A Comprehensive Retrospective Study of Associations Between Diabetes and Treatment with Risperidone, Olanzapine, Quetiapine, and Conventional Antipsychotics

HECON Associates, Inc.

Abstract

Background: Retrospective studies using large patient databases have had conflicting findings regarding diabetes risks associated with antipsychotics. Sensitivity of findings to study design was assessed.

Methods: Claims data were analyzed for thousands of patients with psychoses both treated and untreated with antipsychotics. Screening for pre-existing diabetes, identification of diabetes with prescription claims only, and antipsychotic monotherapy provide better control for confounding influences and represent a stronger study design. Diabetes odds ratios for patients treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics versus untreated patients were estimated varying the above criteria. This was done for all patients and patients stratified by low, medium, and high dose levels. Logistic regression controlled for patient age, sex, type of psychosis, length of observation/treatment, pre-existing excess weight, and use of other drugs with potential diabetogenic effects.

Results: Under a weaker study design, all of the antipsychotics were associated with significantly higher odds of diabetes relative to patients untreated with antipsychotics. Differences among the antipsychotics were relatively small; odds ratios with 12 months of treatment were: risperidone 1.388 (CI: 1.276-1.509), olanzapine 1.331 (CI: 1.224-1.446); quetiapine 1.394 (CI: 1.247-1.559), and conventionals 1.365 (CI: 1.238-1.503). Under a stronger study design, relative odds for quetiapine became statistically insignificant and declined sharply,1.087(CI: .742-1.612), while those for olanzapine and conventional antipsychotics remained significant and increased, 1.858 (CI: 1.549-2.238) and 1.755 (CI: 1.381-2.221) . Risperidone's overall odds ratio also declined and became nonsignificant, 1.224 (CI: .962-1.562). When stratified by dose, quetiapine alone showed a lack of statistical significance at all dose levels. For conventionals antipsychotics odds of diabetes were significantly higher than untreated patients at all dose levels, for olanzapine at medium and high doses, and for risperidone at high dose only. Regardless of statistical significance, however, all three atypicals showed an increasing relationship between estimated odds of diabetes and dose level. Absence of this association for

conventional antipsychotics may be explained by the aggregate nature of this category.

Conclusion: In large database studies, estimated risks of diabetes among antipsychotics are affected by study design. With a more reliable design, the estimated risks associated with quetiapine and risperidone are lower than those associated with olanzapine and conventional antipsychotics.

Introduction

A growing number of case reports and studies suggest that some antipsychotic medications impose a higher risk of diabetes mellitus than others.[1-18] Case findings, prospective trials and chart reviews have strongly implicated olanzapine and clozapine,[1-9] but are limited by small numbers. Restrospective studies based on claims and similar patient records[10-18] often have the advantage of large numbers, but have had more varied results, which may be attributed to differences in study design. For example, some studies have used less precise methods for associating diabetes with specific antipsychotics[10,11,13,15] while this study and earlier studies identified antipsychotic treatment episodes to match the time of diabetes onset with the time of specific antipsychotic use.[14,16,17,18] Because of real world practices of switching antipsychotics and prolonged periods of non-antipsychotic use (possibly characterized by use of other psychotropic drugs), less timing-sensitive methods have a greater likelihood of wrongly associating diabetes cases.

Findings of diabetes risk can also be affected by other aspects of study design including decisions to screen or not screen patients for preexisting diabetes and to identify diabetes using medical or prescription claims versus prescription claims only. Screening for pre-existing diabetes is particularly important if antipsychotics are subject to selection bias. Patients with pre-existing diabetes may be more likely to be initiated on or switched to antipsychotics that are perceived to be safer. The presence of prescription claims for antidiabetics or insulin is a definite indicator of diabetes, while medical claims showing diabetes ICD-CM-9 codes may simply reflect testing for diabetes including tests with negative results. Precautionary testing for diabetes among patients treated with antipsychotics may have become more common with increasing awareness of this adverse effect. Also, mild cases of glucose elevation not requiring treatment should be distinguished from more serious cases requiring antidiabetics or insulin.

Building on our earlier work,[18] this retrospective claims-based study represents a more rigorous assessment of associations of risperidone, olanzapine, quetiapine, and conventional antipsychotics with diabetes mellitus. Estimates of diabetes risk were generated using both a weaker and a stronger study design to demonstrate why retrospective studies have come up with conflicting findings..

Methods

The study was based on claims data for tens of thousands of patients with schizophrenia, bipolar disorder, and major depression obtained from several commercial health plans totaling 33 million lives. The data covered the period 1999 through April 2002.

Methods are similar to those of our earlier studies in that defined treatment episodes were used to associate diabetes cases. A main deviation from earlier work is the focus on all diabetes mellitus rather than just type 2. Type 2 or non-insulin-dependent diabetes mellitus, also known as adult onset diabetes, is distinguished from type 1 or insulin-dependent diabetes mellitus, which usually emerges early in life and is due to a genetic defect that causes the pancreas to under-produce insulin or to produce none at all.[21] Known effects of antipsychotics on weight gain[22,23] and suspected effects of reducing glucose transporters and decreasing pancreatic β-cell responsiveness, resulting in impairment of glucose metabolism,[1,2,19,20] make type 2 diabetes the obvious concern. Case reports have largely focused on type 2 diabetes.[3] Nevertheless,exclusion of type 1 cases now seems inappropriate. First, some researchers have identified reduced insulin secretion (type 1) as being very likely in some antipsychotic-related diabetes cases, particularly those involving diabetic ketoacidosis.[20] Second, in claims data reporting of diabetes type is likely inaccurate. For example, in about 40% of patients it was found that diabetes type was not specified or that both type 1 and type 2 were reported. The latter may reflect a tendency to indicate type 1 if a type 2 patient is prescribed insulin.

