Incidence of diabetes in a general practice population: a database cohort study on the relationship with haloperidol, olanzapine, risperidone or quetiapine exposure

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The present study aimed to estimate the incidence of diabetes in general practice patients who were treated with haloperidol, olanzapine, risperidone or quetiapine mono-therapy and in subjects who were not exposed to antipsychotics. The design was a retrospective, up to 2 years, cohort study, with age-, sex- and length of observation-matching between subjects who were exposed and not exposed to antipsychotic drugs. Data were taken from the Health Search database, which contains information from 550 Italian general practitioners. Participants comprised 2071 subjects taking haloperidol, 266 taking olanzapine, 567 taking risperidone and 109 taking quetiapine, in addition to 6026 age- and sex-matched subjects who were not using antipsychotic drugs during the period of observation. Inclusion was limited to initially non-diabetic and antipsychotic drug-free individuals. The main outcome measure was the incidence of drug-treated diabetes. After age and sex correction by Cox regression analysis, the four groups treated with antipsychotics significantly differed from untreated subjects in hazard ratios for diabetes. The ratios for the haloperidol, olanzapine, risperidone and quetiapine groups were 12.4 (95% confidence interval 6.3–24.5), 20.4 (6.9–60.3), 18.7 (8.2–42.8) and 33.7 (9.2–123.6), respectively, with no significant differences when compared to each other. *Int Clin Psychopharmacol* 20:33–37 © 2005 Lippincott Williams & Wilkins.

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Introduction

Early evidence indicating that antipsychotic drugs may represent a risk factor for diabetes recognizes old routes, when the typical but not the atypical antipsychotics were available (Thonnard-Neumann, 1956; Jori and Bianchetti, 1966). Nevertheless, this problem has become the subject of serious concern only at the turn of the millennium, following the publication of case reports linking atypical antipsychotics to new onset diabetes (Lindenmayer and Patel, 1999; Ober *et al.*, 1999; Rigalleau *et al.*, 2000; Bonanno *et al.*, 2001).

Subsequently, some large-scale studies, mostly based on prescription data and on already existing databases, have confirmed that schizophrenic patients taking atypical antipsychotics show unusually high rates of diabetes (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Kornegay *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Sernyak *et al.*, 2002; Buse *et al.*, 2003).

However, these studies do not lead to any firm conclusions about possible drug- and/or class-specific contributions to the diabetogenic potential associated with the intake of antipsychotics. Indeed, head-to-head comparisons between atypical antipsychotics have produced conflicting results and the typical antipsychotics have been less systematically studied (Caro *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003).

In addition, the published reports available show a lack of a direct estimate of diabetes incidence in the general population (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Kornegay *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002), selection of patients without a previous antipsychotic drug-free period (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002), recruitment of patients exposed to antipsychotic polipharmacotherapy (Caro *et al.*, 2002; Koro *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003) and the use of prevalence rather than incidence rates of diabetes (Sernyak *et al.*, 2002).

In an attempt to overcome some of these limitations, we evaluated retrospectively, by means of a general practitioners database, the incidence of diabetes among patients who had started haloperidol, olanzapine, risperidone or quetiapine monotherapy. Age- and sex-matched individuals who were non-diabetic at study entry, and who were not prescribed antipsychotic drugs during the observational period, were also selected to control for the incidence of diabetes in the general population.

Methods

Study population

The study included subjects from the Health Search Database, a computerized system set-up in the mid-1990s to collect data taken from the daily clinical activity of general practitioners (GP). Currently, the database contains information from 550 GPs from all over Italy with a total of approximately 800 000 patients (i.e. 1.5% of the Italian population). After extensive training on software use, GPs store data in real time and send them to a central server based in Florence, where a GPs association (the Società Italiana dei Medici di Medicina Generale) processes data for research purposes. To ensure quality, every 3 months, all the information collected in the database undergoes extensive monitoring with a scheduled feedback from administrators to users. A unique identification number links all data to an individual patient who remains anonymous and no identifying details are available. Each patient provided a written informed consent to allow processing of data taken by the GPs.

The Health Search Database has demonstrated a good concurrent validity in estimating the prevalence of diabetes mellitus in a subsample of 432 747 subjects compared to an independent population estimate (Cricelli et al., 2003).

