BJPsych The British Journal of Psychiatry (2010) 197, 266–271. doi: 10.1192/bjp.bp.109.076935

Treatment with antipsychotics and the risk of diabetes in clinical practice

Lars Vedel Kessing, Anders Frøkjær Thomsen, Ulla Brasch Mogensen and Per Kragh Andersen

Background
Treatment with antipsychotics seems to increase the risk of developing diabetes but the association is poorly characterised in clinical practice.

Aims
To investigate and characterise the incidence of diabetes for people treated with antipsychotic medication in clinical practice.

Method
The study used the linkage of registers of all prescribed antipsychotics, antidiabetics and diagnoses of diabetes in Denmark during a period from 1996 to 2005 and identified all people treated with antipsychotics in Denmark and a random sample of about 30% of the total Danish population.

Results
In total, 345 937 patients who purchased antipsychotics and 1 426 488 unexposed individuals were included in the study. Among the total population, 50 379 individuals subsequently developed incident diabetes. Compared with unexposed individuals, treatment with first- (rate ratio, RR = 1.53, 95% CI 1.49–1.56) as well as second-generation (RR = 1.32, 95% CI 1.22–1.42) antipsychotics was associated with increased risk of subsequent incident diabetes. The rate of incident diabetes varied substantially between individual second-generation antipsychotic drugs (olanzapine, risperidone clozapine compared with unexposed individuals: low to moderate rate ratio between 1.17 and 1.57; ziprasidone and sertindol: two or more times increased rate ratio; amisulpride, quetiapine and aripiprazole: no significantly increased rate ratio). For both first- and second-generation antipsychotics, the incidence of diabetes increased with the number of prescriptions. Additionally, the incidence of diabetes increased with the number of combined antipsychotic drugs.

Conclusions
In clinical practice, treatment with first- and second-generation antipsychotics is associated with an increased risk of developing incident diabetes with large differences between individual drugs. The risk increases with the duration of treatment and with polypharmacy of antipsychotic drugs.

Declaration of interest
L.V.K. has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth, Servier and Janssen-Cilag.

The use of antipsychotic medication in the general population has been increasing during the recent decade[1] and the prevalence of diabetes has increased to the level of a worldwide 'epidemic'.[2] Findings from studies suggest that schizophrenia[3,4] and bipolar disorder[5] are associated with an increased risk of diabetes. It has been shown that the incidence of diabetes is increased among people treated with second-generation antipsychotics compared with the general population,[6,7] whereas studies comparing second- and first-generation antipsychotics often have found a non-significant tendency towards increased diabetes incidence related to second-generation ones presumably because of low statistical power.[7] A recent systematic review and meta-analysis identified 11 observational studies investigating the risk of diabetes among patients taking antipsychotics and found that second-generation antipsychotics were associated with a small increased risk for diabetes compared with first-generation antipschotics.[8] It was further concluded that 'to date, the evidence is very poor and should not be used alone as a guideline for switching antipsychotic medication or implementing diabetes screening'. The average duration of studies included in the analyses was 12 months, with three studies having a follow-up of only 3 months or less and there were insufficient data to include aripiprazole, ziprasidone and amisulpride. Additionally, results from a few randomised controlled trials have been reported but because of short follow-up periods in these studies the end-point is rarely a manifest diagnosis of frank diabetes,[9] but rather increases in blood glucose. The longest follow-up period in a randomised trial is up to 18 months (the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study) that demonstrated elevation in blood glucose related to olanzapine and somewhat with quetiapine.[10]

In this paper, we present data from a population-based and nationwide register linkage study including all prescribed antipsychotics and all prescribed antidiabetics as well as all diagnoses of diabetes given at hospital contacts during a 10-year period in Denmark. The aim of the study was to investigate whether the incidence of diabetes is increased for people treated with antipsychotic medication in clinical practice compared with the incidence among the general population. Moreover, we wanted to compare whether the incidence of diabetes in clinical practice is greater in individuals treated with second-generation antipsychotics (atypical antipsychotics) than in those treated with first-generation antipsychotics (typical antipsychotics), and whether any of the most commonly used antipsychotics are associated with particularly high risks of subsequent diabetes in clinical practice. We also wanted to test whether incident diabetes increases with the number of prescriptions with antipsychotics and whether simultaneous prescription of two or more antipsychotics increases the risk of incident diabetes. In all analyses we took into account the possibility of switching to or adding on another antipsychotic.