By and large, commercially insured patients with psychoses do not have continuous use of antipsychotics. This is not surprising among individuals with bipolar disorder or major depression where other psychotropic medications such as mood stabilizers and antidepressants have been the principal forms of therapy. (Though off-label use is widespread, antipsychotics, with the exception of olanzapine, have FDA indications for schizophrenia only.) A treatment episode represents continuous or fairly continuous use of an antipsychotic. Antipsychotic use was most continuous for patients with schizophrenia and least continuous for patients with major depression. Prescriptions with fill dates separated by ninety days or less were judged to be part of same treatment episode. For determining the beginning of a treatment episode, it was required that a prescription for a given antipsychotic not be preceded by an earlier prescription for that antipsychotic for at least 120 days. The vast majority of prescriptions were for 30 days supply. Also, to ensure an adequate amount of antipsychotic exposure

and that patients were in fact compliant, only those patients who had at least two consecutive prescriptions (60 days) of an antipsychotic were included. Generally, an antipsyhotic treatment episode was measured from the fill date of the first prescription to the end date of treatment, which was determined by adding the last prescription's days supply to its fill date. A patient's disenrollment date or the end date of the data replaced this calculated date if it came first. These methods are similar those used in three publications on this subject[14,17,18] and are also discussed in a methods publication.[24]

Treatment episodes, rather than patients per se, were the sampling units for which diabetes risk was measured. Use of the patient rather than the antipsychotic treatment episode as the unit of analysis is incompatible with how antipsychotics are used in real world settings. Many patients had multiple treatment episodes with different antipsychotics or even the same antipsychotic. The fact that antipsychotic treatment durations vary considerablyadds to the complexity of using the patient as the ampling unit.. Picking a uniform duration, and therefore observation period, not only limits sample size, but also precludes important information on the relationship between treatment duration and diabetes risk. Making the observation period uniform, while allowing treatment duration to vary also makes little sense. For example, if the observation period were set at 12 months for all patients, a large number of patients would have treatment durations that were far shorter, meaning that diabetes that became manifest long after the treatment ended would be assigned to the antipsychotic. These and related issues were discussed in an earlier publication.[14]

The control population consisted of psychosis patients who were not treated with antipsychotics for extended periods of time. Because diabetes may be associated with schizophrenia, bipolar disorder, and major depression independently of antipsychotic use,[25-29] an untreated psychosis population is more suitable than the general population for measuring the incremental diabetogenic effects of antipsychotics. To avoid confounding the presence or absence of treatment with the length of observation, observation periods for controls were made to vary in length as did antipsychotic treatment episodes. .

Statistical methods

As in earlier published studies,[11,14,15, 17,18] logistic regression was used to estimate diabetes risk associated with specific antipsychotics.The risk of acquiring diabetes was related to the length of time

that an individual was treated with an antipsychotic. Some antipsychotics may not pose a risk and, therefore, there would be no relation with treatment duration. Others may pose a more accelerated risk, while yet others may pose a more gradual risk. In earlier studies[14,17,18] treatment duration was measured as a continuous variable. The effect of each antipsychotic on diabetes risk was related to the number of months that an individual was treated with that antipsychotic. Zero values for all of the antiposychotics specified in the models indicated a control patient. The estimated odds ratio for each antipsychotic indicated the proportion by which one month of treatment with that antipsychotic increased the risk of diabetes relative to an untreated psychosis patient. With continuous variables in logistic regression, the correct procedure for determining the effects of multiple units, months of treatment in this case, is to raise the estimated odds ratio to a power equivalent to the desired number of units (months).[30] For example, if the estimated (one-month) odds ratio for an antipsychotic is 1.05, the odds ratio for twelve months of treatment is $(1.05)^{12} = 1.80$. This means that twelve months of treatment with the antipsychotic increases the risk of diabetes by 80 percent over that of an untreated patient.

Antipsychotic dose levels may also affect the risk of diabetes. To assess differences in diabetes risk associated with antipsychotic dose, patients were grouped into low, medium and high daily dose cohorts with these gradations determined separately for 4 subgroups of patients stratified by: 1) male or female; and 2) child (<18) or adult. Age and gender are correlated with bodyweight, which may influence the effective dose of an antipsychotic. Low, medium, and high dose correspond to the bottom, middle, and top third of the daily dose range for each antipsychotic and patient subgroup Because conventional antipsychotics were grouped into one category and because of concurrent use of antipsychotics, dose was measured in risperidone-equivalent milligrams. For each antipsychotic, the mean daily milligrams for patients falling in the highest and lowest 10 percent of the range were calculated. These were then averaged. Averages of the other antipsychotics were divided into that of risperidone to create conversion factors. Overall means were not used to calculate conversion factors because they are more sensitive to case mix differences among the antipsychotics and may have also reflect prevailing dosing practices.

Diabetes frequencies and logistically estimated odds ratios for treated versus untreated patients were generated irrespective of antipsychotic dose levels as well as separately for patients treated with low, medium, and high doses. To demonstrate the sensitivity of results to study design, comparisons were

made under two extreme designs reflecting weaker and stronger controls for confounding influences. Under the weaker design, patients were not screened for preexisting diabetes, diabetes was identified with medical or prescription claims, and concurrent use of different antipsychotics was allowed. Under the stronger design, patients were screened for preexisting diabetes at eight months prior to observation/treatment, diabetes was identified with prescription claims only, and antipsychotic monotherapy was required.