Cohorts

The cohort at risk included all non-diabetic patients who started haloperidol, olanzapine, risperidone or quetiapine in monotherapy and who were followed-up for a maximum of 2 consecutive years, provided that they had experienced an antipsychotic drug-free period from their last visit to study entry. The period under scrutiny started on 1 January 1996 and ended on 31 March 2002. Emergence of diabetes, co-therapies with other antipsychotic drugs, death or loss of the patient to follow-up for any reason were identified as the causes of truncated observations. New onset diabetes was defined as the prescription of any anti-diabetic drug after the entry visit.

In turn, the unexposed cohort was randomly selected from the database according to a list that included only those individuals who were non-diabetic and antipsychotic-free at study entry and who were not prescribed antipsychotics during the follow-up. Two rigorously age- and sex-matched subjects were extracted for each patient treated with an antipsychotic drug.

Each subject was evaluated for new onset diabetes during the same period of observation as the linked, exposed patient.

Sex, age, the length of the observational period, the interval between entry visit and the onset of diabetes, and the number of prescriptions of antipsychotics for exposed individuals comprised the study variables.

Statistical analysis

First order associations were analysed by the chi-square test or univariate analysis of variance, when appropriate. Cox regression model was applied to evaluate the hazard ratios for diabetes onset and the independent effect of age, sex and treatment on risk estimates. Linear contrasts were used to test for differences between exposed and unexposed subjects and among treatments. Power analysis was used to estimate the sample sizes needed to achieve statistical significance ($\alpha = 0.05$, $1 - \beta = 0.80$) in the comparison of different antipsychotics, taking the detected diabetes rates as reference.

All statistics were performed with the SPSS package (version 10.1) (SPSS Inc., Chicago, Illinois, USA).

Results

The haloperidol, olanzapine, risperidone and quetiapine groups included 2071, 266, 567 and 109 patients, respectively. According to the 1–2 sampling rate, the unexposed group comprised 6026 individuals.

The four treatment groups differed in age, sex and treatment variables but not in sex distribution (Table 1). The raw incidence of diabetes (per 1000 person-years) in patients taking haloperidol, olanzapine, risperidone and quetiapine was 19.6, 22.8, 24.9 and 52.7, respectively. The incidence in unexposed subjects was 1.5 (Table 2). After age and sex correction with Cox analysis, each of the four groups of patients treated with an antipsychotic drug had a hazard ratio for new-onset diabetes that was higher compared to that of the unexposed group ($P < 0.001$) (Table 3). The ratios estimated for haloperidol, olanzapine, risperidone and quetiapine were not significantly different when compared to each other.

Among all individuals who were treated with antipsychotics, patients with and without diabetes had a similar number of prescriptions, 4.4 versus 3.4 (Student's t-test 1.4, $P = $ NS). Furthermore, the time needed for the onset of diabetes from the beginning of the antipsychotic therapy overlapped (248.1, 236.6, 299.5 and 275.3 days) in the groups treated with haloperidol, olanzapine,

Table 1 Sociodemographic and clinical features of patients taking olanzapine, risperidone, quetiapine or haloperidol

Variable	Olanzapine (n=266)	Risperidone (n=567)	Quetiapine (n=109)	Haloperidol (n=2071)	P-value
Age (mean ± SD)	52.6 ± 20.4	58.3 ± 23.3	65.0 ± 21.3	66.5 ± 21.0	F=47.5, P<0.001 (3 d.f.)[a]
Sex (%)					
Males	49.2	43.9	37.6	40.7	Chi-square 8.9, P=0.03 (3 d.f.)
Females	50.8	56.1	62.4	59.3	
Total prescriptions (mean ± SD)[d]	3.5 ± 3.7	2.5 ± 3.1	3.9 ± 5.0	3.7 ± 6.0	F=7.2, P<0.001 (3 d.f.)[b]
Follow-up days (mean ± SD)[e]	301.7 ± 221.8	335.9 ± 238.6	190.7 ± 135.2	430.7 ± 262.8	F=60.5, P<0.001 (3 d.f.)[c]

[a]In the post-hoc analysis, significant differences (P<0.05) in the pairs: haloperidol/olanzapine, haloperidol/risperidone, olanzapine/risperidone, olanzapine/quetiapine and risperidone/quetiapine.
[b]In the post-hoc analysis, significant differences (P<0.05) in the pairs: olanzapine/risperidone, risperidone/quetiapine and haloperidol/risperidone.
[c]In the post-hoc analysis, significant differences (P<0.05) in the pairs: haloperidol/olanzapine, haloperidol/quetiapine, haloperidol/risperidone, olanzapine/quetiapine and risperidone/quetiapine.
[d]Prescriptions were included only if given directly by general practitioners.
[e]If longer, truncated at 2 years.

