Incidence of diabetes in patients taking haloperidol, olanzapine, risperidone, and quetiapine: an up to two-year, one case-two control study of 9039 general practice patients

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Abstract

1. **Context**. Current knowledge that antipsychotic drugs may act as a risk factor for diabetes cannot be fully ~~transferred~~ translated into clinical practice due to controversy about possible drug and/or class-specific contributions.
2. **Objective**. To compare the incidence of new-onset diabetes in patients exposed to ~~a~~ monotherapy with haloperidol, olanzapine, risperidone or quetiapine and in controls without antipsychotic drugs.
3. **Design.** An up to two year, 1 case-2 control, retrospective cohort study.
4. **Setting**. A database containing information from 550 general practitioners
5. **Patients**. 2,071 haloperidol, 276 olanzapine, 567 risperidone and 109 quetiapine patients plus 6,026 age- and sex-matched controls without prescriptions of antipsychotic drugs during the observational period; inclusion limited to initially non-diabetic and antipsychotic drug-free subjects.
6. **Main Outcome Measure.** Incidence of drug-treated diabetes.
7. **Results:**

   After age and sex correction with Cox regression analysis, the four treatment groups differed, at a 0.001 level of significance, from controls in the hazard ratios for diabetes. The ratios of 12.4 (95% c.i. 6.3 – 24.5), 20.4 (6.9 – 60.3),18.7 (8.2 – 42.8), and 33.7 (9.2 – 123.6) found in the haloperidol, olanzapine, risperidone and quetiapine groups were ~~instead~~ not significantly different when compared to each others. Power analysis showed that, with the exception of quetiapine, very large numbers of subjects would be needed (from 25,702 to 175,150) to get a

significant difference in the comparisons of haloperidol, olanzapine, and risperidone.

8. Conclusions. The lack of drug-or class-specific effects on the abnormally high risk for new onset diabetes in groups exposed to a monotherapy with haloperidol, olanzapine, risperidone, or quetiapine makes recommendable that clinicians are alerted to this possible adverse event whenever they prescribe the studied antipsychotic drugs. ~~Contigently~~Contingently, this precaution could be extended to all the marketed antipsychotics, given the absence of robust evidence favouring some drugs over others. Furthermore, physicians should regularly revise diabetes risk factors in candidates for antipsychotic therapy, monitor glucose metabolism in at-risk cases, and also plan psycho-educational interventions directed to promote healthy behaviours counteracting some diabetes vulnerabilities.

Introduction

Early evidence that the exposition to antipsychotic drugs may be a risk factor for diabetes recognizes old routes, when the typical but not atypical antipsychotics were into the market (1,2). Nevertheless, this problem has become an object of major concern only at the turn of the millennium, when some case-reports linked atypical antipsychotics to new onset diabetes (3,4,5,6).

Since that time, some large-scale studies, mostly based on prescription claims and already existing databases, have consensually replicated that schizophrenia patients taking atypical antipsychotics share unusually high rates of diabetes (7,8,9,10,11,12,13). However, these studies do not allow a firm conclusion about possible drug and/or class-specific contributions to the diabetogenic potential associated with ~~the expositione~~exposure to antipsychotics: in fact, ~~the~~ head-to-head comparisons between atypical antipsychotics have produced conflicting results, and the typical antipsychotics have been less systematically included (7,8,12,13).

Furthermore, a number of relevant methodological weaknesses ~~characterize~~characterise, with differences among the studies, most of the published reports. Among the most misleading factors should be considered the lack of a direct estimate of diabetes incidence in the general population (7,8,10,11,13,), the absence of a group of psychotic patients not exposed to antipsychotics (7,8,12), the selection of patients without a previous antipsychotic drug-free period (7,11), the recruitment of patients treated with antipsychotic poly~~i~~pharmacotherapy (7,8,12,13), the inclusion of patients with multiple prescriptions of atypical antipsychotics int~~o~~ more than one pharmacological group (8,13) and the use of prevalence rather than incidence rates of diabetes (9).

To reduce these controversies and limitations, we decided to evaluate retrospectively, by means of a general practitioner database, the incidence of diabetes among patients who started haloperidol, olanzapine, risperidone, or quetiapine ~~in~~ as monotherapy. Age and sex-matched individuals who were non-diabetic at study entry and without prescriptions of antipsychotic drugs during the observational period were also selected to control for the incidence of diabetes in the general population.

