Association between atypical antipsychotic agents and type 2 diabetes: review of prospective clinical data

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Background Most evidence suggesting an association between schizophrenia, antipsychotic medications and diabetes has been based on retrospective studies not controlled for important confounders.

Aims To compare diabetogenic risk between antipsychotic medications; and to describe the limitations of current prospective data-sets.

Method Systematic review of prospective clinical data.

Results No difference in the incidence of glycaemic abnormalities between placebo cohorts and antipsychotic medication cohorts was identified. No significant difference between any of the antipsychotic medications studied in terms of their association with glycaemic abnormalities was identified. Treatment-related weight gain did not appear to increase the risk of developing diabetes.

Conclusions Diabetogenic potential ascribed to atypical antipsychotic drugs, resulting from retrospective studies, may be incorrect. Cohort sizes and incomplete sampling must preclude any definitive conclusions. Long-term, large, comparative prospective trials are needed, along with agreement upon glucose measurement of choice.

Declaration of interest C.B. is employed by Eli Lilly & Co. Ltd. B.L. has been consultant to Eli Lilly & Co. in regard to diabetes and schizophrenia.

Despite almost a century of acknowledgement that an association exists between schizophrenia and type 2 diabetes, most of the available evidence is retrospective in nature. The limitations of such retrospective data in confirming causality between any drug and any illness are well recognised. In the past 2 years several major retrospective studies have been published, which have evaluated large databases of over 150,000 patients in an effort to define the exact nature of the relationship between antipsychotic medications and type 2 diabetes (Kornegay et al., 2002; Koro et al., 2002; Sernyak et al., 2002; Buse et al., 2003; Cunningham et al., 2003). Unfortunately, no study has been able to control for all important confounders, such body mass index, gender, family history of diabetes, levels of screening for blood glucose abnormalities, severity of psychosis and diagnostic accuracy. This severely weakens the evidence and makes it hard to draw valid conclusions.

The precise definition of exactly how diabetes has been diagnosed in these studies is also unknown. The limitations of measures of fasting and random blood glucose levels in terms of sensitivity of diagnosis are now well recognised, and may be exacerbated by the difficulties of obtaining blood samples from people with schizophrenia. None of the above studies specifies how many patients received a diagnosis of diabetes based on an oral glucose tolerance test (currently regarded as the gold standard).

METHOD

A systematic review was made of publicly available prospective clinical data, focusing mainly on studies with placebo cohorts.

RESULTS

Establishing true prevalence rates

Recent cross-sectional epidemiological studies have clearly demonstrated that in order to establish true prevalence figures for both type 2 diabetes and impaired glucose tolerance, it is essential to undertake some form of blood glucose testing to confirm the diagnosis (Cohn et al., 2002; Ryan et al., 2003; Subramaniam et al., 2003). None of the retrospective epidemiological studies conducted to date reported the numbers of patients within each cohort who had been actively screened for blood glucose abnormalities, and some studies (Buse et al., 2003; Cunningham et al., 2003) used the prescription of anti-diabetic medication as a proxy for a diagnosis of diabetes. Because around a quarter of patients manage their type 2 diabetes with dietary adjustment and lifestyle changes alone, this approach is likely to significantly underestimate the true prevalence of diabetes in any population.