Identification and removal of preexisting diabetes cases may be necessary to accurately measure antipsychotic-induced diabetes. This is particularly so where selection bias is a likely factor. A growing number of case reports and studies have already made some antipsychotics more suspect than others. Reports and studies on associations between antipsychotics and excessive weight gain, a major risk factor for type 2 diabetes, may have also affected practitioner perceptions regarding certain antipsychotics. Consequently, in more recent years, there may have been a tendency to prescribe "safer" antipsychotics to patients with diabetes or patients perceived to be at greater risk. Therefore, an analysis performed on a patient population not screened for preexisting diabetes would likely be biased. The historical tendency of practitioners to prescribe quetiapine as a second-line antipsychotic may have made it more susceptible to selection bias. In some instances quetiapine may have been switched to because of the preceding antipsychotic's side effects, including effects on patient glucose levels and weight.

In our first two studies,[14,17] we counted as diabetes cases all patients reporting this condition on one or more medical claims or having one or more prescription claims for antidiabetes products. In our third study[18] we took a more conservative approach requiring for proof of its presence treatment of diabetes as evidenced by prescription claims.. The problem with the earlier, more liberal approach is that a medical claim showing an ICD-9-CM code for diabetes does not necessarily mean that the patient tested positively for this condition. (Claims are payment instruments and not medical records.) Also, testing for diabetes may not even be indicative of a "potential" problem with the new therapy. It may reflect concerns over a problem, say excessive weight gain, caused by a prior therapy. The likelihood of carry-over concerns with prior therapies is greater for quetiapine, which historically was more likely than risperidone and olanzapine to have been used as a second-line antipsychotic. While more accurate,

reliance on prescription claims only, excludes cases of modest glucose elevation and thereby tends to favor antipsychotics with relatively mild diabetogenic effects.

The data for this and earlier studies reveal that a considerable proportion of psychosis patients use two or more antipsychotics concurrently. While this is largely explained by a recommended overlap when transitioning from one antipsychotic to another,[31] there were many cases of prolonged concurrent use. In our earlier diabetes studies, the confounding effects of concurrent use were dealt with in two ways. First, a variable was specified in the models that indicated the presence and degree of concurrent treatment with another or other antipsychotics. Second, because treatment episodes overlapped where there was concurrent use, diabetes manifesting during the overlap was assigned to both antipsychotics. Nevertheless, these remedies may be inadequate. Where there are overlaps, there is no way of avoiding assignment of diabetes to antipsychotics that in actuality have no or weaker diabetogenic effects, since this cannot be known a priori.

The following measures were specified as control variables in the logistic models.

Age	The risk of type 2 diabetes, also known as adult-onset diabetes, increases with age. Patient age was specified as a continuous variable.
Gender	Patient gender was specified as a categorical (1,0) variable. Case reports and some patient record reviews have revealed a higher proportion of males with antipsychotic associated diabetes.[3,32] This finding, however, is contradicted by other findings that show a higher proportion of females with antipsychotic associated diabetes[12] or suggest that the higher proportion of males reflects the higher proportions treated with specific antipsychotics.[2]
Other drugs w/ diab. Effect.	Categorical variables were specified to indicate patient use of each of the following drugs known or suspected of having diabetogenic effects: 1) thiazide diuretics; 2) beta-blockers; 3) protease inhibitors; 4) SSRI's; 5) valproate sodium; and 6) lithium.[33-36] In

	addition, the total amount spent on these prescriptions per patient per month was specified to capture intensity of use.
Prior excess weight problem	A categorical variable was specified to indicate if a patient had a prior (i.e. prior to observation) excess weight problem, as indicated by prior prescriptions for diet medications or medical claims for this condition.
Substance abuse/dependence	Type 2 diabetes can result from excessive use of alcohol or drugs. A categorical variable was specified to indicate if a patient had present or past evidence of alcohol or drug abuse or dependence. This will be evidenced by medical claims with the appropriate ICD-9-CM codes (292.xx, 293.xx, 304.xx, 304.xx).
Switch from other antipsychotic	A categorical variable was specified to indicate whether the patient initiated on risperidone, olanzapine, quetiapine, or a conventional switched from another antipsychotic. Switches were defined as treatment episodes showing another antipsychotic prescription within 60 days prior to their begin dates.
Concurrent use of oth antipsych	This was measured with a continuous variable which is the ratio of the concurrent antipsychotic's total days supply to the index antipsychotic's total days supply within the index antipsychotic's treatment episode. This variable was used only in the scenario not restricted to monotherapy.
Type of psychosis	Risk of diabetes mellitus may be psychosis-related,[22-26] and because of their different pathogeneses, the different forms of psychosis may pose different risks. Type of psychosis was indicated by two categorical variables representing bipolar disorder and schizophrenia, with zeros for both of these representing major depression. Where more than one of the three types of psychosis was reported on a patient's medical claims, classification was based on the most recent because this was judged to be the more accurate (being based on more patient history).

Length of observation	For psychosis patients treated with antipsychotics, observation periods, which correspond to treatment episodes, vary in length. Observation periods for untreated patients were also be made to vary in length to avoid confounding. Since the likelihood of observing diabetes (or most any illness) in an individual increases with time of observation, it is necessary to control for these differences.
Type of insurance coverage	Because of differing emphases on preventive care, type of coverage may affect risk of diabetes. It may also affect access to care and, therefore, diagnosis of diabetes. Four categorical variables captured the four main types of insurance coverage represented in the database: HMO, preferred provider, point of service, and indemnity. Zero values for all of these represent other lesser types of coverage.