Table 2 Raw incidence of diabetes in subjects taking haloperidol, olanzapine, risperidone or quetiapine and unexposed subjects

Treatment	Year of follow-up	Number entering the interval	Censored subjects	Population at risk	Incident diabetes	Cumulated days of observation[a]	Incidence/ 1000 person-years
Haloperidol	First	2071	843	1649.5	33	892 001	19.6
	Second	1195	532	929	15		
Olanzapine	First	266	166	183	4	80 240	22.8
	Second	96	74	59	1		
Risperidone	First	567	338	398	9	190 430	24.9
	Second	220	131	154.5	4		
Quetiapine	First	109	97	60.5	3	20 787	52.7
	Second	9	9	4.5	–		
Unexposed subjects	First	6026	2912	4570	8	2 406 446	1.5
	Second	3106	1570	2321	2		

[a]Estimated on the overall observation time (first and second years); follow-ups longer than 2 years were truncated at 2 years.

Table 3 Hazard ratios[a] for diabetes in the four treatment groups

Treatment[b]	Ratio	95% confidence interval	P-value
Olanzapine	20.35	6.86–60.33	<0.001
Risperidone	18.71	8.18–42.81	<0.001
Quetiapine	33.68	9.18–123.55	<0.001
Haloperidol	12.40	6.27–24.52	<0.001

[a]Cox proportional hazard regression analysis after correction for Age (ratio 1.03; 95% confidence interval 1.01–1.04; P<0.001) and Sex (ratio of females 1.04; 95% confidence interval 0.66–1.65; P=0.87).
[b]Unexposed subjects=reference group.

Table 4 Power analysis estimates of sample sizes needed to reach a significant difference between treatment groups in observed diabetes incidence

Drugs compared	No. of subjects
Risperidone versus haloperidol	25 702
Olanzapine versus haloperidol	67 237
Quetiapine versus haloperidol	1063
Risperidone versus olanzapine	175 150
Risperidone versus quetiapine	1609
Olanzapine versus quetiapine	1356

risperidone and quetiapine, respectively (F = 0.23, P = NS).

According to power analysis, the number of patients required to differentiate the risk of diabetes between the four groups treated with an antipsychotic ranged between 1063 and 175 150, where the lowest figure is for comparisons involving quetiapine, and with values increasing progressively for comparisons between risperidone and haloperidol, olanzapine and haloperidol, and risperidone and olanzapine, respectively (Table 4).

Discussion
Two key-points best summarize the results of the multiple comparisons performed. The first is that, after an antipsychotic drug-free interval, the groups treated with haloperidol, olanzapine, risperidone or quetiapine monotherapy shared a higher risk for new-onset diabetes compared to untreated subjects. The second is that the hazard ratios computed for the four treatments were not significantly separated.

Our study design was based on cohort selection (exposed versus unexposed), and not on a simpler case–control design (diabetes versus no diabetes), to ensure estimation of the incidence of the disorder within a given time frame and to compare our results with recent studies (Caro *et al.*, 2002; Gianfrancesco *et al.*, 2002; Lee *et al.*, 2002; Buse *et al.*, 2003) that have selected cohorts in the same way.

The inclusion of a rigorously age- and sex-matched group of untreated subjects and the selection of patients exposed to only one antipsychotic after a drug-free period

were major strong points in our study compared to most published studies.

To our knowledge, this is the first study explicitly evaluating diabetes incidence in patients treated with quetiapine: this original contribution provides added value to the study despite the relatively small size of the quetiapine sample.

The lack of information concerning life-styles, comorbidities and other variables known to facilitate the onset of diabetes represents a weak point of our study because we were unable to analyse the contribution of these risk factors. However, the very high degree of significance in all the comparisons opposing exposed and unexposed subjects, together with similar diabetes rates found in haloperidol, olanzapine, risperidone and quetiapine groups, suggests a high probability of a truly generalized phenomenon, with a reduced risk of type I errors and other spurious second-order associations.

A possible dose-dependent effect of antipsychotic drugs on the risk of new onset diabetes cannot be ruled out because doses were not recorded. However, any possible dose effect would have dampened, rather than inflated, the increased incidence of diabetes in our patients treated with antipsychotics because GPs often underdose antipsychotics (Raschetti et al., 1993).