Method

Danish register data

Data were obtained by linking Danish population-based registers using the unique personal identification number (CPR-number),

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press

which is assigned to all 5.4 million people living in Denmark, thus ensuring accurate linkage of information between registers, irrespective of changes in name, etc.[11] In this way, the Medicinal Product Statistics[12] was linked with the Danish Medical Register on Vital Statistics,[13] the Danish National Hospital Register[14] and the Danish Psychiatric Central Register.[15]

The Medicinal Product Statistics contains data on all prescribed medication purchased at pharmacies from 1 January 1995 onwards.[12] In Denmark, all medications prescribed by doctors, such as antipsychotics and antidiabetics, are purchased only at pharmacies. When prescribed medication is purchased at the pharmacies the following data are electronically recorded in the Medicinal Product Statistics: the CPR-number of the person, the ATC-code of the drug (Anatomical Therapeutical Chemical classification system)[16] and the dose and the number of tablets. Neither the daily dosing of the medication nor the indication for treatment are registered.

The Danish Medical Register on Vital Statistics[13] contains data on death. The Danish National Hospital Register contains data on all participants treated at all somatic hospitals as in- or out-patients in Denmark from 1 January 1977 onwards as a part of the official Danish health survey.[14] Likewise, all psychiatric admissions have been registered in a nationwide register, the Danish Psychiatric Central Register[15] from 1 April 1970 onwards. The ICD–8[17] was used before 1994 and the ICD–10 since 1 January 1994 for both registers.[18]

The study period was from 1 January 1996 to 31 December 2005, although the period prior to 1996 was used to exclude people with diabetes diagnosed prior to the study period.

Study sample

All Danish individuals who purchased antipsychotic medication in a study period from 1996 to 2005 were identified in the Medicinal Product Statistics and were categorised in two groups according to their first purchase: those purchasing one of the first-generation antipsychotics marketed in Denmark within the study period and those purchasing one of the second-generation antipsychotics marketed. Similarly, a random sample of approximately 30% of the total Danish population was identified, corresponding to 1.52 million individuals who were born before 1 January 1996.

To identify incident diabetes only, all individuals who had a hospital discharge diagnosis of diabetes (as an in-patient or out-patient) or who purchased antidiabetic medication prior to 1 January 1996 (ICD–8 code: 250–250.09, ICD–10: E10–14.9; back to 1977 in the Danish National Hospital Register and back to 1970 in the Danish Psychiatric Central Register) or prior to the date of the first purchase of any antipsychotic were excluded from the study. It should be noted that the registers do not include data on indications for prescribing of an antipsychotic.

Antidiabetic medication included all formulations of injectable insulin and all oral formulations of tolbutamide, glibenclamide, gliclazide, glimepiride, glipizide, repaglinide, metformin, pioglitazone, rosiglitazone and acarbose. This medication is prescribed for diabetes only and can only be purchased at pharmacies; this is reported to Medicinal Product Statistics covering Denmark nationwide.

Statistical analysis

Poisson regression analyses were conducted with incident diabetes as the outcome. Incident diabetes was defined as the first purchase of an antidiabetic medication or in-patient or out-patient hospital contact with a main or auxiliary discharge diagnosis of diabetes (ICD–10 code: E10–4.9) during the years 1996–2005 inclusive. The rate of incident diabetes was compared for individuals who purchased antipsychotics with the rate for the unexposed general population. Further, the rate of incident diabetes was compared for individuals who purchased first- *v.* second-generation antipsychotics. Individuals were censored (i.e. excluded from further analysis from the event date) in the event of: death, emigration from Denmark, prescription of an antipsychotic medication from the comparison group (i.e. a first- or second-generation antipsychotic) or end of the study period (31 December 2005). Additionally, the rate of incident diabetes as a function of the number of different antipsychotic drugs given to an individual (0, 1–2, 3–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40+ prescriptions) was also modelled with a Poisson regression analysis. Finally, the rate of incident diabetes was analysed for different antipsychotic drugs and compared with the rate for unexposed individuals. The latter analyses were undertaken in two different ways. First, analysis of the rate of incident diabetes during the period with prescription of the first antipsychotic drug, i.e. analysis of antipsychotic-naive individuals, censoring at the time point when the individual switched to another antipsychotic or when another antipsychotic was added. Second, analysis where observation of an individual continued beyond the time of switching to or adding another antipsychotic with mutual adjustment for the different types of antipsychotics. The time-fixed covariate gender (male/female), and the time-dependent covariates age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–100 years), calendar year (1996, 1997, etc. to 2005) and prescription of lithium or anticonvulsants (yes/no) were included in the models. In additional analyses, prescription of any other medication than antipsychotics, lithium or anticonvulsants (yes/no) was also included in the models as a time-dependent covariate.