Although it was done in other studies,[11] the inclusion of other mental disorder comorbidities is questionable in that the direction of causality is uncertain. For example, depression and anxiety may result from diabetes.[37]

Results

Sample and Patient Characteristics

There were a total of 37,318 treatment episodes with risperidone, olanzapine, quetiapine or conventional antipsychotics that were initiated within the period 1999 through 2001 and had at least 60 consecutive days of the defining antipsychotic. The number of unique patients represented by these treatment episodes was somewhat smaller because some patients were counted more than once, being treated at different times with the same or a different antipsychotic. The control group consisted of 33,272 psychosis patients who were not treated with antipsychotics or not treated for long periods. Treated and untreated psychosis patients consisted mainly of persons with major depressive disorder (46% and 56%) followed by bipolar disorder.(34% and 39%). The number of schizophrenia patients was relatively small in both groups (20% and 4%), particularly the untreated group.

Characteristics of untreated psychosis patients and patients treated with risperidone, olanzapine, quetiapine, or conventional antipsychotics are shown in Table 1. These characteristics correspond to the control variables specified in the logistic regression models. Patients treated with conventionals were considerably older than those treated with the atypicals, particularly risperidone. Untreated patients fell in between. Females were generally more prevalent than males among both treated and untreated patients. Risperidone and olanzapine-treated patients had relatively higher proportions males. Major depression and bipolar disorder were the dominant psychosis types among both treated and untreated patients, with schizophrenia patients being relatively few particularly in the untreated group. Observation periods, which are equal to treatment durations for treated patients, averaged the longest for the untreated group and the shortest for olanzapine. Median observation periods/treatment durations, however, were more similar. Among treated patients, antipsychotic daily dose, measured in risperidone-equivalent milligrams, averaged highest for conventionals. This is consistent with the fact that conventional-treated patients by far had the highest proportion of schizophrenia. Median daily doses show the same ranking but are less disparate.

Other medications with suspected diabetogenic effects were generally more widely used by treated than untreated patients, as reflected in the percentages as well as in the per capita expenditures per patient per month. SSRIs were the most widely used of these drugs followed by lithium. Risperidone-treated patients had the highest use of SSRIs while conventional-treated patients had the highest use of beta-blockers, consistent with their older age. Substance dependence/abuse was most prevalent among olanzapine-treated patients followed by quetiapine. Quetiapine-treated patients had the highest proportion with prior excess weight problems followed by conventionals, while untreated patients had the smallest proportion. Conventional-treated patients had the smallest proportion on antipsychotic monotherapy followed by quetiapine. A considerably higher proportion of quetiapine-treated patients were switched from another antipsychotic, which is consistent with the greater prevalence of prior excess weight problems within this group. The mix of insurance coverage did not differ greatly between groups, with HMO generally being the dominant type.

Comparisons of Diabetes Frequencies

In Table 2 diabetes frequencies of patients treated with risperidone, olanzapine, quetiapine, and conventional antipsychotics are compared to each other and to those of psychosis patients untreated with antipsychotics. This is done under both a weaker and stronger study design. Patients are stratified by antipsychotic treatment duration or length of observation. Treated patients are also stratified by low, medium, and high antipsychotic dose. Under both designs relative frequencies generally increase with treatment duration. There is also a general tendency for relative frequencies to increase with dose among all of the antipsychotics except conventionals

Under the weaker study design – no pre-screening, diabetes identified with medical or prescription claims, and monotherapy not required– diabetes relative frequencies for treated patients are higher than those for patients untreated with antipsychotics for every observation/treatment length and for every dose level. Among treated patients, conventionals had the highest relative frequencies irrespective of dose level while risperidone had the lowest followed closely by quetiapine. This ranking is also apparent when frequencies are stratified by dose. Generally, differences among the three atypicals are not large.

Under the stronger study design –pre-screening at 8 months, diabetes identified with prescription claims only, and monotherapy required - differences in diabetes frequencies between untreated patients and quetiapine-treated patients became relatively small. If fact, patients treated with low doses of quetiapine had lower diabetes frequencies than untreated patients . In addition, diabetes frequencies for quetiapine are lowest among the antipsychotics followed closely by risperidone. Frequencies for olanzapine and conventionals are much higher overall and in each of the three dose levels and exceed those of untreated patients by considerable margins. Among all three of the atypical antipsychotics , there was a clear tendency for diabetes frequencies to increase with dose level. The absence of this relationship for conventional antipsychotics may be explained by the aggregate nature of this category.

Odds ratios estimated with logistic regression

Odds ratios reflecting 12 months of treatment with risperidone, olanzapine, quetiapine, or conventionals versus psychosis patients untreated with antipsychotics are reported in Table 3. These were estimated

irrespective of dosage level and separately for patients grouped into low, medium and high dose cohorts. Ratios under the weaker and stronger study designs were estimated with logistic regression and reflect control for patient differences reported in Table 1. Under the weaker study design, odds ratios measured over all dose levels were statistically significant and similar for all antipsychotic categories, ranging from 1.331 for olanzapine to 1.394 for quetiapine. With the exception of low-dose risperidone, odds of diabetes were significantly higher than untreated patients among all of the antipsychotics at all three dose levels. Odds ratios generally increased with antipsychotic dose, with this tendency being notably weaker for conventionals. .