Subramaniam et al. (2003) provide unequivocally evidence for the importance of blood glucose screening when attempting to establish the prevalence of diabetes and impaired glucose tolerance. These investigators undertook a chart review of 607 patients with chronic schizophrenia (all receiving typical antipsychotic medication such as chlorpromazine and haloperidol), and found a prevalence of type 2 diabetes of 4.9%. Patients known to have diabetes were then excluded from any further analysis in this study. After informed consent was given by 194 of the remaining patients, a fasting blood glucose level was assessed and an oral glucose tolerance test (OGTT) was performed. The prevalence of previously unrecognised type 2 diabetes was found to be 16.1%, taking the true prevalence rate in the study population to around 21%. A further 31% of patients were found to have impaired glucose tolerance. Comparative prevalence figures in the general population are reported to be 1.2–6.3% for diabetes and 5.2–11.8% for impaired glucose tolerance (Gourdy et al., 2001; Ryan et al., 2003), the latter data being age-adjusted (35–64 years) data from a relatively recent study (1995–1997) in France (Gourdy et al., 2001). Cohn et al. (2002) studied another group of patients with schizophrenia, and found that 67% of true glycaemic abnormalities were only uncovered following an OGTT. As in other studies, most patients with previously unrecognised diabetes had impaired glucose tolerance. Taylor et al. (2003) described similar findings in patients with schizophrenia at the Maudsley Hospital in London. After prospective blood glucose
testing, an apparent prevalence rate of
glycaemic abnormalities (diabetes and
impaired glucose tolerance) in a population
of 607 patients rose from 8.6% to 19.4%
(D. M. Taylor, personal communication,
2003).

Citrome (2003) has highlighted an
equally important issue of differential
screening within patient populations when
patients take different antipsychotic med-
cations. In his retrospective epidemiologi-
cal study conducted in New York, Citrome
found that patients with schizophrenia
taking clozapine were far more likely to
have been prospectively screened for blood
glucose abnormalities than comparator
populations, which calls into question
the apparent finding that clozapine is
associated with the greatest risk of diabetes
of all the atypical antipsychotic agents.

These data-sets suggest that many psy-
chiatrists who do not routinely screen their
patients with schizophrenia using some
form of blood glucose testing will fail to
diagnose most cases of diabetes. Moreover,
without prospective screening for glycaemic
abnormalities, almost all cases of impaired
glucose tolerance will be overlooked.
Because it is highly likely that a significant
proportion of these patients will develop
type 2 diabetes within a few years (Alberti,
1996), lack of routine blood glucose screen-
ing in this population is a matter of grave
concern.

Confounding variables

Family history

A positive family history of diabetes should
be considered a major confounder in epi-
demiological studies of patients with
schizophrenia, because 17–30% of people
with schizophrenia have family members
with a diagnosis of type 2 diabetes (Dynes,
1969; Mukherjee et al., 1989; Cheta et al.,
1990; Lamberti et al., 2003).

The importance of a positive family
history of diabetes was demonstrated most
clearly in the recent cross-sectional preva-
ience study by Lamberti et al. (2003). It
was found that the cohort of patients with
schizophrenia who did not have a family
history of diabetes had a prevalence of
type 2 diabetes of just 10%, whereas the
cohort with a positive family history had
a prevalence of 33%.

Psychosis

Although severity of psychosis may repre-
sent a true independent risk factor for type
2 diabetes, there is an additional potential
confounder in that psychotic stress appears
to lead to transient and reversible changes
in glucose and insulin levels, and in para-
meters of insulin resistance (Shloha et al.,
2003).

Importance of an appropriate placebo group

Design difficulties encountered with retro-
spective database analyses are further com-
pounded because it is almost impossible to
obtain a valid placebo group for compara-
tive purposes. Use of the general population
as a ‘placebo’ group is far from ideal when
assessing the impact of antipsychotic
medications on the development of type 2
diabetes because of the inherently higher
risk of glycaemic abnormalities associated
with schizophrenia.

Developments in knowledge about the
clinical course and outcome of schizo-
phrenia have made it unethical to conduct
placebo-controlled studies in normal
circumstances. Lieberman et al. (2003)
found that in a prospective randomised
controlled trial (RCT) with first-episode
patients given either chlorpromazine or
clozapine, longer duration of untreated psy-
chosis was associated with lower odds of
achieving remission. Even in studies that
included a placebo group, the protocol
design is such that the placebo cohorts
are much smaller than the comparator
groups (Meehan et al., 2001; Wright et al.,
2001).

Several recent studies assessing novel
molecules in the treatment of schizophrenia
have, nevertheless, been able to use placebo
groups (Rein & Arvantis, 2003). Although
small, these placebo groups can provide
valuable data on blood glucose levels prior
to antipsychotic drug administration. The
Food and Drug Administration (2003) and
Sowell et al. (2003) give other examples of
data-sets that include placebo cohorts from
prospective placebo-controlled studies such
as those relating to aripiprazole.