Because of the lack of information on diagnoses, it was not possible to establish to what extent different psychiatric disorders can affect the risk of diabetes. This might be the case for schizophrenia (Ryan et al., 2003). However, a strong effect of second-order associations mediated by schizophrenia is unlikely in our sample of GP patients: a wide diagnostic heterogeneity is to be expected in the four treatment groups because GPs frequently prescribe antipsychotics to control the symptoms of many clinical conditions outside the spectrum of schizophrenia (Hohmann, 1989).

Numerical, but not significant, differences in the hazard ratios for diabetes onset among groups of patients treated with different antipsychotics must be interpreted with caution because the lack of balance in sample sizes may have caused false negatives. Nevertheless, power analysis, based on our incidence rates, shows that several thousand patients would be needed to achieve statistical significance in head-to-head comparisons between haloperidol, olanzapine and risperidone groups. Even if the differences between the three treatments are real, these should have questionable clinical relevance. The case of quetiapine is partially different. Relatively few patients were treated with this drug and power analysis indicates that significance in the comparisons with the other antipsychotics can be provided by relatively small

samples. Therefore, any conclusion should be postponed. In the meantime, the quetiapine-associated risk for diabetes should be regarded as being equal to that of haloperidol, olanzapine and risperidone.

Our results substantially agree with those obtained in recent studies investigating the incidence of diabetes with novel antipsychotics. Regarding olanzapine and risperidone, rates of 17.0 and 16.0/1000, respectively, were reported by Caro et al. (2002); 25.3 and 33.3/1000, respectively, were reported by Lee et al. (2002); and 42.0 and 21.0/1000 (within the 8–12 months follow-up group), respectively, were reported by Gianfrancesco et al. (2002). The studies of Koro et al. (2002) and Kornegay et al. (2002) were based on a case–control design, so that 1-year prevalence rates could not be estimated.

Only Buse et al. (2003) have reported higher incidence rates for olanzapine and risperidone (58 and 79/1000). However, the same authors also reported a diabetes incidence in unexposed subjects (15.7/1000) that clearly exceeded the rates commonly observed in general population samples: 1.0–1.5/1000 in Njolstad et al. (1998); 0.15/1000 (type I) and 2.7/1000 (type II diabetes) in Berger et al. (1999); 3.7/1000 in Burke et al. (2002); and 2.2/1000 in the Duch study of Ubink-Veltmaat et al. (2003) involving the database of 61 general practitioners. The rate of 1.5/1000 found in our study is very similar to these reports.

A series of suggestions appears justified for clinical practice. The main emerging recommendation is that clinicians and patients who need antipsychotic drugs should be updated on diabetes risk during treatment with these compounds. Clear, non-dramatizing information about possible hyperglycaemia-related adverse events inserted in the product labelling of antipsychotic drugs might represent the most direct and convenient operative way. The lack of clinically relevant drug- or class-specific effects on diabetes risk highlights the need for a generalized warning for both typical and atypical antipsychotics. At least two other considerations point in this direction. One is that the estimate of the risk for new onset diabetes is likely to be more conservative for haloperidol than for olanzapine, risperidone and quetiapine because the typical antipsychotics are generally associated with a relatively poorer treatment adherence (Barnes and McPhillips, 1998). The second is that, among the typicals, haloperidol most likely has one of the most benign diabetogenic profiles because abnormal glucose metabolism has been more often associated with low potency antipsychotics (Gianfrancesco et al., 2002).

Given the lack of robust evidence favouring some antipsychotics over others, clinicians should also focus on early identification of first-line candidates for diabetes

to prevent this adverse event. For early detection, physicians should carry out a careful, periodically revised, assessment of diabetes vulnerability factors and test glucose metabolism in at-risk patients (ADA *et al.*, 2004). For prevention, once it is accepted that antipsychotic drugs are needed for psychotic patients and that psychoeducational intervention reduces diabetes incidence in non-psychiatric populations (Knowler *et al.*, 2002), strong psychoeducational programmes should be tailored to the special needs of patients exposed to antipsychotics to ensure the promotion of appropriate healthy behaviour.

For research purposes, the separation of specific and non-specific antipsychotic drug effects on diabetes risk merits priority. The ideal study should not only include all the most widely prescribed antipsychotics, but also emphasize the strongest diabetes risk factors and putative diagnosis-related effects. However, an exhaustive collection of data on predisposing variables is largely beyond the reach of even the best database, and the need to start with antipsychotics as soon as possible precludes the recruitment of large samples of drug-free psychotic patients. Therefore, prospective studies recording the most relevant risk factors, controlling psychiatric diagnoses and involving enough centres to give adequate statistical power, represent the most desirable strategy.

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