Large differences among the antipsychotics emerged when a stronger study design was applied.. Over all dose levels, olanzapine and conventionals alone had odds of diabetes that were significantly higher than untreated patients (OR=1.858 and OR=1.755, respectively). Overall odds ratios for quetiapine (1.087) and risperidone (1.224) were statistically insignificant and much lower than those for olanzapine and conventionals. When patients were separated by dose level, conventionals had significantly higher odds of diabetes than untreated patients at all dose levels (p=.0007, .0009, and .0425 for low, medium, and high dose). Olanzapine had significantly higher odds at medium (p<.0001) and high (p<.0001) dose levels while risperidone had significantly higher odds at the high dose level only (p=.0249). Quetiapine's odds ratios were not statistically significant at any dose levels (p = .3452, .3552, and .1596 for low, medium and high dose). Despite the lack of significance, quetiapine's odds ratios increased with dose as did olanzapine's and risperidone's and this ~~in itself may suggest~~ relationship of some diabetogenic effect. The absence of an increasing relationship between diabetes odds and dose for conventional antipsychotics seems counterintuitive. This result, however, may be explained by the aggregate nature of this category (over 20 conventionals are represented). The mix of conventional antipsychotics may have changed considerably from one dose level to the next.

Among the control variables, patient age, a diagnosis of schizophrenia, a preexisting excessweight problem, and use of beta-blockers were consistently significant and positively associated with diabetes risk. Each additional year of age increased diabetes risk by 4-6% depending on study design and dose cohort. Patients with schizophrenia had a 40-100% greater risk of diabetes than patients with major depression and about a 30-70% greater risk than patients with bipolar disorder. Patients with a prior weight problem had about a150% greater risk of diabetes. Use of beta-blockers increased diabetes risk

by 75-90%. Male gender, use of thiazide diuretics and SSRIs, and switching from another antipsychotic also had significant positive associations with diabetes risk, but were less consistent.

Discussion

Evidence from case reports, prospective studies, and chart reviews generally support the conclusion that olanzapine and clozapine have stronger diabetogenic effects than other atypical antipsychotics.[1-9] Retrospective studies based on claims orsimilar patient data, and involving much larger numbers, have had more mixed results. These studies have compared the atypicals to one another, to conventionals, and to persons untreated with antipsychotics. The studies have varied considerably in research design including decisions to screen (e.g., Koro et al., 2002,[12] and Gianfrancesco et al., 2002 [14]) or not screen (e.g. Sernyak, 2002,[11] and Lee et al., 2003[15]) for pre-existing diabetes; to use medical or prescription claims (e.g., Gianfrancesco et al., 2002[14]) versus prescription claims only (Gianfrancesco et al., 2003,[18] and Buse et al., 2003[16]) to identify diabetes; to restrict (e.g. Buse et al.,2003[16]) or not restrict (e.g., Caro et al.,2002[13]) comparisions to antipsychotic monotherapy; and to use more (e.g.,Gianfrancesco et al., 2002,[14] and Buse et al.,2003[16]) or less (e.g., Hendenmalm et al., 2002,[10] and Sernyak et al., 2002,[11]) precision in relating time of diabetes onset to time of specific antipsychotic use. A main goal of the present study has been to assess the sensitivity of findings to study design and, through this exercise, arrive at a more definite determination of the relative diabetes risks associated with the various antipsychotics.

Failure to screen for pre-existing diabetes can bias comparisons if prescribing behavior is sensitive to the perceived risks associated with antipsychotics. For example, mounting evidence regarding antipsychotic effects on glucose levels and body weight may have created a tendency to prescribe "safer" products to patients with diabetes or at greater risk for this condition. Use of medical claims to identify diabetes may also bias comparisons in a manner unfavorable to safer products. Medical claims showing diabetes codes but unaccompanied by prescription claims for anti-diabetics do not necessarily establish the presence of this condition. They may reflect tests with negative results, and growing concerns over antipsychotic-induced diabetes may have made precautionary testing more widespread. Even where tests are positive, glucose elevations may be insufficient to warrant medical intervention. Prescription claims are more definite indicators of significant diabetogenic effects. Lastly, comparing situations where different antipsychotics are used concurrently can further bias comparisons against safer products. Since

diabetes emerging where two antipsychotics overlap must be attributed to both, the safer product is placed at a disadvantage. Comparing only situations of antipsychotic monotherapy avoids this sort of bias.

Consistent with the above arguments, this study has shown that estimates of relative diabetes risk are highly sensitive to screening for preexisting diabetes, to how diabetes is identified and to whether or not comparisons are restricted to situations of antipsychotic monotherapy. Differences among the antipsychotic categories were relatively small under a study design without pre-screening, not restricted to antipsychotic monotherapy, and where diabetes was identified using medical or prescription claims rather than prescription claims only. Under this weaker approach, all of the antipsychotic categories were found to be associated with a significantly higher risk of diabetes than psychosis patients untreated with antipsychotics.

Quetiapine's, and to a lesser extent risperidone's, relative position improved when comparisons were restricted to monotherapy, diabetes was identified with prescription claims only, and with 8 months pre-screening. Under this stronger study design odds of diabetes for quetiapine-treated patients, at all dose levels, were not significantly different from those of psychosis patients untreated with antipsychotics. In contrast, odds for olanzapine-treated patients were significantly higher at medium and high dose levels and those for conventionally-treated patients, at all dose levels. Risperidone showed significantly higher odds at the high dose level only. Patients treated with medium and high doses of olanzapine appear to face twice the risk of diabetes than psychosis patients untreated with antipsychotics. Patients treated with conventional antipsychoticss appear to face 60% more to twice the risk. Regardless of statistical significance, however, estimated odds ratios for all three atypicals increased with dose, which ~~in itself may suggest the presence of~~ a diabetogenic effect. Conventionals did not show an increasing relationship between odds of diabetes and dose, a result that is likely explained by the aggregate nature of this category. For example, the mix of conventional antipsychotics (about 20 different products) may differ in the low, medium, and high dose ranges.