Diabetologists emphasise that even
with intensive blood glucose monitoring
and the use of effective treatment regimens,
the typical pattern in type 2 diabetes is a
gradual worsening of glucose homeosta-
sis. Data are available from diabetes studies
in the general population and from schizo-
phrenia clinical trials that support the con-
cept of expecting a gradual worsening in
blood tolerance (Wang et al., 2003; UK
Prospective Diabetes Study Group, 1995,
1998). The UK Prospective Diabetes Study
(the largest and longest diabetes study ever
performed in patients with type 2 diabetes)
found that traditional oral monotherapy
agents (metformin and the sulphonylureas)
failed to maintain long-term blood glucose
control (UK Prospective Diabetes Study
Group, 1995). After 3 years of treatment,
half of the patients needed combination
therapy, and after 4 years, glycosylated
haemoglobin (HbA1c) concentrations had
risen to above pre-treatment levels. Data from
the same study in 1998 showed similar
findings (UK Prospective Diabetes
Study Group, 1998).

Data from prospective RCTs in patients
with schizophrenia also confirm that a
deterioration in glucose control is a com-
mon and consistent finding, and unrelated
to individual treatments (Wang et al.,
2003). Over the course of a series of clinical
trials involving olanzapine, haloperidol
and valproate (with an average duration of 7
months), 22% (15/69) of patients with
schizophrenia and 32% (6/19) of patients
with bipolar disorder needed an increase
in their antidiabetic medications, which is
consistent with historical data in people
without mental illness.

Placebo cohorts in such schizophrenia
studies allow prospective evaluations to be
made using preplanned blood glucose test-
ing. In essence, what can be measured in
these medication-free cohorts represents
the natural progression of both diabetes
and schizophrenia, combined with the
impact of lifestyle risk factors such as poor
diet, smoking and lack of exercise. These
risk factors are well recognised in the
schizophrenia population.

Prospective data collection

Value of prospective data collection

The value of data collected from prospec-
tive RCTs, where most recognised confoun-
ders can be eliminated, is clear. Patients
taking a prospective schizophrenia study
are, by necessity, screened for glycaemic
abnormalities prior to study entry, and
those with abnormal levels of blood glucose
are generally excluded. Randomisation
minimises the effects of potential confoun-
ders and reduces bias. True incidence fig-
ures for both type 2 diabetes and impaired
glucose tolerance in a particular trial can
thus be established, allowing robust com-
parisons to be made between individual
antipsychotic medications, and offering
the potential to rank all antipsychotic
medications in terms of their diabetogenic potential.

Potential limitations
Clinical trials should recruit appropriately sized cohorts in order to reduce the likelihood of spurious results. When possible, there should be clear agreement as to the major parameters to be evaluated. Groups chosen should be demographically similar to each other and representative of the population to be studied.

A specific limitation of blood glucose level evaluation in prospective studies is lack of agreement on the most appropriate tests to be used and the specific time points that create relevance to the long-term treatment of patients with schizophrenia. Where this becomes apparent in schizophrenia trials is the difficulty in obtaining fasting blood glucose levels. Very little information is currently available about the prospective use of OGTTs.

Comparisons of antipsychotics with placebo
A number of prospective placebo-controlled RCTs are reported either singly or in combination on the Food and Drug Administration (FDA) website (Food and Drug Administration, 2003), and form part of the data submitted to support the safety evaluations of aripiprazole by the FDA. Five double-masked RCTs are reported, comparing 416 placebo-treated patients and 932 aripiprazole-treated patients. In general, the short-term studies performed with aripiprazole were 4 weeks in duration and used dosages of 10–30 mg a day (Marder et al, 2002; Marder, 2003) of hyperglycaemia, are not recommended for glucose abnormalities are used in this data-set. A clear trend emerges that whatever comparison is made, there appears to be no significant difference between treatment with aripiprazole and placebo. Despite limitations associated with the placebo data from these studies (i.e. follow-up was short and individual study cohorts were small), the incidence of glucose abnormalities seen in the placebo groups was similar to that reported with each antipsychotic medication.