Results

In the Medicinal Product Statistics Register we identified a total of 345 937 individuals who had purchased at least one prescription of an antipsychotic drug within the study period from 1 January 1996 to 31 December 2005 and who had not had a hospital diagnosis of diabetes or purchased antidiabetic medication prior to 1 January 1996 or prior to the date of the first purchase of any antipsychotic. Among these, 257 095 purchased a first-generation antipsychotic drug only, 35 477 purchased a second-generation antipsychotic drug only and 53 365 purchased both a first- and a second-generation antipsychotic drug during the study period. To put these numbers into perspective of the total Danish population of approximately 5.4 million individuals, about 6.4% were treated with antipsychotic medication within the study period. From the total Danish population on 1 January 2006, a control sample of 1 426 488 individuals who were unexposed to antipsychotics was identified in the Medicinal Product Statistics Register. Thus, the total study population consisted of 1 772 425 individuals.

Among the individuals in the study population, a total of 50 379 subsequently received a diagnosis of diabetes at a hospital contact and/or were treated with an antidiabetic drug during the study period. Table 1 presents characteristics of individuals exposed to first- and/or second-generation antipsychotics, and of people unexposed to antipsychotics, according to gender, age, number of people with a diagnosis of diabetes and censoring, as well as crude rates of incident diabetes.

In Poisson regression analysis, men had an increased rate of incident diabetes compared with women (rate ratio, RR = 1.42, 95% CI 1.40–1.45) and the rate increased significantly with

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press

Table 1 Characteristics of individuals exposed to first-generation antipsychotics only, second-generation antipsychotics only, both first- and second-generation antipsychotics and those unexposed during the study period, with respect to gender, age, number of people with diabetes, diabetes rate and censoring[a]

Exposure status	Exposed to first-generation antipsychotics only	Exposed to second-generation antipsychotics only	Exposed to both first- and second-generation antipsychotics	Unexposed
At end of follow-up, *n*	257 095	35 477	53 365	1 426 488
Total, person-years	1 532 426	119 706	208 750	13 699 876
Gender, person-years				
Male (%)	581 877 (38.0)	56 494 (47.2)	96 524 (46.2)	6 799 970 (49.6)
Female (%)	950 549 (62.0)	63 212 (52.8)	112 226 (53.8)	6 899 905 (50.4)
Age at inclusion				
Age, years: median (quartiles)	58.1 (42.7–74.4)	59.7 (34.5–79.5)	46.5 (32.3–69.7)	36.7 (20.8–53.5)
Number of participants with diabetes and diabetes rates				
Total, *n* (%)	10 346 (3.8)	669 (2.6)	1 646 (2.6)	37 718 (2.8)
Rate of diabetes per 10 000 person-years, total	67.5	55.9	78.9	27.5
Men with diabetes, *n*	4367	325	728	21 236
Rate of diabetes per 10 000 person-years, men	75.1	57.5	75.4	31.2
Women with diabetes, *n*	5979	344	918	16 482
Rate of diabetes per 10 000 person-years, women	62.9	54.4	81.8	23.9
Censoring, *n* (%)				
Death	87 522 (34.0)	10 278 (29.0)	12 928 (24.2)	120 441 (8.4)
End of study	159 227 (61.9)	24 530 (69.1)	38 791 (72.7)	1 268 329 (88.9)

a. First-generation antipsychotics: chlorpromazine, chloprothixene, fluphenazine, flupentixol, haloperidol, levomepromazine, melperon, periciazine, perphenazine, pimozide, pipamperone, prochlorperazine, zuclopenthixol or tetrabenazine. Second-generation antipsychotics: amisulpride, aripiprazole, clozapine, olanzapine, risperidone, sertindole or ziprazidone.

increasing age groups (d.f. = 9, $\chi^2 = 36.54$, $P < 0.01$). There was no significant effect of treatment with lithium (RR = 1.04, 95% CI 0.97–1.12) but a minor effect of anticonvulsants (RR = 1.10, 95% CI 1.06–1.15). Treatment with all other medication than antipsychotics, lithium and anticonvulsants was associated with a 1.26 (95% CI 1.19–1.34) times increased rate of diabetes compared with the rate among individuals unexposed to medication.