Materials and methods

The study included subjects extracted from the Health Search Database, a computerized system that ~~had been~~was set-up in the mid 90s for the collection of data from the daily clinical activity of general practitioners (GP). Currently, the database contains information from 550 GPs from throughout Italy with a total size of over 800,000 patients, that is about 1.5% of the Italian population. After ~~an~~ extensive training to use the software, the GPs store data in real time and send them to a central server based in Florence, where a corporateion of the GPs, the Società Italiana dei Medici di Medicina Generale, processes data for research purposes. To ensure quality, all ~~the~~ information collected in the database undergoes every three months extensive monitoring with a scheduled feedback given from administrators to users. A unique identification number links all data for an individual patient in anonymous way and no identifying details are available.

All ~~the~~ non-diabetic patients who started haloperidol, olanzapine, risperidone, or quetiapine ~~in~~ monotherapy were selected and followed-up for a maximum of 2 accrual years, provided that they had had an antipsychotic drug-free period spanning from the last visit to study entry. The period under scrutiny started on January 1st, 1996 and closed on

March 31st, 2002. Emergence of diabetes, co-therapies with other antipsychotic drugs, death, or loss for any reason to follow-up were the causes of truncated observations.

For each patient exposed to an antipsychotic drug, two rigorously age- and ~~sex-~~sex-matched controls were automatically selected from the database according to a ~~randomization~~randomisation list that included only subjects who were both non-diabetic and antipsychotic drug-free at study entry and had not prescriptions of antipsychotics during the follow-up. Each control was evaluated for new onset diabetes during the same observational period ~~of~~ as the linked case.

Incident cases of diabetes were defined by the prescription of any anti-diabetic drug after the entry visit.

The sex and age of the subjects, the length of the observational period, the interval between entry visit and diabetes onset, and the number of visits with the prescription of an antipsychotic were the investigated variables

First order associations were tested with Chi Square or univariate analysis of variance, when appropriate. Cox regression model was applied to evaluate the hazard ratios for diabetes onset and to evaluate the independent effect of covariates on risk estimate, being age, sex, and treatments the covariates. Linear contrasts were used to test for differences between patients and controls and among treatments. Power analysis was used to estimate the sample sizes needed to get a 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).

Results

The haloperidol, olanzapine, risperidone, and quetiapine groups included 2,071, 266, 567, and 109 patients, respectively. According to the 1-case/2-controls design of the study, the control group ~~was made of~~comprised 6,026 individuals.

The four treatment groups differed in age and treatment variables but not in sex distribution (Table 1).

The incidence of diabetes in controls was 1.5/1,000 person-years, a rate manifold lower than that of each group taking an antipsychotic in monotherapy (Table 2). After age and sex correction with Cox analysis (Table 3), each of the four groups of patients taking an antipsychotic drug had a hazard ratio for new-onset diabetes that was higher, at a 0.001 level of significance, compared to the control group; the ratios estimated for haloperidol, olanzapine, risperidone and quetiapine were instead not significantly different when compared to each others.

Among the subjects exposed to an antipsychotic treatment, patients with and those without diabetes had a similar number of prescriptions, 4.4 vs. 3.4 (Student t 1.4, p=n.s). In turn, the time needed for the development of diabetes from the beginning of the antipsychotic therapy closely overlapped – 248.1, 236.6, 299.5, and 275.3 days – in the groups treated with haloperidol, olanzapine, risperidone, and quetiapine, respectively (F = 0.23, p = n.s.).

According to power analysis (Table 4), the number of subjects needed to differentiate diabetes risk between the four groups exposed to an antipsychotic ranged from 1,063 to 175,150, with the lower estimates for the comparisons involving quetiapine, followed in

an increasing rank order by those between risperidone and haloperidol, olanzapine and haloperidol, and risperidone and olanzapine, respectively.

Discussion

The major finding that emerged from the multiple comparisons we performed is that, after an antipsychotic drug-free interval, the groups exposed to a monotherapy with haloperidol, olanzapine, risperidone, or quetiapine shared a dramatically higher risk for new-onset diabetes when compared to untreated controls, but were not appreciably differentiated from each other according to their hazard ratios.

A number of comments deserve to be outlined.

First, The Health Search Database resulted a valuable tool in capturing cases with emergent diabetes: the disease incidence in the control group substantially overlapped with figures recently found in other databases (15,16). This conclusion is far from surprising, because the Health Search Database showed a good concurrent validity in estimating the prevalence of diabetes mellitus in a subsample of 432,747 subjects when compared to an independent population estimate (17).

Second, the inclusion of a rigorously age and sex-matched group of untreated controls and the exclusive selection of patients exposed to only one antipsychotic after a drug-free period is a major strength of our study when compared to most of published studies.

Third, as far as we are aware, this is the first study which explicitly evaluated diabetes incidence in patients exposed to quetiapine: this original contribution gives added value to the study, ~~in spite of~~ despite the relatively small size of the quetiapine sample.

