabetes development that usually takes many years to develop. We hypothesized that use of olanzapine during the first year after initiation of antipsychotics, and current use of olanzapine or clozapine would be associated with the development of diabetes.

Methods and Materials

Sample:

This cohort study was approved by the Danish Data Protection Agency, National Board of Health and Statistics Denmark. Subjects for the analyses were identified by having an onset of an ICD-10 F20 schizophrenia diagnosis in the Danish Central Psychiatric Research Registry (Munk-Jorgensen and Mortensen, 1997) in the period from January 01, 1997 until December 31, 2007. The register has a high validity and has contributed significantly to epidemiological research (Barr *et al*, 1990; Bock *et al*, 2009; Laursen *et al*, 2005; Pedersen and Mortensen, 2001; Qin and Nordentoft, 2005).

Prescription data for the included subjects were obtained from the national prescription database from January 1, 1996 through December 31, 2007. Prescription data were assessed at least one year before onset of schizophrenia to exclude cases with a history of diabetes before the first prescription of antipsychotics. Index date was the date of first antipsychotic prescription ever, even if this predated the formal diagnosis of schizophrenia. To ensure a minimum of 3-years of follow-up, subjects having a first antipsychotic prescription after December 31, 2004 were excluded. Only subjects receiving at least one prescription of an antipsychotic were included in the analysis. The prescription database contains information about number of sold Daily Defined Doses (DDD), which are assigned and reviewed by researchers of the World Health Organization Collaborating Centre of Drug Statistics Methodology (WHO, 2009). Subjects with a history of any psychotic disease prior to January 01, 1997 (i.e., ICD-10: F2 and ICD-8: 295-299) were also excluded. Follow-up time was defined as time from first prescription of antipsychotics until onset of diabetes, death or end of register Dec 31, 2007.

Diabetes onset was defined as receiving a diagnosis of type II diabetes (ICD10: E11) from a somatic hospital or outpatient clinic, or filling at least one prescription for an oral antidiabetic (ATC: A10B), whichever came first. Patients with diabetes onset before first antipsychotic prescription (N=91) were excluded from further analyses. Prescription of insulin was not used in the definition of diabetes onset due to the risk of including subjects with a type I diabetes. Furthermore, insulin is rarely used as the only antidiabetic agent for type II diabetes. In this dataset, only five cases received insulin alone after the onset of antipsychotic prescription, and these were also excluded.

Statistical analyses:

Statistical analyses were performed with STATA 10 at Statistics Denmark server via remote access. Since cardiovascular risk factors, e.g. age, sex, obesity, hypertension, and dyslipidemia, contribute to the development of type II diabetes, the following variables were used in the multivariate statistical models in addition to antipsychotic medications: age, sex, receiving lipid lowering medications or antihypertensive medications. Furthermore, two variables were created as a proxy measure of severity of illness: percentage of follow-up time as an in-patient and average antipsychotic DDD during follow-up. Days with inpatient status were excluded from the calculation of average DDD because medications dispensed during hospitalization are not included in the national prescription database.

Antipsychotics were divided FGA and SGA, and FGA were subdivided in low, mid and high potency FGA. The low potency FGA group consisted of chlorpromazine, levomepromazine,

chlorprothixen, melperone and pipamperone. The mid potency FGA group consisted of zuclopenthixol, periciazine, prochlorperazin and perphenazine. The high potency FGA group consisted of haloperidol, pimozide, flupenthixol and fluphenazine. The SGA group consisted of olanzapine, quetiapine, sertindole, amisulpride, risperidone, ziprasidone, sulpride and clozapine.

“Initial” antipsychotic treatment was defined as receiving at least 180 DDD of the same antipsychotic drug within the first 365 days after first antipsychotic prescription, which could pre-date the diagnosis of schizophrenia. Bed-days were excluded in this definition, as inpatient medications were not available. “Current” antipsychotic treatment was defined as filling at least one prescription of an antipsychotic drug within the last three months period before diabetes onset, death or end of registry. If patients were on more than one antipsychotic, diabetes risk counted to each antipsychotic.