Individuals exposed to second-generation antipsychotics as a class had a 1.32 (95% CI 1.22–1.42) times increased rate of subsequent incident diabetes compared with unexposed individuals when adjusted for gender, age, calendar period, use of lithium, antipsychotics or anticonvulsants. The corresponding rate ratio for individuals exposed to first-generation antipsychotics was 1.53 (95% CI 1.49–1.56). Individuals treated with second-generation antipsychotics had a 0.87 (95% CI 0.82–0.91) times decreased rate of incident diabetes when compared with participants treated with first-generation antipsychotics. Table 2 shows the rate ratios of people exposed to first- or second-generation antipsychotics, respectively, as a function of the number of prescriptions, and adjusted for gender, age, calendar period and use of lithium or anticonvulsants. For both classes of antipsychotics there was a significant association between the number of prescriptions and the rate of incident diabetes (d.f. = 10, $\chi^2 = 69.49$, $P < 0.01$), with increasing rate ratios of incident diabetes with the number of purchased antipsychotic prescriptions; however, this was most pronounced for first-generation antipsychotics. The rate ratios of subsequent incident diabetes for the most commonly used first-generation antipsychotics and for all the currently used second-generation antipsychotics are presented in Table 3. The rate of incident diabetes was estimated in two different ways, for the first antipsychotic drug (drug-naive individuals) and for the antipsychotic of interest regardless of whether people had received other antipsychotics previously (combined). The results were rather similar for the two types of analyses falling in three different risk categories. First, antipsychotics with low to moderate but significantly increased rates of incident diabetes compared with the general population (rate ratios between 1.17 and 1.57: zuclopenthixol, perphenazine, haloperidol, clozapine (only significant in combined analysis), olanzapine and risperidone). Second, antipsychotics with significantly higher increased rates of incident diabetes (rate ratios increased two or more times: ziprasidone and sertindole). Finally, antipsychotics with no increased rate of incident diabetes (amisulpride, quetiapine and aripiprazole).

All analyses presented in Tables 2 and 3 were also conducted without any adjustment and further with adjustment for the potential diabetogenic effect of being treated with all other medications than antipsychotics, lithium or anticonvulsants. Unadjusted as well as adjusted rate ratios for all other medications only differed marginally (results not presented) from the rate ratios adjusted for gender, age, calendar period and use of lithium or anticonvulsants.

Table 4 shows the rate ratios of incident diabetes in relation to the number of simultaneously given antipsychotic drugs. There

Table 2 Rate of diabetes related to number of prescriptions for antipsychotics (reference: no prescriptions)[a]

Prescriptions, *n*	Rate ratio (95% CI)	
	First-generation antipsychotics	Second-generation antipsychotics
0	1	1
1–2	1.33 (1.29–1.38)	0.98 (0.84–1.14)
3–4	1.46 (1.38–1.55)	1.61 (1.30–2.00)
5–9	1.53 (1.45–1.62)	1.47 (1.23–1.76)
10–14	1.54 (1.44–1.66)	1.09 (0.83–1.43)
15–19	1.59 (1.46–1.73)	1.49 (1.12–1.99)
20–24	1.79 (1.63–1.97)	1.30 (0.90–1.87)
25–29	1.85 (1.67–2.06)	1.90 (1.32–2.73)
30–34	2.01 (1.80–2.25)	1.74 (1.11–2.73)
35–39	1.93 (1.70–2.19)	0.63 (0.26–1.50)
⩾40	2.04 (1.92–2.16)	1.81 (1.36–2.42)

a. Adjusted for gender, age, calendar period and use of lithium or anticonvulsants.

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press

Table 3 Rate of diabetes related to different antipsychotics (reference: no prescriptions)[a]