In comparison to the other antipsychotics, results for quetiapine are more sensitive to screening for pre-existing diabetes, the method used to identify diabetes, and to whether comparisons are restricted to antipsychotic monotherapy. Sensitivity to pre-screening and to how diabetes is identified is perhaps

associated with the fact that historically quetiapine was more likely to have been used as a second-line therapy. As reported in Table 1, 35.3% of patients initiated on quetiapine were switched from another antipsychotic versus 17.4% for risperidone and 20.6% for olanzapine, which is also consistent with the fact that a higher percentage of quetiapine-treated patients had prior excess weight problems (3.5% versus 2.6% for risperidone and 2.4% for olanzapine). A medical claim for diabetes does not necessarily mean that a patient has this condition. It may simply reflect testing and testing may have been induced by circumstances, such as excess weight gain, brought on by a prior antipsychotic. Furthermore, even if medical claims are associated with elevated glucose, the absence of prescription claims for antidiabetic medications or insulin suggest that the elevation is not serious. In comparison with the other antipsychotics, particularly olanzapine and conventionals, quetiapine is associated with relatively few diabetes cases requiring medical intervention. The improvement in quetiapine results with monotherapy further attests to its weaker diabetogenic effects. Estimates based on monotherapy more clearly indicate the diabetes risks imposed by each of the antipsychotics, both with respect to each other and with respect to untreated patients.

Effects of study design on estimates of diabetes risk are revealed in other studies. Consider, for example, the study by Sernyak et al (2002)[11] in which a large Veterans Affairs database was used to perform a retrospective comparison of schizophrenia patients treated with typical and atypical antipsychotics. Diabetes was identified with medical claims (ICD-CM-9 codes), there was no screening for preexisting diabetes, and comparisons were not strictly confined to monotherapy. In addition, treatment episodes were not defined, which prevented control for treatment duration and reduced assurance that diabetes onset coincided with the time of specific antipsychotic use. Not surprising, the study found that quetiapine in conjunction with olanzapine and clozapine had significantly higher odds of diabetes than conventional antipsychotics; in fact, quetiapine's estimated odds ratio was the highest. Similarly, a more recent and yet unpublished study by Cunningham et al (2003),[38] also focusing on schizophrenia patients in a large Veterans Affairs database, found quetiapine, olanzapine, and risperidone, but not clozapine, to have significantly higher risks for diabetes in comparison to conventionals. Also, estimated hazard ratios for risperidone and quetiapine were larger than that for olanzapine. While the study controlled for pre-existing diabetes, medical claims were used to identify diabetes and it does not appear, from the limited details available, that comparisons were restricted to monotherapy and that antipsychotic treatment durations were measured and used to refine the analysis.

The above studies' findings with respect to quetiapine are not only at odds with this study, but also conflict with a study involving chart reviews, a clinical trial, and another retrospective study using a very large database. In an examination of medical charts for several hundred patients treated with typical and atypical antipsychotics, Wirsching et al (2002)[9] found significant glucose elevations from baseline for clozapine, olanzapine, and haloperidol, but not for quetiapine and risperidone. In a clinical trial involving 65 schizophrenia patients who were initiated on clozapine and then switched to a clozapine-quetiapine combination, Reinstein et al. (1999)[6] found that glucose levels improved in patients who had developed this condition under clozapine monotherapy. A recent study by Buse et al (2003)[16] exemplifies what we have defined as a "stonger study design": prescription claims only were used to identify diabetes; comparisons were restricted to antipsychotic monotherapy; patients were screened for pre-existing diabetes at 12 months; and antipsychotic treatment duration was measured to ensure that diabetes onset coincided with time of antipsychotic use. Quetiapine was found to have a relatively low diabetes risk in comparison to patients treated with other atypicals and conventionals.

While all of the antipsychotics were associated with significantly higher risks than the general population, this may in part have been due to the underlying psychoses in the treated population.

Lastly, findings from this and other more recent database studies may be affected by a growing practitioner awareness of the potential diabetogenic effects associtiated with specific antipsychotics. There may be an increasing tendency to avoid products that are perceived to be less safe. Since evidence from case reports and past studies has been more negative with respect to olanzapine and clozapine, it is not unreasonable to assume that use of these products is declining among patients at greater risk for diabetes. This tendency would bias more recent database findings against "safer" products such as risperidone and quetiapine.

Conclusion

This study has demonstrated that, in retrospective analyses using claims or other such data, findings of diabetes risk may be strongly influenced by study design. Specifically, because there has been historically a greater tendency to use quetiapine as a second-line antipsychotic, findings relating to its potential diabetogenic effects are highly sensitive to screening for preexisting diabetes, to whether diabetes is identified solely with the more definite indicator, prescription claims, and to whether comparisons are restricted to antipsychotic monotherapy. With an approach incorporating these refinements, quetiapine was found to have the weakest diabetogenic effects, particularly in relation to olanzapine and conventionals.