In addition, continuation of the type of antipsychotics three months before and after onset of diabetes was determined to assess whether patients were continued on diabetogenic antipsychotic drugs. Aripiprazole and ziprasidone are considered low metabolic risk antipsychotics, which make them suitable for first line treatment and for metabolically vulnerable patients. Prior treatment with low metabolic risk antipsychotic was assessed in order to determine whether treatment with these drugs had been attempted before the use of higher metabolic risk antipsychotics.

Age of diabetes onset and age at last observation were transformed by square root and transformed back to obtain the mean and 95% confidence intervals. Age of schizophrenia and

age of first antipsychotic prescription was transformed by the natural logarithm. Percentages of psychiatric inpatient time were not normally distributed without the possibility for transformation. Consequently, the non-parametric Wilcoxon rank sum test was used to compare rates between patients with and without diabetes. Binary variables were tested with a chi square test.

The effect of initial treatment variables on the time to onset of diabetes was tested using the Cox regression model that was adjusted for sex, and age of first antipsychotic prescription. The effect of current treatment variables was tested in a multiple regression model. Variables entered into the Cox model and the multiple regression model were those significantly associated with diabetes determined by stepwise forward logistic regression, including variables with $p < 0.1$, followed by a stepwise backward logistic regression excluding variables with $p > 0.05$. For the multiple regression model of current antipsychotic use, both Crude and odds ratios (ORs) adjusted for observation time were calculated. This was done due to the continuous introduction of atypical antipsychotics during the study period. Antipsychotics with initial use associated with an increased risk of diabetes were divided in subjects who continued the treatment for more than 1 year and those who discontinued treatment. The discontinuers were compared to subjects never treated with the drug. In the multivariate models, the following continuous variables were treated as discrete variables: age, percentage of psychiatric inpatient time, and DDD. This was done to be able to calculate (ORs) and Hazard Ratios (HRs), which indicate an increase in age from year to year, in percent of time hospitalized by one percent (e.g., 2% to 3%, etc), and in DDD by 1 DDD (i.e., 1 vs. 2 DDD, etc).

Results

Altogether, 7,139 first episode schizophrenia subjects (mean age at first antipsychotic prescription: 29.7 years, 59.7% male) without diabetes prior to first antipsychotic prescription were included in this study, with a total observation time of 47,297 patient years and a mean observation time of 6.6 (SD=2.4) years. Table 1 displays patient demographics as well as characteristics of the initial treatment and the treatment during the last three months. In total, 307 patients developed diabetes during the follow up, translating into an annual diabetes incidence rate of 0.65% per patient year. The mean age of onset of type II diabetes was 41.7 (40.4-43.1), and the median onset after first antipsychotic prescription was 3.9 years (25 and 75 percentiles: 2.3 and 6.0 years).

Effect of Variables Present During the First Year of Antipsychotic Treatment

In the Cox regression model, time to diabetes onset was significantly shorter in patients with higher age (HR:1.03, CI:1.02-1.03) and those with “initial” treatment of olanzapine (HR:1.41, CI:1.09-1.83), mid-potency first-generation antipsychotics (FGAs) (HR: 1.60, CI:1.07-2.39), antihypertensive (HR:1.87, CI:1.13-3.09) or lipid lowering drugs (HR:4.67, CI:2.19-10.00) (Table 2). Low potency FGAs also had a trend towards an increased risk of diabetes but remained insignificant (OR: 1.63 CI: 0.93-2.84, $p>0.086$). Discontinuers of olanzapine had no increased risk compared to patients not receiving olanzapine at anytime within the study period. Similar was found for mid-potency FGA.