Antipsychotic	*n*	Age at first prescription Years: median (25–75%)	Female gender, %	Antipsychotic drug-naive RR (95% CI)	Antipsychotic combined RR (95% CI)
Zuclopenthixol	57 065	65.0 (41.9–82.3)	59.1	**1.40 (1.30–1.50)**	**1.40 (1.33–1.47)**
Perphenazine	21 473	50.0 (36.4–68.2)	56.5	**1.60 (1.45–1.77)**	**1.57 (1.48–1.67)**
Haloperidol	27 872	72.2 (54.6–82.3)	56.6	**1.32 (1.17–1.49)**	**1.17 (1.08–1.26)**
Clozapine	6014	41.1 (30.1–58.7)	43.5	1.29 (0.98–1.70)	**1.45 (1.28–1.64)**
Olanzapine	42 408	46.7 (32.3–69.5)	52.3	**1.35 (1.18–1.54)**	**1.29 (1.20–1.37)**
Risperidone	44 110	54.8 (33.0–78.5)	57.1	**1.24 (1.09–1.40)**	**1.23 (1.15–1.32)**
Ziprasidone	5950	32.7 (24.1–43.3)	60.4	**3.09 (1.54–6.17)**	**1.94 (1.62–2.31)**
Sertindole	371	34.1 (27.2–42.6)	53.1	**9.53 (1.34–67.63)**	**1.94 (1.32–2.84)**
Amisulpride	882	33.4 (24.9–43.5)	47.7	1.72 (0.24–12.23)	1.42 (0.88–2.30)
Quetiapine	12 402	42.3 (28.3–68.0)	57.9	0.71 (0.43–1.18)	1.15 (0.99–1.34)
Aripiprazole	4523	31.3 (23.3–41.5)	51.3	1.99 (0.50–7.97)	1.16 (0.83–1.62)

RR, rate ratio.
a. Adjusted for gender, age, calendar period and use of lithium or anticonvulsants. Results in bold are statistically significant.

was a clear tendency towards higher rates of diabetes with increasing polypharmacy.

Discussion

The present population-based and nationwide register linkage study had up to 10 years of follow-up and is the study with the largest number of individuals exposed and unexposed to antipsychotics and with the longest follow-up period that has ever been conducted. The study is naturalistic in nature and design, i.e. our data on the association between antipsychotics and subsequent risk of developing diabetes reflects the association in clinical practice in which doctors choose to prescribe antipsychotics, continue or switch to another drug, and monitor people for diabetes and metabolic syndrome based on their individual current knowledge. We found that in clinical practice, treatment with first- as well as second-generation antipsychotics was associated with increased risk of subsequent incident diabetes compared with unexposed individuals. There was a dose–response effect of antipsychotic treatment in two different ways: the incidence of diabetes increased with the number of prescriptions and the number of combined antipsychotic drugs (i.e. polypharmacy). Treatment with second-generation antipsychotics as a class was not associated with an increased risk of diabetes compared with first-generation antipsychotics as a class; in fact, the risk was slightly decreased 0.87 (95% CI 0.82–0.91), but behind this general class effect there were large differences in the individual drugs association with subsequent diabetes (Table 3).

Overall, our results confirm prior findings of an increased incidence of diabetes among people treated with second-generation antipsychotics compared with the general population.[6,7] Further, our data show that in clinical practice, the risk of incident diabetes is also increased for individuals treated with first-generation antipsychotics such as zuclopenthixol (adjusted RR = 1.40, 95% CI 1.30–1.50, drug-naive analysis), perphenazine (RR = 1.60, 95% CI 1.45–1.77) and haloperidol (RR = 1.32, 95% CI 1.17–1.49) compared with unexposed individuals, in accordance with findings in prior studies.[19,20] The rates of incident diabetes increased during periods with a higher number of prescriptions for second- as well as first-generation antipsychotics (Table 2) and during polypharmacy (Table 4) suggesting that development of diabetes was related to the antipsychotic drugs *per se* rather than to the psychiatric illnesses, although an effect of illness cannot be excluded. Dose–response effects like these have not been investigated previously but our results are in accordance with the finding of an increasing rate of incident diabetes with increasing dose of the antipsychotic and with increasing exposure time.[19,20]

Table 4 The rate ratios of incident diabetes in relation to the number of different antipsychotic drugs as modelled in the Poisson regression (reference: no prescriptions of antipsychotics)

Antipsychotic drugs compared with reference, *n*	RR ratio (95% CI)
1 antipsychotic *v.* 0	1.48 (1.44–1.51)
2 antipsychotics *v.* 0	1.68 (1.61–1.76)
3 antipsychotics *v.* 0	1.96 (1.82–2.10)
4 antipsychotics *v.* 0	2.38 (2.13–2.65)
5 or more antipsychotics *v.* 0	3.41 (3.03–3.83)

RR, rate ratio.