Comparisons between antipsychotic drugs
This data-set consists of four randomised controlled trials or series (Food and Drug Administration, 2003; Lieberman et al, 2003; Lindenmayer et al, 2003; Sowell et al, 2003) and a single cohort study in a first-episode, treatment-naïve cohort (Ryan et al, 2003). Each study or series defined 'glucose abnormality' in a different way, and the use of random blood glucose samples in some studies suggests that fasting blood glucose tests were not always feasible in these patients. Single random blood glucose tests, in the absence of symptoms of hyperglycaemia, are not recommended by the American Diabetes Association (1977), the World Health Organization (1999) or Diabetes UK for diagnostic purposes, and HbA1c levels were not available in any of these study groups. Sowell

<table>
<thead>
<tr>
<th>Table I</th>
<th>Summary of placebo-controlled, randomised prospective studies with aripiprazole (Food and Drug Administration, 2003; Marder et al, 2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose parameter</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Patients with fasting blood glucose values above upper limit of normal during study, normal at baseline (% (n/N))</td>
<td>5.5 (6/109)</td>
</tr>
<tr>
<td>Patients with random blood glucose abnormalities (% (n/N))</td>
<td>1.4 (9/648)</td>
</tr>
<tr>
<td>Patients with treatment-emergent diabetes as an adverse event (% (n/N))</td>
<td>0.2 (2/926)</td>
</tr>
<tr>
<td>Decrease in mean fasting blood glucose values from baseline (mg/dl (mmol/l))</td>
<td>0.37 (0.021)</td>
</tr>
<tr>
<td>(n=120)</td>
<td>(n=34)</td>
</tr>
</tbody>
</table>

1. Increase from <160 mg/dl to 200 mg/dl (<8.8 mmol/l to >11.1 mmol/l).
Lindenmayer et al (2003) found an incidence of abnormally high blood glucose levels of 14% (14/101) in a follow-up period of only 14 weeks (Table 2). Fasting blood glucose levels greater than 6.9 mmol/l were used as the standard definition of diabetes, and patients with existing diabetes were excluded from the study. The exceptionally high incidence of glycaemic abnormalities seen in this study can be partly explained by the nature of the study population (i.e., patients with treatment-resistant schizophrenia) and the high medication dosages used. The rates of blood glucose abnormalities observed were, however, equally distributed between the individual cohorts of patients receiving olanzapine, risperidone or clozapine.

The FDA website contains currently unpublished data from a 26-week study comparing aripiprazole and olanzapine (Food and Drug Administration, 2003). Rates of glycaemic abnormalities reported were similar in the aripiprazole (4.7%) and olanzapine (4.5%) cohorts (Table 2). No association was found between weight gain and blood glucose abnormalities. Indeed, over the 6-month study period, patients treated with olanzapine gained a mean of 3.6 kg, whereas those receiving aripiprazole lost a mean of 0.9 kg.

The final set of prospective data comes from a 12-month RCT in which 160 patients in China with first-episode schizophrenia were randomised to treatment with clozapine or chlorpromazine (Lieberman et al, 2003). Fasting blood glucose levels were tested at 3-month intervals after baseline assessment. No treatment difference was seen between the patient groups, and no incident case of diabetes was reported. Initial fasting blood glucose levels of 4.8 mmol/l in the chlorpromazine cohort and 4.7 mmol/l in the clozapine cohort rose slightly by 12 weeks to 4.9 mmol/l and 5.1 mmol/l, respectively. At 52 weeks, there was no between-group difference, with fasting blood glucose levels of 5.5 mmol/l and 5.3 mmol/l, respectively (95% CI –0.32 to 0.67; P=0.49).