Effect of Variables Present During the Entire Follow Up and of Treatment Variables Present During the Last Three Months Prior to Diabetes Onset or At Study Completion

In the adjusted multivariate model, significant factors associated with diabetes incidence within three month of its development included “current” treatment with low-potency FGAs (OR:1.56, CI: 1.17-2.07), olanzapine (OR:1.96, CI:1.48-2.58) and clozapine (OR:2.48, CI:1.68-3.66), whereas aripiprazole (OR:0.51, CI:0.36-0.86), not receiving antipsychotics (OR:0.57 CI:0.41-0.79) and male sex (OR:0.71, CI: 0.55-0.90) were associated with lower diabetes incidence (Table 3).

Neither sole treatment with either SGAs nor FGAs during the entire follow-up period was associated with an increased risk of diabetes. Higher dosages of antipsychotics during follow-up was associated with an increased risk for diabetes OR:1.10, CI: 1.02-1.19, $p < 0.01$ only in a univariate logistic regression model.

Antipsychotic Treatment At The Time of Diabetes Onset and Three Months Later

Patients developing diabetes were to a large extent on high metabolic risk antipsychotics, such as olanzapine (27.7%), low-potency FGAs (25.1%) and clozapine (11.7%) during diabetes onset of. Three months after diabetes onset 84% of patients treated with olanzapine, 94% with clozapine, 91% with quetiapine, 86% with risperidone and 86% treated with low- or mid-potency FGAs remained on these medications. During the same time frame, only 8 (4%) and 5 (2%) patients had initiated treatment with one of the two low metabolic risk antipsychotics, aripiprazole and ziprasidone, respectively. Of patients with diabetes, only 80 (26.1%) had previously been treated with one of the low risk metabolic drugs, i.e., aripiprazole: 41 (13.4%) and ziprasidone: 53

(17.6%).

Discussion

Results from this largest cohort study of antipsychotic-naïve schizophrenia patients indicate that in addition to general diabetes risk factors, such as higher age, hypertension and dyslipidemia (indicated by treatment received for these conditions) (Narayan et al., 2003; Lorenzo et al., 2003), diabetes is promoted by initial treatment with olanzapine and mid potency FGAs, as well as by current treatment with low-potency FGAs, olanzapine and clozapine, whereas current aripiprazole treatment and male sex were associated with a reduced diabetes risk.

The finding that the current use of the SGAs, olanzapine and clozapine, increases the risk of diabetes is consistent with prior findings (Gianfrancesco *et al*, 2002; Ramaswamy *et al*, 2006; Smith *et al*, 2008; Stahl *et al*, 2009; Yood *et al*, 2009). However, to our knowledge, this is the first study showing that the metabolic effects of olanzapine early on during treatment can alter the trajectory to diabetes. This could be explained by the fact that the weight that was gained initially is maintained throughout the course of the illness, adversely affecting insulin resistance. Alternatively, it is also possible that direct effects on the pancreatic beta cell predispose vulnerable individuals to an earlier diabetes onset. These findings call into question the use of olanzapine as a first line treatment for first episode schizophrenia (Moore *et al*, 2007) and underscore that the anticipated benefits of using olanzapine early on in the treatment algorithm should clearly outweigh the increased risk for diabetes; otherwise lower metabolic risk antipsychotics should be used.

By contrast, the situation for clozapine use differs because it is indicated for treatment resistant schizophrenia and reserved for the most severely ill, refractory patients (Nielsen *et al*, 2009; Taylor *et al*, 2003), which can affect the risk for diabetes through perhaps even poorer healthy lifestyle behaviors than is common in schizophrenia patients in general (Sharpe *et al*, 2006). Furthermore, the superior efficacy of clozapine in treatment refractory patients (Kane *et al*, 1988) indicates that the increased diabetes risk has to be balanced with the chance for enhanced efficacy.