Fourth, the differences of our experimental design from those of other large-scale studies (7,8,9,10,11,12,13) make comparison of results of poor heuristic value. However, a summary of major similarities and discrepancies with previous literature may be informative to some degree. Specifically, olanzapine data fit with two (8,12) out of four

(7,8,12,13), two (8,12) out of three (8,12,13) and four out of four studies (10,11,12,13), as far as the comparisons with risperidone, typical antipsychotics, and no treatment at all, respectively. In turn, risperidone data agree with three out of three (8,12,13) and two (10,12) out of four (10,11,12,13) studies as far as patients exposed to typical antipsychotics and healthy controls, respectively. Finally, assuming haloperidol ~~as~~ to be roughly representative of typical antipsychotics, our findings are comparable with all the three studies (10,11,12) that tested differences with subjects not exposed to antipsychotics.

Fifth, the lack of information about life-styles, comorbidities and other variables known to facilitate diabetes onset is a weakness of our study, since we could n~~o~~t ~~analyze~~analyse the contribution of these risk factors. However the very high degree of significance reached in each of the comparisons opposing patients and controls, together with similar diabetes rates found in haloperidol, olanzapine, risperidone, and quetiapine groups suggest a high probability of a really generalized phenomenon, with a valuable protection against type I errors and other spurious second order associations.

Sixth, a possible dose-dependent effect of the antipsychotic drugs on the risk of new onset diabetes cannot be ruled out because doses were not recorded. However, if a dose effect was operating, this should have eventually dampened rather than increased incidence of diabetes in our patients exposed to antipsychotics: setting aside the repetitions of a psychiatrist's prescription, GPs often ~~under~~ under-dose antipsychotics (18,19,20)

Seventh, the absence of detailed diagnoses did not allow to weight for the effect of specific psychiatric disorders on diabetes risk. This might be the case of schizophrenia. A

recent report (21) of impaired fasting glucose tolerance and augmented insulin resistance in first-episode, drug naïve schizophrenia patients has in fact replicated, with advanced techniques, some claims of the pre-psychopharmacological era (22,23). Furthermore, evidence also exists that the relatives of schizophrenia patients have abnormally high rates of type II diabetes (24). However, an heavy effect of second order association mediated by schizophrenia is unlikely in our sample GPs' patients; a wide diagnostic heterogeneity is presumable in the four treatment groups, because the GPs' frequently choose to prescribe antipsychotics for the symptomatic control of many clinical conditions, possibly unrelated to schizophrenia spectrum disorders (25,26).

Eight, the numerical but not significant differences of the hazard ratios for diabetes onset among the groups exposed to antipsychotic medication must be interpreted with some caution because the unbalanced sample sizes could have given way to false negatives. Nevertheless, the power analysis based on our incidence rates show that many thousand patients are needed to reach statistical significance in the head to head comparisons between the haloperidol, olanzapine and risperidone groups: even if some differences really exist between the four treatments, these should be viewed of questionable clinical relevance. The case of quetiapine appears instead different to some degree; the indication of the power analysis that is relatively small samples are needed to get a significance compared to the three other antipsychotics invites to contingently suspend any conclusion. In the meanwhile, quetiapine-associated risk for diabetes should be regarded at least as the same as that of haloperidol, olanzapine and risperidone.

Keeping in mind all these comments, a series of suggestions seems justified for both research and clinical practice.

For research purposes, the design of studies aimed at separating 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 couple the stratification for the most robust diabetes risk factors with the inclusion of untreated schizophrenia patients to remove 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 schizophrenia patients: therefore, prospective studies which record the most relevant risk factors, control for the psychiatric diagnoses, and involve enough ~~Centers~~centres to give adequate statistical power are the most amenable strategy.

In turn, as far as the transfer into the daily clinical practice of the current knowledge on diabetes risk during treatment with antipsychotic drugs, the emerging general recommendation is that both the clinicians and the candidates to receive these drugs should be updated on this issue without further delay. A clear, non-dramatizing information about possible ~~hyperglicemia~~hyperglycemias-related adverse events in the product labelling of the antipsychotic drugs should plausibly represent the most direct and convenient operative way to cover this need. In any case, and independently from the privileged communication strategies, the lack of clinically evident drug- or class- specific effects on diabetes risk calls for a generalized warning applied to both the typical and the atypical antipsychotics. At least two supplementary considerations point to extend the proposal also to the case of the typical antipsychotics. One is that the estimate of the risk for incident diabetes is likely to be relatively more conservative for haloperidol than for olanzapine, risperidone, and quetiapine, because the typical antipsychotics are generally

associated with a relatively poorer treatment adherence (27,28). The other is that, among the typicals, haloperidol has probably one of the most benign diabetogenic profiles, since abnormal glucose metabolism has been more often associated with low potency antipsychotics (1,2,11).