Whatever the mechanism behind the emergence of diabetes in patients with schizophrenia, clearly no single risk factor is solely responsible. Although the number of individual risk factors present at baseline was shown to be an independent risk factor for treatment-emergent diabetes, the presence of weight gain (defined as an increase of at least 7% in body weight) during the trials was not found to be an independent risk factor for diabetes development (Sowell et al, 2003).

Hyperprolactinaemia may also lead to insulin resistance, and this is seen to a greater extent in patients taking risperidone than in those treated with conventional antipsychotics (David et al, 2000; Kinon et al, 2003). In a point prevalence study, Kinon et al (2003) found that the prevalence of hyperprolactinaemia in female patients taking risperidone was 88% v. 47.6% in those taking conventional antipsychotics. David et al (2000) report data from Purdon et al (2000) over 54 weeks showing that prolactin levels in those treated with risperidone had risen by a mean of 79.8 µg/l in comparison with 17.1 µg/l in those taking haloperidol (P<0.001). Nevertheless, even when allowing for the spectra of antipsychotic-associated weight gain (higher with olanzapine and clozapine, lower with aripiprazole and quetiapine) seen with all atypical antipsychotics, other than maybe ziprasidone (Taylor & McAskill, 2000; Taylor et al, 2003), and hyperprolactinaemia (higher with risperidone and amisulpride, lower with olanzapine and quetiapine), it is difficult to propose a unifying mechanism to explain why patients with schizophrenia might develop diabetes. Certainly, factors associated with schizophrenia itself probably account for many cases.

Prospective data from treatment-naive patients with first-episode schizophrenia suggest that glycaemic abnormalities might be present prior to the initiation of any antipsychotic treatment (Ryan et al, 2003). In a study of 26 patients with schizophrenia, 4 patients (15%) were found to have impaired glucose tolerance, in contrast to no patient in the control group (Ryan et al, 2003). The additional finding of raised cortisol levels and insulin resistance in the treatment-naive patients, combined with data from the same group showing that they had 3.4 times as much visceral fat as the control group, lends support to the hypothesis that schizophrenia itself might lead to raised cortisol levels and insulin resistance and this, in turn, might lead to the metabolic syndrome (Ryan & Thakore, 2002).
In summary, in all the prospective RCTs and prospective cohort studies conducted to date, no difference has been reported between the antipsychotic medications in terms of their association with glucose abnormalities. The evaluation and comparison between different antipsychotics of numbers of incident cases of diabetes proves difficult owing to the small numbers of such incident cases. A lack of demographic data also hinders any extrapolation to the wider general population of patients with schizophrenia.

**Prosp ective case series**

Three case reports or series can be found in the literature involving patients with diabetes who have started treatment with atypical antipsychotic medications. Yu et al (2002) described 22 patients known to have diabetes in whom no worsening of diabetic control was seen after antipsychotic treatment was begun. Indeed, in 4 of the 11 patients prescribed olanzapine, improvements in glucose control were seen; one patient was switched from insulin to oral hypoglycaemic therapy. Lindenmayer et al (2003) reported that in their cohort, 5 out of 7 patients known to have diabetes showed improved glucose control after beginning treatment with atypical antipsychotic medications. Green (2003) described a female patient who, by improving her mental health with olanzapine, was able to improve her glucose control.

**DISCUSSION**

Currently available prospective clinical data assessing glucose control in patients with schizophrenia being treated with antipsychotic medications does not support any difference in diabetogenic potential between the atypical antipsychotic drugs that have been studied. Indeed, where placebo data have been available, no difference in the rates of emergence of glucose abnormalities has been seen between placebo cohorts and cohorts receiving active drug comparators.

The prospective data available to date suggest that the diabetogenic potential previously ascribed to atypical antipsychotic drugs as a result of retrospective studies may be incorrect. Blood glucose data from placebo groups indicate that type 2 diabetes is a progressive illness, and that a natural vulnerability to diabetes in patients with schizophrenia (when combined with other lifestyle factors) may be enough to trigger glucose abnormalities in these individuals.