Individual antipsychotics and incident diabetes

At first glance, our findings in relation to some of the individual antipsychotics may look somewhat controversial. We found that in clinical practice in Denmark, clozapine, olanzapine and risperidone were associated with the same rate of subsequent incident diabetes as were first-generation antipsychotics (zuclopenthixol, perphenazine, haloperidol), i.e. a low to moderate increased rate with a rate ratio around 1.2 to 1.6 compared with unexposed individuals (Table 3). Amisulpride, quetiapine and aripiprazole were not associated with an increased risk of subsequent diabetes, whereas other newer marketed drugs such as ziprasidone (RR = 3.09, 95% CI 1.54–6.17) and sertindole (RR = 9.53, 95% CI 1.34–67.63) were associated with a substantially increased risk of subsequent incident diabetes (the wide confidence intervals reflect high uncertainty in these analyses because of the relatively limited number of people included (5950 taking ziprasidone and 371 taking sertindole)). Our findings are somewhat in contrast to the US Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes from 2004 concluding that clozapine and olanzapine are associated with the greatest risk for type 2 diabetes (and dyslipidemia and weight gain), whereas risperidone and quetiapine have discrepant results regarding the risk of diabetes, and for

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press

the two newest antipsychotic drugs on the market – ziprasidone and aripiprazole – the limited long-term data available show no association with diabetes.[21] As our study used observational, non-randomised data from clinical practice the associations between individual antipsychotics and subsequent incident diabetes were a result of the knowledge and clinical practice of the individual prescribing doctor. In fact, a nationwide US survey revealed that 90% of psychiatrists considered metabolic issues when selecting atypical antipsychotic therapy and 85% were prompted to change to another antipsychotic with the emergence of metabolic dysfunction.[22] Thus, in our study, individuals at higher risk of diabetes because of a personal history of obesity or inactivity, a family history of diabetes or other risk factors may have been prescribed agents perceived to confer a lower risk of diabetes.[22,23] Doctors may not have prescribed olanzapine and clozapine to such individuals at high risk of developing diabetes or may have switched to other drugs if signs of metabolic syndrome emerged. In this way, doctors in Demark prescribed and monitored treatment with olanzapine and clozapine that resulted in low to moderate increased rates of diabetes only (Table 3). People with risk factors for diabetes may alternatively have been prescribed antipsychotics such as ziprasidone and sertindole believed to have a favourable lipo-metabolic profile, with decreased risk of attenuating diabetes resulting in higher rates of incident diabetes related to these drugs (Table 3). Such selection of drugs based on clinical evaluation of individual patient risk factors for diabetes was, however, not a systematic phenomenon, as aripiprazole was not associated with diabetes (Table 3) even though it was marketed in the same way and during the same recent period as ziprasidone and sertindole.

Strengths and limitations

The Danish population is ethnically (the vast majority are White) and socially homogeneous and with a very low migration rate. Psychiatric and medical care is well developed so people can easily come into contact with general practitioners or specialists in psychiatry or endocrinology. As psychiatric and other medical treatment is available free of charge in Denmark, and as 75% of the cost for prescribed medication (e.g. antipsychotics and anti-diabetics) is refunded by the state, the study is not likely to be biased by socioeconomic differences.

Data from the Medicinal Product Statistics is close to 100% accurate and the positive predictive value of having purchased one prescription of an antidiabetic as a criterion for diagnosed diabetes is approximately 98%.[24,25] In our study, the outcome measure of diabetes was defined as either a first purchase of an antidiabetic or a first-ever hospital discharge diagnosis of diabetes to increase the validity of the measure further. We are reasonably confident that only incident diabetes was included in the outcome measure as we excluded all individuals who purchased antidiabetics in a period back to 1995 and all individuals who had a hospital diagnosis of diabetes in a period back to 1970 and further, when such events occurred prior to the date of purchase of the first antipsychotic (from 1996 to 2005). Exclusion periods were considerably shorter in prior studies due to shorter total study periods (e.g. 6 months in one 2-year follow-up study[26] and maximum 2 years and 4 months in another study)[23] increasing the risk that the outcome measure, incident diabetes, was confounded by prevalent diabetes.