Initial treatment with mid-potency FGAs and current treatment with low potency FGAs was also associated with an increased risk for diabetes. This finding is somewhat at odds with a recent meta-analysis (Smith *et al*, 2008) that found a significantly increased risk for diabetes with SGAs compared to FGAs (OR: 1.13, CI:1.15-1.51). However, in this meta-analysis, insufficient data were available for ziprasidone and aripiprazole, the latter of which was associated with a lower risk for diabetes during current use in our study. This result, together with our finding of the independently increased risk for diabetes with low- and mid-potency FGAs highlights the fact that diabetes development is not solely an issue with FGAs, and, more importantly, that SGAs and FGAs are heterogeneous classes that should not be lumped together. Initial treatment with low potency FGA were not associated with an increased risk of diabetes which might be due to low numbers. Rather, medications should be considered separately, or grouped by individual cardiometabolic risk, which cuts across SGAs and FGAs (Citrome *et al*, 2007; Hagg *et al*, 1998).

In this study, the mean age of diagnosis of schizophrenia is somewhat higher than found in other studies where the age is generally around the mid twenties (Bertelsen *et al*, 2009; Kahn *et al*, 2008; Robinson *et al*, 1999). However, these studies usually have an upper age limit of around 40 years and/or focus also on first episode psychosis instead of first episode schizophrenia, explaining the lower mean age compared to our study where no upper age limit was set. In our study, the mean age of diabetes onset was around 41 years. This is lower than in the general population and similar to results from previous studies with antipsychotics (Cohen *et al*, 2006). In first half of the last century, female sex was considered as risk factor for type II diabetes, but this difference had vanished by the end of the last century (Gale and Gillespie, 2001). However, in a review of pharmacoepidemiologic studies of antipsychotic use and diabetes, an association with female sex was also found like in our study (Ramaswamy *et al*, 2006). Future studies should investigate sex differences regarding the antipsychotic effects and lifestyle influences that could affecting diabetes risk in antipsychotic treated individuals.

Of note, a high rate of the patients developing diabetes during treatment with high-risk metabolic drugs, olanzapine and clozapine, were maintained on this treatment 3 months after diabetes onset, suggesting that either switching to a lower risk metabolic drug was not clinically feasible, or that psychiatrists were not considering this option. It is further possible that clinicians did not believe that removing the high metabolic risk antipsychotic would reverse the diabetes, even though this has been described in case series before (De Hert *et al*, 2006). Similarly, fewer patients with diabetes had been treated with a low metabolic risk antipsychotic in the past compared to patients who did not develop diabetes, implying that some cases of diabetes might have been

prevented or postponed by using lower cardiometabolic risk antipsychotics, especially in the early illness course. This is supported by our finding that olanzapine discontinuers had no increased risk of diabetes.

The findings of this study have to be interpreted within its limitations. These include the observational study design, lack of randomized treatment assignment, lack of a control group, and potential influence of unmeasured and unknown confounding factors that cannot be controlled for, such as family history of diabetes, diet and exercise behaviors, body composition, medication adherence, severity of psychiatric illness and changes in prescribing patterns. Moreover, findings are associations, and causal inferences cannot be made. In addition, we only studied in detail the influence of initial and current treatment, and treatment periods in between might have also influenced the outcome. Furthermore, the metabolic screening procedure might have differed between the antipsychotic drugs, e.g. clozapine patients might have had more frequent blood draws due to the mandatory hematological monitoring. In contrast patients treated with low metabolic risk drugs e.g. aripiprazole might have had less monitoring due to psychiatrists' perception that these drugs are not causing diabetes and this could have delayed the diabetes diagnosis. Unfortunately, we did not have access to measure the screening procedure. Furthermore, it is not fully possible to control for confounding by indication, i.e., choosing a low-risk metabolic drug for a metabolically vulnerable patient. However, despite this potential bias, current use of aripiprazole was still associated with a reduced diabetes risk. Despite these limitations, the size of this sample, the relatively long-term follow-up duration, focus on first episode schizophrenia patients and the follow-up from the beginning of antipsychotic prescribing in previously antipsychotic-naïve subjects are clear strengths of this study.