In all studies where comparative prospective data are available, no difference has been found in the incidence rates of type 2 diabetes over follow-up periods that have extended up to 1 year. Such data are currently available for all atypical antipsychotic medications except quetiapine and amisulpride.

No conclusion can currently be drawn regarding the incidence of diabetes in patients with schizophrenia. The incidence rates for new cases over a 6-month period are likely to be around 0.8%, as seen for aripiprazole and olanzapine (Food and Drug Administration, 2003). The findings from this review are in agreement with the opinions expressed and recommendations made recently by the FDA (further details available from the authors on request). Essentially, these recommendations for appropriate blood glucose monitoring in all patients with schizophrenia who fall into the high-risk groups (Bushe & Holt, 2004, this supplement: Discussion) seem to be timely. The reality is that this indeed means all patients with schizophrenia. The request that all manufacturers of atypical antipsychotic medication amend their prescribing information to include more warnings relating to blood glucose abnormalities in patients with schizophrenia appears to be appropriate. Further acknowledgement that background factors are present in patients with schizophrenia and are likely to complicate the issue of glucose control represents enlightened thinking.

A number of problems in the interpretation of blood glucose assessment data from studies of schizophrenia remain. There are clearly difficulties in obtaining fasting blood glucose samples from people with mental health problems. Consequently, most studies to date have used random blood glucose measurements, which are less reliable predictors of diabetes. Some studies have not yet reported their data in full, and some have used definitions of glycaemic abnormalities that do not conform to the diagnostic guidelines of international bodies such as the American Diabetes Association (1997) and the World Health Organization (1999). The data discussed do not always appear to represent the full cohort of patients who participated in the relevant clinical trial. Selection bias cannot be excluded as a cause for an individual study’s results.

The significance of impaired glucose tolerance in schizophrenia needs to be fully determined within a physical health framework that would allow patients with schizophrenia who have this abnormality to receive all necessary treatment and advice. Diabetologists have talked about undertaking diabetes prevention studies, and the high risk of diabetes and impaired glucose tolerance in patients with schizophrenia would make them an ideal study population.

There remains a pressing need for adequate, longitudinal, prospective, comparative data from patients treated with atypical antipsychotic drugs. Whether further data are required for the conventional antipsychotic agents is a matter for debate. Current recommendations from the National Institute for Clinical Excellence (2002) in the UK make it clear that all new patients and most existing patients with schizophrenia should preferably receive atypical antipsychotic medication.

The available prospective data do not help to clarify the possibility that the diabetogenic potential of atypical antipsychotic medications may be greater than for conventional agents. Any future studies will need to consider carefully the options for random blood glucose measurements as opposed to traditional fasting blood glucose testing. Clear guidelines will also be required for appropriate glucose monitoring in patients with schizophrenia, both with and without medication. Such guidelines should include recommendations about which glucose tests should be performed and how often they should be undertaken.

There is little doubt that greater awareness of the risk of diabetes and impaired glucose tolerance associated with schizophrenia will increase the workload of many health care services. Decisions need to be made about when and where the future diagnosis and management of glycaemic abnormalities should occur, and who should assume responsibility for providing these services. Further and fuller guidance (and possibly funding) for these services may be required.

**REFERENCES**


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**CLINICAL IMPLICATIONS**

- **Patients with schizophrenia are at increased risk of developing glycaemic abnormalities and should be tested routinely, whether they receive antipsychotic medications or not.**
- All atypical antipsychotic medications have been associated with impaired glucose metabolism, but there is no convincing evidence of any difference between agents and no convincing evidence that the relationship is causal.
- In the limited clinical studies published to date, there is no evidence that treatment-related weight gain is a strong risk factor for type 2 diabetes.

**LIMITATIONS**

- No comparative prospective data are currently available for quetiapine or amisulpride.
- It is difficult to obtain fasting plasma glucose levels in people with a serious mental illness such as schizophrenia, and therefore difficult to confidently categorise glucose abnormalities. The glucose tests used and the definitions of abnormality differ between studies.
- The studied cohorts are too small and have been followed for too short a time to permit any definitive statement.


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