The present pharmacoepidemiological study is by far the largest, with the longest follow-up time. The study included 345 937 individuals exposed to antipsychotics and 1 426 488 unexposed individuals; a total of 50 379 individuals subsequently developed incident diabetes during the 10-year follow-up, corresponding to 2.8%. In comparison, the largest other pharmacoepidemiological study that was published prior to the present study included 55 287 individuals exposed to antipsychotics (and no unexposed individuals), among whom 357 individuals developed incident diabetes during a follow-up period of up to 2 years and 4 months, corresponding to 0.7 %.[23] It is well-known that the largest group of people will develop diabetes over longer periods of time, during which weight gain and obesity further worsen insulin sensitivity, whereas a subset of people who develop diabetes, those with diabetic ketoacidisis or hypoosmolar diabetes or coma, may develop diabetes early as a result of a direct triggering antipsychotic drug effect.[27] Thus, our study identified far more individuals with incident diabetes, presumably owing to the accuracy of our data and the long follow-up time.

The incidence of diabetes among the unexposed individuals in our study was about 27.5 per 10 000 person-years (Table 1), somewhat lower than the estimated incidence in the USA of 49 to 69 per 10 000 person-years (1998 and 2003 respectively)[28] but similar to incidence in Sweden (26.5 per 10 000 person-years, 1995),[29] England (22.1 per 10 000 person-years, 1998)[30] and Italy (22 per 10 000 person-years, 1995),[31] which strengthens the validity and generalisability of our findings.

We chose to compare the rate of incident diabetes for the individual antipsychotics with the rate among the general population and not with haloperidol as done in most studies. Haloperidol may be prescribed for more alternative indications than most other antipsychotics making such a comparison less relevant. As can be seen from Table 3, people treated with haloperidol were substantially older (72.2 years, quartiles: 54.6–82.3) than individuals treated with other drugs, presumably as haloperidol was more often prescribed for elderly people with organic psychosis than those with non-organic psychosis such as schizophrenia and bipolar disorder.

Danish registers do not include data on diagnoses from primary care and the majority (approximately 60%) of individuals in the present study got their first antipsychotic prescribed by a doctor in primary care, i.e. by general practitioners or specialists within private practice. Thus, although the majority of antipsychotics may have been prescribed for schizophrenia or bipolar disorder, it is likely that some antipsychotics were prescribed off-label for other conditions.[1] For example, quetiapine is often used in low doses for many conditions other than schizophrenia and bipolar disorder, and the doses are often small. Further, we do not have data on the daily intake of the antipsychotics so we cannot investigate whether there is an effect of the consumed daily dose of the drug with regard to incident diabetes.

We did not take gaps in prescription of antipsychotics, i.e. temporary non-adherence, into account in the analyses, as this would imply that we had to include arbitrary defined specifications of such time-gap periods. Thus, individuals were considered at risk of developing diabetes related to a group of antipsychotics (first- or second-generation) or an individual antipsychotic regardless of whether they in fact took the drug or not. In this way, the differences in the rates of incident diabetes between groups of antipsychotics or between individual antipsychotics may have been underestimated.

Our study included all people treated with antidiabetic medication and all individuals with a diagnosis of diabetes in hospital in-patient or out-patient care. We do not have information about individuals with milder forms of diabetes that are managed with diet or lifestyle interventions (i.e. without antidiabetic medication) in primary care settings. Thus, our data do not relate to the association between antipsychotics and the mildest forms of diabetes.

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press

Implications

This population-based and nationwide register linkage study had up to 10 years of follow-up and showed that in clinical practice, both treatment with first- as well as second-generation antipsychotics are associated with increased risk of subsequent incident diabetes. The risk increases with the duration of treatment and with polypharmacy. Treatment with second-generation antipsychotics as a class was not associated with an increased risk of diabetes compared with first-generation antipsychotics as a class, but there were large differences between individual drugs. Our findings show that drugs, which are usually considered a high risk for developing diabetes, such as olanzapine and clozapine, are prescribed and used in clinical practice in a way so that the risk of developing incident diabetes is low. On the other hand, some second-generation antipsychotics such as ziprasidone and sertindole, for which no data has shown increased rates of diabetes, seem to be prescribed to people at increased risk of developing diabetes, whereas amisulpride, quetiapine and aripiprazole were used in individuals without increased risk for diabetes and without increasing the risk of developing diabetes in such individuals. Regardless of risk factors for diabetes and type of prescribed antipsychotic drug, individuals taking antipsychotics should be monitored carefully for diabetes and somatic syndrome as suggested by the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes[21] and further, polypharmacy of antipsychotics should be avoided.