Based on the results from this and prior studies, clinicians should focus on preventing initial weight gain because subsequent long-term weight loss is difficult to achieve, either via behavioral or pharmacologic (Marder *et al*, 2004) interventions. Moreover, all patients receiving antipsychotics should undergo routine monitoring of weight and metabolic parameters (ADA, 2004), and, preferentially, medications with low metabolic liabilities should be used (Meyer *et al*, 2009). Given recent data that monitoring has not increased after the warnings about metabolic risks of antipsychotics (Morrato *et al*, 2010), educational actions and quality control and improvement initiatives should be taken and studied to improve cardiometabolic outcomes in the vulnerable schizophrenia patients. Finally, from a metabolic syndrome point of view patient should initially receive treatment with antipsychotics possessing a low risk for weight gain in order to minimize the burden of metabolic side-effects.

Acknowledgement: None.

Jimmi Nielsen 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.

Disclosures/conflict of interest

J. Nielsen has received research grants from H. Lundbeck for clinical trials and received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen Pharmaceutica, and Eli-Lilly.

Søren Skadhede has no financial disclosures.

C.U. Correll has been a consultant to or has received honoraria from Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GSK, Hoffmann-La Roche, Lundbeck; MedAvante; Medicure; Janssen/J&J, Schering-Plough; Otsuka, Pfizer, Supernus; Takeda and Vanda.

Role of funding source:

This study was funded by Aalborg Psychiatric Hospital which had no influence on data analysis and preparation of the manuscript.

References

- ADA (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* **27**(2): 596-601.
- Barr CE, Mednick SA, Munk-Jorgensen P (1990). Exposure to influenza epidemics during gestation and adult schizophrenia. A 40-year study. *Arch Gen Psychiatry* **47**(9): 869-874.
- Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, Le Quach P, *et al* (2009). Course of illness in a sample of 265 patients with first-episode psychosis--five-year follow-up of the Danish OPUS trial. *Schizophr Res* **107**(2-3): 173-178.
- Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV (2009). Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health* **5**: 4.
- Citrome LL, Holt RI, Zachry WM, Clewell JD, Orth PA, Karagianis JL, *et al* (2007). Risk of treatment-emergent diabetes mellitus in patients receiving antipsychotics. *Ann Pharmacother* **41**(10): 1593-1603.
- Cohen D, Correll CU (2009). Second-generation antipsychotic-associated diabetes mellitus and diabetic ketoacidosis: mechanisms, predictors, and screening need. *J Clin Psychiatry* **70**(5): 765-766.
- Cohen D, Stolk RP, Grobbee DE, Gispen-de Wied CC (2006). Hyperglycemia and diabetes in patients with schizophrenia or schizoaffective disorders. *Diabetes Care* **29**(4): 786-791.
- Colton CW, Manderscheid RW (2006). Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* **3**(2): A42.
- Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK (2009). Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* **302**(16): 1765-1773.
- De Hert M, Hanssens L, van Winkel R, Wampers M, Van Eyck D, Scheen A, *et al* (2006). Reversibility of antipsychotic treatment-related diabetes in patients with schizophrenia: a case series of switching to aripiprazole. *Diabetes Care* **29**(10): 2329-2330.
- Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, Hennekens CH, Lambert M, Leucht S, *et al* (2008). Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. *J Clin Psychiatry* **69**(4): 514-519.
- Gale EA, Gillespie KM (2001). Diabetes and gender. *Diabetologia* **44**(1): 3-15.

Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA (2002). Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* **63**(10): 920-930.

Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* **339**(4): 229-234.

Hagg S, Joelsson L, Mjorndal T, Spigset O, Oja G, Dahlqvist R (1998). Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J Clin Psychiatry* **59**(6): 294-299.

Henderson DC, Copeland PM, Borba CP, Daley TB, Nguyen DD, Cagliero E, *et al* (2006). Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J Clin Psychiatry* **67**(5): 789-797.

Houseknecht KL, Robertson AS, Zavadoski W, Gibbs EM, Johnson DE, Rollema H (2007). Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology* **32**(2): 289-297.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, *et al* (2008). Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* **371**(9618): 1085-1097.

Kane J, Honigfeld G, Singer J, Meltzer H (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* **45**(9): 789-796.