Given the lack of robust evidence favouring some antipsychotics over the others, clinicians must promote early individuation of first-line candidates for diabetes and operatively privilege the prevention of this adverse event. For purposes of an early individuation, the physician should carry out a careful, periodically revised assessment of personal and familial factors of vulnerability for diabetes and test glucose metabolism in at-risk cases. In turn, for prevention, a strong psycho-educational effort involving both the patients and their families and directed to promote healthy behaviours (29) useful to contrast some of the vulnerabilities for diabetes is indicated: the termination of an antipsychotic treatment is in fact an unacceptable option due to the associated, dramatic risk of recurrence of psychotic symptoms. Future, prospective comparisons of patients with and without *ad hoc* psycho-educative interventions are indicated to test for the efficacy of this simple and relatively inexpensive intervention for controlling the emergence of diabetes during treatment with antipsychotics.

Table 1

Sociodemographic and Clinical Features of Patients taking Olanzapine, Risperidone, Quetiapine, or Haloperidol

Variable		Olanzapine	Risperidone	Quetiapine	Haloperidol	Test, p value
Age [y (SD)		52.6 (20.4)	58.3 (23.3)	65.0 (21.3)	66.5 (21.0)	F = 47.5, p < 0.01 (3 d.f.) (#)
Sex	Males	49.2%	43.9%	37.6%	40.7%	Chi sq. 8.9, p=.03
	Females	50.8	56.1	62.4	59.3	(3 d.f.)
Duration of therapy (days, SD) (°)		134.8 (206.4)	130.5 (263.9)	75.8 (116.8)	273.7 (488.2)	F = 26.7, p<.001 (3 d.f) (^)
Total prescriptions (mean, SD)		3.5 (3.7)	2.5 (3.1)	3.9 (5.0)	3.7 (6.0)	F = 7.2, p<.001 (3 d.f.) (ø)
Follow-up days (§) (mean, SD)		301.7 (221.8)	335.9 (238.6)	190.7 (135.2)	430.7 (262.8)	F = 60.5, p<.001 (3 d.f.) (λ)

(#) in the post-hoc analysis significant differences (<.05) in the pairs: haloperidol/olanzapine, haloperidol/risperidone, olanzapine/risperidone, olanzapine/quetiapine, risperidone/quetiapine
(^) in the post-hoc analysis significant differences (<.05) in the pairs: haloperidol/risperidone, haloperidol/olanzapine, haloperidol/quetiapine
(ø) in the post-hoc analysis significant differences (<.05) in the pairs: olanzapine/risperidone, risperidone/quetiapine, haloperidol/risperidone
(λ) in the post-hoc analysis significant differences (.05) in the pairs: haloperidol/olanzapine, haloperidol/quetiapine, haloperidol/risperidone, olanzapine/quetiapine, risperidone/quetiapine
(°) subjects with a single prescription excluded
(§) if longer, truncated at two years

Table 2

Incidence of Diabetes in Subjects taking Haloperidol, Olanzapine, Risperidone, or Quetiapine and Controls

Group	Year of follow-up	Number entering the interval	Censored cases	Population at risk	Incident cases	Cumulated days of observation (*)	Incidence/1000 person-years
Haloperidol pts.	1st	2,071	843	1,649.5	33	892,001	19.6
	2nd	1,195	532	929	15		
Olanzapine pts.	1st	266	166	183	4	80,240	22.8
	2nd	96	74	59	1		
Risperidone pts.	1st	567	338	398	9	190,430	24.9
	2nd	220	131	154.5	4		
Quetiapine pts	1st	109	97	60.5	3	20,787	52.7
	2nd	9	9	4.5			
Controls	1st	6,026	2,912	4,570	8	2,406,446	1.5
	2nd	3,106	1,570	2,321	2		

(*) estimated on the overall observation time (1st and 2nd years), follow-ups longer than 2 years were truncated at 2 years

Table 3

Hazard Ratios (§) for Diabetes in the Four Treatment Groups

Variables	Ratio	95% c.i.	P value
Treatment (°)			
1. olanzapine	20.35	6.86-60.33	<.001
2. risperidone	18.71	18.18-42.81	<.001
3. quetiapine	33.68	9.18-123.55	<.001
4. haloperidol	12.40	6.27-24.52	<.001

(§) Cox proportional regression analysis after correction for age (ratio 1.03; 95% c.i. 1.01-1.04; p<.001) and sex (ratio of females 1.04; 95% c.i. 0.66-1.65; p=0.87)

(°) untreated 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	# of subjects
Risperidone vs. haloperidol	25,702
Olanzapine vs. haloperidol	67,237
Quetiapine vs. haloperidol	1,063
Risperidone vs. olanzapine	175,150
Risperidone vs. quetiapine	1,609
Olanzapine vs. quetiapine	1,356