Lars Vedel Kessing, MD, DMSc, **Anders Frøkjær Thomsen**, MD, PhD, Department of Psychiatry, University Hospital of Copenhagen, Rigshospitalet; **Ulla Brasch Mogensen**, MSc, **Per Kragh Andersen**, MSc, PhD, DMSc, Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark

Correspondence: Lars Vedel Kessing, Department of Psychiatry, University Hospital of Copenhagen, Rigshospitalet, Blegdamsvej 9, DK 2100 Copenhagen Ø, Denmark. Email: lars.vedel.kessing@regionh.dk

First received 22 Dec 2009, final revision 25 May 2010, accepted 24 Jun 2010

References

1 Domino ME, Swartz MS. Who are the new users of antipsychotic medications? *Psychiatr Serv* 2008; **59**: 507–14.

2 Dabelea D. The accelerating epidemic of childhood diabetes. *Lancet* 2009; **373**: 1999–2000.

3 Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 1996; **37**: 68–73.

4 Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull* 2000; **26**: 903–12.

5 Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I affective and schizoaffective disorders independent of psychotropic drug use. *J Affect Disord* 2002; **70**: 19–26.

6 Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol* 2003; **56**: 164–70.

7 Ramaswamy K, Masand PS, Nasrallah HA. Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. *Ann Clin Psychiatry* 2006; **18**: 183–94.

8 Smith M, Hopkins D, Peveler RC, Holt RIG, Woodward M, Ismail K. First- *v.* second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2008; **192**: 406–11.

9 Saddichha S, Manjunatha N, Ameen S, Akhtar S. Diabetes and schizophrenia – effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia. *Acta Psychiatr Scand* 2008; **117**: 342–7.

10 Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353**: 1209–23.

11 Malig C. *The Civil Registration System in Denmark. Technical Paper No 66*. International Institute for Vital Registration and Statistics, 1996.

12 Danish National Board of Health, Lægemiddelstyrelsen. *Medicinal Product Statistics*. Lægemiddelstyrelsen, 2002 (http://www.laegemiddelstyrelsen.dk).

13 Juel K, Helweg-Larsen K. The Danish registers of causes of death. *Dan Med Bull* 1999; **46**: 354–7.

14 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–8.

15 Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull* 1997; **44**: 82–4.

16 WHO Collaborating Centre for Drug Statistics Methodology. *ATC Index with DDDs*. WHO Collaborating Centre for Drug Statistics Methodology, 2003.

17 World Health Organization. *Glossary of Mental Disorders and Guide to their Classification for Use in Conjunction with the International Classification of Diseases, 8th Revision*. WHO, 1974.

18 World Health Organization. *International Statistical Classification of Diseases and Health Related Problems, 10th revision* [Danish version]. Munksgaard, 1993.

19 Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry* 2002; **63**: 920–30.

20 Gianfrancesco F, Grogg A, Mahmoud R, Wang RH, Meletiche D. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. *Clin Ther* 2003; **25**: 1150–71.

21 American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry* 2004; **65**: 267–72.

22 Newcomer JW, Nasrallah HA, Loebel AD. The Atypical Antipsychotic Therapy and Metabolic Issues National Survey: practice patterns and knowledge of psychiatrists. *J Clin Psychopharmacol* 2004; **24**: S1–6.

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

24 Kristensen JK. *Identification of the Type 2 Diabetes Population in a Danish County and Evaluation of the Performed Care in a Five-Year Period*. Aarhus Universitet, 2000.

25 Drivsholm TB, Frederiksen K, de Fine ON, Odegaard B, Kristensen JK. The prevalence of diabetes in Denmark. Development of a method for a registry-based assessment [in Danish]. *Ugeskr Laeger* 2003; **165**: 2887–91.

26 Leslie DL, Rosenheck RA. Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. *Am J Psychiatry* 2004; **161**: 1709–11.

27 Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. *Ann Clin Psychiatry* 2002; **14**: 59–64.

28 Centers for Disease Control and Prevention. *National Diabetes Surveillance System*. Centers for Disease Control and Prevention, 2009 (http://apps.nccd.cdc.gov/ddtstrs/).

29 Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. *Diabetes Care* 1999; **22**: 773–8.

30 Ryan R, Newnham A, Khunti K, Majeed A. New cases of diabetes mellitus in England and Wales, 1994-1998: database study. *Public Health* 2005; **119**: 892–9.

31 Garancini MP, Gobbi C, Errera A, Sergi A, Gallus G. Age-specific incidence and duration of known diabetes. The Cremona Study. *Diabetes Care* 1996; **19**: 1279–82.

https://doi.org/10.1192/bjp.bp.109.076935 Published online by Cambridge University Press