Kinon BJ, Stauffer VL, Kollack-Walker S, Chen L, Sniadecki J (2008). Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. *J Clin Psychopharmacol* **28**(6): 601-607.

Koopman RJ, Mainous AG, 3rd, Diaz VA, Geesey ME (2005). Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. *Ann Fam Med* **3**(1): 60-63.

Laursen TM, Labouriau R, Licht RW, Bertelsen A, Munk-Olsen T, Mortensen PB (2005). Family history of psychiatric illness as a risk factor for schizoaffective disorder: a Danish register-based cohort study. *Arch Gen Psychiatry* **62**(8): 841-848.

Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, *et al* (2004). Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* **161**(8): 1334-1349.

Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, *et al* (2008). Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res* **101**(1-3): 273-286.

Meyer JM, Stahl SM (2009). The metabolic syndrome and schizophrenia. *Acta Psychiatr Scand* **119**(1): 4-14.

Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, *et al* (2007). The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry* **68**(11): 1751-1762.

Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, *et al* (2010). Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry* **67**(1): 17-24.

Munk-Jorgensen P, Mortensen PB (1997). The Danish Psychiatric Central Register. *Dan Med Bull* **44**(1): 82-84.

Newcomer JW (2005). Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* **19 Suppl 1**: 1-93.

Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, *et al* (2002). Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* **59**(4): 337-345.

Nielsen J, Dahm M, Lublin H, Taylor D (2009). Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacol*.

Pedersen CB, Mortensen PB (2001). Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. *Arch Gen Psychiatry* **58**(11): 1039-1046.

Qin P, Nordentoft M (2005). Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. *Arch Gen Psychiatry* **62**(4): 427-432.

Ramaswamy K, Masand PS, Nasrallah HA (2006). Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. *Ann Clin Psychiatry* **18**(3): 183-194.

Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, *et al* (1999). Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* **156**(4): 544-549.

Sharpe JK, Stedman TJ, Byrne NM, Wishart C, Hills AP (2006). Energy expenditure and physical activity in clozapine use: implications for weight management. *Aust N Z J Psychiatry* **40**(9): 810-814.

Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K (2008). First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* **192**(6): 406-411.

Stahl SM, Mignon L, Meyer JM (2009). Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand* **119**(3): 171-179.

Taylor DM, Young C, Paton C (2003). Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry* **64**(1): 30-34.

Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, *et al* (2009). 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*.

WHO (2009). World Health Organization, collaborating centre Drug Statistics Methodology.

Yood MU, DeLorenze G, Quesenberry CP, Jr., Oliveria SA, Tsai AL, Willey VJ, *et al* (2009). The incidence of diabetes in atypical antipsychotic users differs according to agent--results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf* **18**(9): 791-799.