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Table 1. Profile of Study Population

	Without antipsychotic Treatment	Risperidone	Olanzapine	Quetiapine	Conventionals
Maximum N	33272	12427	12572	6476	5843
Age					
Mean (SD)	35.7 (14)	33.1 (17.2)	36.1 (15)	34.7 (14.6)	41 (13.7)
Median	37	35	38	37	42
Sex (percent)					
Female	65.9	57.1	56.5	67.4	64.8
Male	34.1	42.9	43.5	32.6	35.2
Diagnosis (percent)					
Schizophrenia	4.2	16.3	18.7	14.9	33
Bipolar and Manic	39.5	33.2	38.2	36	27.4
Major Depression	56.3	50.5	43.1	49.1	39.6
Observation Period/antipsych treat duration (months)					
Mean (SD)	10.7 (7.3)	7.7 (6.4)	7.4 (6.3)	7.5 (6.2)	8.1 (6.9)
Median	5	5.5	5.2	5.5	5.7
Antipsychotic Dose (risp equiv mgs)					
Mean (SD)	NA	2.7 (4.2)	3 (3.8)	2.8 (3.2)	3.8 (7.1)
Median	NA	2	2.4	2.1	2.6
Use of Other Drugs with Diab risk					
Valproate sodium (pct of patients)	.29	.64	.83	.57	.87
Lithium (pct of patients)	10.4	13.5	15.2	15.1	15.6
SSRIs (pct of patients)	32.8	40.1	36.8	35.2	32.3
Beta-blockers (pct of patients)	6.1	7.5	8.3	9.6	11.6
Thiazide diuretics (pct of patients)	2.1	2.8	2.9	3.1	4.1
Protease inhibitors (pct of patients)	.09	.08	.15	.05	.29
Mean (SD) dollars of above drugs per patient per month	23.8 (48.4)	42.2 (92.6)	40.1 (152.2)	41.2 (112.9)	37.4 (75.9)
Substance abuse/depend (percent)	3.5	5.0	6.1	5.4	4.9
Prior weight gain problem (percent)	1.9	2.6	2.4	3.5	3
Antipsych monotherapy (percent)	NA	80.4	78.3	73.4	66.3

Switch from other antipsych (percent)	NA	17.4	20.6	35.3	26.6
Type of insurance coverage (percent)					
HMO	47.7	51.9	50.4	47.4	50.9
Preferred provider	25.4	21.2	21.8	25.3	21.1
Point of service	16.9	13	13.3	14.8	12.5
Indemnity	5.1	4	4.4	5.4	5.4
Other	4.9	9.9	10.1	7.1	10.1

NA means "not applicable."

Table 2. Frequency of Diabetes Among Antipsychotic Categories by Treatment Duration and Dose – Weaker Versus Stronger Study Designs

Group	Weaker study design: no screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required		Stronger study design: screening for preexisting diabetes at 8 months prior to observation/treatment, diabetes identified with prescription claims only, and monotherapy required	
	N	Pct diab.	N	Pct diab.
Without antipsychotic treatment				
≤4 months observation	3124	3.14	664	0.00
>4≤8 months observation	13578	4.40	11351	.45
>8≤12 months observation	9078	5.56	8789	.79
>12≤20 months observation	4325	7.49	4165	1.49
> 20 montha observation	3158	7.19	3075	2.15
Average		5.56		.98
		All Dose	**Levels**	
Risperidone				
≤4 months observation/duration	4453	6.15	2868	.66
>4≤8 months observation/duration	3730	7.86	2326	.82
>8≤12 months observation/duration	1857	7.92	1143	1.22
>12≤20 months observation/duration	1602	9.99	940	1.70
> 20 montha observation/duration	785	12.61	356	2.25
Average		8.91		1.33
Olanzapine				
≤4 months observation/duration	4809	5.51	3119	.51
>4≤8 months observation/duration	3757	7.00	2313	1.17
>8≤12 months observation/duration	1744	9.12	1040	2.12
>12≤20 months observation/duration	1496	11.70	815	3.44
> 20 montha observation/duration	766	13.84	344	6.10
Average		9.43		2.67
Quetiapine				
≤4 months observation/duration	2336	5.91	1453	.62
>4≤8 months observation/duration	1994	8.48	1171	.51

>8≤12 months observation/duration	979	8.17	575	.70
>12≤20 months observation/duration	791	9.99	436	1.61
> 20 montha observation/duration	376	12.23	168	1.79
Average		8.96		1.05
Conventionals				
≤4 months observation/duration	2085	7.43	1065	.94
>4≤8 months observation/duration	1639	10.49	783	.89
>8≤12 months observation/duration	857	12.49	386	3.37
>12≤20 months observation/duration	794	16.37	331	3.02
> 20 montha observation/duration	468	14.32	161	8.70
Average		10.82		3.38
		Low	**Dose**	
Risperidone				
≤4 months observation/duration	1314	5.86	985	.91
>4≤8 months observation/duration	1476	6.91	1045	1.05
>8≤12 months observation/duration	773	6.99	531	.75
>12≤20 months observation/duration	633	7.74	421	1.66
> 20 montha observation/duration	248	9.68	135	1.48
Average		7.44		1.17
Olanzapine				
≤4 months observation/duration	1038	5.30	773	.39
>4≤8 months observation/duration	1228	6.84	895	1.45
>8≤12 months observation/duration	548	8.39	390	1.79
>12≤20 months observation/duration	449	10.25	278	1.80
> 20 montha observation/duration	201	9.95	116	3.45
Average		8.15		1.78
Quetiapine				
≤4 months observation/duration	705	5.25	525	.76
>4≤8 months observation/duration	813	8.12	586	.85
>8≤12 months observation/duration	402	6.97	291	.69
>12≤20 months observation/duration	289	10.03	197	.51
> 20 montha observation/duration	118	11.02	88	0.00
Average		8.28		.56