Table 1. Demographic, Illness and Treatment Characteristics Characteristics

Baseline Characteristic	Total (N=7,139)	No Diabetes (N=6,832)	Diabetes (N=307)	P-value
Demographic characteristics				
Age at first antipsychotic prescription	29.4 (29.1-29.6)	29.2 (28.9-29.4)	34.1 (32.8-34.4)	0.001
Age at first schizophrenia diagnosis (years)	31.2 (30.9-31.5)	31.0 (30.7-31.3)	36.1 (34.8-37.5)	0.001
Age at last observation (years)	36.4 (36.1-36.7)	36.2 (35.9-36.4)	41.7 (40.4-43.1)	0.001
Mean duration of follow-up (years)	6.63 (6.57-6.69)	6.74 (6.68-6.79)	4.18 (3.91-4.45)	0.001
Male Sex, N (%)	4,261 (59.7%)	4,101 (60.0%)	160 (52.1%)	0.006
Schizophrenia Diagnosis, N (%)				
Paranoid F20.0	4,016 (56.3%)	3,827 (56.0%)	189 (61.6%)	NS
Hebephrenic F20.1	134 (1.9%)	130 (1.9%)	4 (1.3%)	NS
Catatonic F20.2	47 (0.7%)	46 (0.7%)	1 (0.3%)	NS
Undifferentiated F20.3	864 (12.1%)	826 (12.1%)	38 (12.4)	NS
Simple F20.6	357 (5.0%)	340 (5.0%)	17 (5.5%)	NS
Unspecified F20.9	1,605 (22.5%)	1,553 (22.7%)	52 (17.0%)	0.02
Other F20.4+F20.5+ F20.7+F20.8	72 (1.0%)	69 (1.01%)	3 (1.0%)	NS
Median % of in-patient stay during follow-up				
25 % - 75 % percentiles	0.03%-10.3%	0.03-10.2%	0 %-14.4%	
Mean antipsychotic DDD during follow-up	0.46 (0.45-0.48)	0.46 (0.44-0.47)	0.62 (0.53-0.74)	0.001
Living in an institution at end of study	495 (6.9%)	465 (6.8%)	30 (9.8%)	0.045
Early retirement pension	4,225 (59.2%)	4,011 (58.7%)	214 (69.7%)	0.01
Unmarried	5,822 (81.6%)	5,583 (81.2%)	239 (77.9%)	NS
Antipsychotic Treatment during entire follow-up				
FGA only (%)	660 (9.2%)	611 (8.9)	49 (16.0%)	0.001
SGA only (%)	4,825 (67.6%)	4,622 (67.7%)	203 (66.1%)	NS
FGA+SGA (%)	1,654 (23.2%)	1,599 (23.4%)	55 (17.9%)	0.03
Antipsychotic Treatment from first AP prescription (min. 180 DDD)				
Aripiprazole	117 (1.6%)	111 (1.6%)	6 (2.0%)	NS
Olanzapine	1,503 (21.1%)	1,425 (20.9%)	78 (25.4%)	NS
Quetiapine	329 (4.6%)	316 (4.6%)	13 (4.2%)	NS
Risperidone	550 (7.7%)	527 (7.7%)	23 (7.5%)	NS
Ziprasidone	223 (3.1%)	212 (3.1%)	11 (3.6%)	NS
High potency FGA	120 (1.7%)	113 (1.7%)	7 (2.3%)	NS
Mid potency FGA	372 (5.2%)	346 (5.1%)	26 (8.5%)	0.009
Low potency FGA	207 (2.9%)	194 (2.8%)	13 (4.2%)	NS
Antipsychotic Treatment during the Last 3 Months Prior to Endpoint (Total N exceeds the N of individual patients)				
Aripiprazole	878 (12.3%)	855 (12.5%)	23 (7.5%)	0.009
Clozapine	489 (6.9%)	453 (6.6%)	36 (11.7%)	0.001
Olanzapine	1,262 (17.7%)	1,177 (17.2%)	85 (27.7%)	0.0001