Conventionals				
≤4 months observation/duration	470	7.66	323	1.24
>4≤8 months observation/duration	553	8.14	357	.56
>8≤12 months observation/duration	339	10.62	199	2.01
>12≤20 months observation/duration	323	15.79	173	3.47
> 20 montha observation/duration	192	16.67	81	8.64
Average		11.78		3.18
		Medium	**Dose**	
Risperidone				
≤4 months observation/duration	1530	6.14	1083	.37
>4≤8 months observation/duration	1331	7.96	869	.69
>8≤12 months observation/duration	666	7.81	442	1.81
>12≤20 months observation/duration	561	9.45	365	1.64
> 20 montha observation/duration	309	14.89	155	1.29
Average		7.85		1.16
Olanzapine				
≤4 months observation/duration	1716	5.77	1241	.81
>4≤8 months observation/duration	1444	6.65	942	.74
>8≤12 months observation/duration	681	7.78	431	3.02
>12≤20 months observation/duration	531	10.92	333	3.60
> 20 montha observation/duration	306	12.75	148	6.08
Average		8.77		2.85
Quetiapine				
≤4 months observation/duration	712	6.46	521	.58
>4≤8 months observation/duration	605	6.12	393	0.00
>8≤12 months observation/duration	298	8.05	183	1.09
>12≤20 months observation/duration	236	7.63	151	1.99
> 20 montha observation/duration	1.36	11.03	76	2.63
Average		7.86		1.26
Conventionals				
≤4 months observation/duration	424	7.31	262	1.53
>4≤8 months observation/duration	422	10.66	231	1.30
>8≤12 months observation/duration	220	13.18	101	4.95

>12≤20 months observation/duration	185	14.05	92	3.26
> 20 montha observation/duration	108	12.96	36	8.33
Average		11.63		3.87
		High	**Dose**	
Risperidone				
≤4 months observation/duration	1609	6.40	800	.75
>4≤8 months observation/duration	923	9.21	412	.49
>8≤12 months observation/duration	418	9.81	170	1.18
>12≤20 months observation/duration	408	14.22	154	1.95
> 20 montha observation/duration	228	12.72	66	6.06
Average		10.47		2.09
Olanzapine				
≤4 months observation/duration	2055	5.40	1105	.27
>4≤8 months observation/duration	1085	7.65	476	1.47
>8≤12 months observation/duration	515	11.65	219	.91
>12≤20 months observation/duration	516	13.76	204	5.39
> 20 montha observation/duration	259	18.15	80	10.00
Average		11.32		3.61
Quetiapine				
≤4 months observation/duration	919	5.98	407	.49
>4≤8 months observation/duration	576	11.46	192	.52
>8≤12 months observation/duration	279	10.04	101	0.00
>12≤20 months observation/duration	266	12.03	88	3.41
> 20 montha observation/duration	122	14.75	24	4.17
Average		10.85		1.72
Conventionals				
≤4 months observation/duration	1191	7.39	480	.42
>4≤8 months observation/duration	664	12.35	195	1.03
>8≤12 months observation/duration	298	14.09	86	4.65
>12≤20 months observation/duration	236	18.53	66	1.52
> 20 montha observation/duration	168	12.50	44	9.09
Average		12.97		3.34

Table 3. Odds Ratios for 12 Months of Treatment with Risperidone, Olanzapine, Quetiapine, or Conventionals Versus Psychosis Patients Untreated with Antipsychotics , Overall and Stratified by Dose - Weaker Versus Stronger Study Design

Group	Weaker study design: No screening for preexisting diabetes, diabetes identified with medical or prescription claims, and monotherapy not required*	Stronger study design: screening for preexisting diabetes at 8 months prior to observation/treatment, diabetes identified with prescription claims only, and monotherapy required*
Risperidone		
All dose levels	1.388 (1.276-1.509)	1.224 (.962-1.562)
Low dose	1.134 (.985-1.307)	1.132 (.766-1.762)
Medium dose	1.502 (1.331-1.695)	1.140 (.784-1.657)
High dose	1.568 (1.363-1.805)	1.683 (1.069-2.645)
Olanzapine		
All dose levels	1.331 (1.224-1.446)	1.858 (1.549-2.238)
Low dose	1.207 (1.041-1.401)	1.394 (.987-1.970)
Medium dose	1.262 (1.111-1.434)	1.996 (1.541-2.586)
High dose	1.511 (1.334-1.712)	2.283 (1.658-3.144)
Quetiapine		
All dose levels	1.394 (1.247-1.559)	1.087 (.742-1.612)
Low dose	1.404 (1.171-1.684)	.667 (.288-1.545)
Medium dose	1.276 (1.049-1.552)	1.279 (.760-2.151)
High dose	1.561 (1.193-1.621)	1.677 (.817-3.445)
Conventionals		
All dose levels	1.365 (1.238-1.503)	1.755 (1.381-2.221)
Low dose	1.340 (1.162-1.545)	1.753 (1.267-2.426)
Medium dose	1.353 (1.128-1.623)	2.013 (1.331-3.045)
High dose	1.391 (1.193-1.621)	1.620 (1.017-2.581)

*12 month Odds ratios with 95 percent confidence intervals.

NOTES: Logistic regressions controlled for patient age, sex, type of psychosis (schizophrenia, bipolar disorder, major depression), observation period length, use of other drugs having potential diabetogenic effects, prior excess weight problem, substance abuse/dependence, switch from other antipsychotic, and type of insurance coverage. Age, schizophrenia, observation period length, use of beta-blockers and thiazide, and prior excess weight problem were consistently significant and associated with higher odds of diabetes.