Baseline Characteristic	Total (N=7,139)	No Diabetes (N=6,832)	Diabetes (N=307)	P-value
Quetiapine	969 (13.6%)	923 (13.5%)	46 (15.0%)	NS
Risperidone	1,141 (16.0%)	1090 (15.9%)	51 (16.6%)	NS
Ziprasidone	384 (5.4%)	364 (5.3%)	20 (6.5%)	NS
Other SGA (sertindole, amisulpride)	163 (2.3%)	160 (2.3%)	3 (1.0%)	NS
High potency FGA	158 (2.2%)	146 (2.1%)	12 (3.9)	0.039
Mid potency FGA	556 (7.8%)	522 (7.6%)	34 (11.1%)	0.03
Low potency FGA	1,125 (10.8%)	1,048 (15.3%)	77 (25.1%)	0.001
No antipsychotics	2,505 (35.1%)	2,444 (35.8%)	61 (19.9%)	0.001
Antipsychotic polypharmacy ¹	1,802 (38.9)	1,704 (38.9%)	98 (40.0%)	NS
Non-antipsychotic Treatment the first year after first AP prescription				
Anxiolytics/Hypnotics (N, %)	3,906 (54.7%)	3,696 (54.1%)	210 (68.4%)	0.001
Antidepressants (N, %)	4,298 (60.2%)	4,083 (59.8%)	215 (70.0%)	0.001
Mood Stabilizers				
Valproic acid/Divalproex (N, %)	136 (1.9%)	130 (1.9%)	6 (1.9%)	NS
Lithium (N, %)	143 (2.0%)	133 (2.0%)	10 (3.3%)	NS
Lipid lowering drugs (N, %)	27 (0.4%)	20 (0.3%)	7 (2.3%)	0.001
Antihypertensive drugs (N, %)	150 (2.1%)	132 (1.9%)	18 (5.9%)	0.001
Non-antipsychotic Treatment 3 months before end				
Anxiolytics/Hypnotics (N, %)	2,287 (32.0%)	2,159 (31.6%)	128 (41.7%)	0.001
Antidepressants (N, %)	2,203 (30.9%)	2,061 (30.2%)	142 (46.3%)	0.001
Mood Stabilizers				
Valproic acid/Divalproex (N, %)	126 (1.8%)	121 (1.8%)	5 (1.6%)	NS
Lithium (N, %)	1,462 (20.5%)	1,444 (21.1%)	18 (5.9%)	0.001
Lipid lowering drugs (N, %)	177 (2.5%)	145 (2.1%)	32 (10.4%)	0.001
Antihypertensive drugs (N, %)	121 (1.7%)	110 (1.6%)	11 (3.6%)	0.009
Low metabolic risk drugs prescribed at any time during follow-up				
Aripiprazole	1,803 (25.3%)	1,762 (25.8%)	41 (13.4%)	0.001
Ziprasidone	1,528 (21.4%)	1,475 (21.6%)	53 (17.3%)	NS
Aripiprazole or ziprasidone	2,695 (37.8%)	2,615 (38.3%)	80 (26.1%)	0.001
High potency FGA	1112 (15.6%)	1060 (15.5%)	52 (16.9%)	NS

1) Percentage is only of those receiving antipsychotics within the last 3 months before endpoint.

Table 2. Cox regression showing variables during initial treatment affecting time until onset of diabetes.

Variable	HR	z	p	95 % CI	
Male gender	0.80	-1.95	0.051	0.63	1.00
Age of first prescription of antipsychotics*	1.02	5.96	0.001	1.02	1.03
Olanzapine	1.41	2.62	0.009	1.09	1.83
Mid potency FGA	1.60	2.28	0.023	1.07	2.39
Receiving antihypertensive medication	1.87	2.45	0.014	1.13	3.09
Receiving lipid lowering medication	4.67	3.97	0.001	2.19	10.00

AP: antipsychotic FGA: first generation antipsychotic

*) Percentage of time being hospitalized is used as a continuous variable, i.e. odds ratio (OR) indicates increase from e.g. 2% to 3%, etc.

Table 3. Factors associated with altered risk for type II diabetes during the last 3 months of follow-up.

Variable	Crude				Adjusted for observation time			
	OR	z	p	95 % CI	OR	z	p	95 % CI
Aripiprazole	0.51	-2.95	0.003	0.33 0.80	0.53	-2.8	0.005	0.34 0.82
Receiving no antipsychotics	0.57	-3.36	0.001	0.41 0.79	0.60	-2.97	0.003	0.43 0.84
Percentage of time being hospitalized*	1.02	3.89	0.001	1.01 1.02	NS			
Age of first prescription of antipsychotics*	1.03	7.31	0.001	1.02 1.04	1.01	3.53	0.001	1.01 1.02
Olanzapine	1.44	2.53	0.011	1.09 1.91	1.57	2.97	0.003	1.17 2.11
Low potency FGA	1.52	2.84	0.005	1.14 2.02	1.45	2.44	0.015	1.08 1.96
Clozapine	1.67	2.61	0.009	1.14 2.46	2.31	4.12	0.001	1.55 3.44

AP: antipsychotic FGA: first generation antipsychotic

*) Percentage of time being hospitalized is used as a continuous variable, i.e. odds ratio (OR) indicates increase from e.g. 2% to 3%, etc.