Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications

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Aims In this retrospective analysis, we assessed the short-term risk of treatment-emergent diabetes (TED) among patients with schizophrenia during clinical trials of antipsychotic medications.

Method From a non-diabetic cohort of patients with schizophrenia (n=5013), the relationship between baseline non-fasting glucose measurement, presence at baseline of risk factors for diabetes, weight gain and therapy assignment on the risk of treatment-emergent diabetes were assessed.

Results At the baseline assessment, about a third of patients identified with TED during treatment had non-fasting glucose levels over 7.8 mmol/l and two-thirds had multiple diabetes risk factors. Both baseline non-fasting glucose level and the presence of multiple pre-existing diabetes risk factors appeared to have a major impact on the risk of developing diabetes.

Conclusions Overall, risk factors for diabetes in patients with schizophrenia overlap those in the general population. The results also suggest that many patients identified with TED might have had pre-existing glycaemic abnormalities or a high baseline burden of diabetes risk factors.

Declaration of interest The study was sponsored by Eli Lilly and Company.

A number of reports have described new-onset diabetes in temporal association with atypical antipsychotic treatment (Koller et al, 2001, 2003; Koller & Doraiswamy, 2002). In many of the reported cases, diabetes was noted in relatively young patients (mean age about 40 years) and was diagnosed within 3-6 months of first prescription of the atypical antipsychotic medication. Evaluation of the relatedness of diabetes to atypical antipsychotic use from case reports is complicated by a number of factors, including the increasing prevalence of diabetes in the general population and data indicating that a substantial number of individuals with diabetes are undiagnosed.

Data from the National Health and Nutrition Examination Survey (NHANES III (1988–1994)) indicate that diagnosed diabetes was present in 5.1% of the US adult population (Harris et al, 1998). Subsequent reports from the Center for Disease Control have described a continued increase (about 30%) in the prevalence of diabetes during the 1990s, with the largest increase (70%) in individuals in the 30–39 year age range (Mokdad et al, 2000). Further data from NHANES III suggested that diabetes was undiagnosed in as many as a third of patients (Harris et al, 1998). Results from another large survey support this finding that approximately half of patients in Australia with diabetes were undiagnosed (Dunstan et al, 2002).

The prevalence of diagnosed diabetes in patients with schizophrenia appears to exceed that of the general population by 2-fold (Dixon et al, 2000). Patients with schizophrenia generally have poorer physical health (Brown et al, 1999; Osborn 2001), and less than adequate overall health care (Phelan et al, 2001; Wang et al, 2002a) compared with the general population. The symptoms of the psychosis itself may hinder the ability or willingness of the patient to communicate potential physical problems (Felker et al, 1996;Jeste et al, 1996). Thus, it is likely that the prevalence of undiagnosed diabetes in patients with schizophrenia is at least as high as that in the general population.

Reasons for an increased prevalence of diabetes among patients with schizophrenia remain speculative. However, Dixon et al (2000) reported that in a survey of several large databases containing medical information on patients with schizophrenia, the patients with diabetes were more likely to be older, non-White, and to have hypertension – findings consistent with those in the general population. In a more recent review of 45 published case reports of new-onset diabetes in patients receiving atypical agents, Jin et al (2002) noted that 84% of the patients were overweight at baseline assessment, 42% had a positive family history of diabetes and 49% had high-risk ethnic backgrounds (African or Hispanic). The assessment of case reports is complicated by several factors, which include inconsistent reporting of important demographic and other variables that might affect glycaemic control, reporting bias and lack of an adequate control group. In addition, case reports cannot be used to determine causal relationships between individual therapies and treatment-emergent diabetes.

Weight gain – a body mass index (BMI) of more than 25 kg/m² – is a risk factor for diabetes (Chan et al, 1994; Colditz et al, 1995), and weight gain can occur during treatment with most of the atypical antipsychotic medications (Allison et al, 1999). However, in some cases, new-onset diabetes has been reported in patients without weight gain (Koller et al, 2001; Henderson, 2002; Koller & Doraiswamy, 2002). Further, no association between weight gain and new-onset diabetes was noted in a naturalistic study of patients receiving clozapine (Henderson et al, 2000). These observations have led to further speculation that some of the atypical antipsychotic medications may increase risk for diabetes by a weight-independent mechanism.

Given the growing interest in a possible association between diabetes and antipsychotic medications, a systematic re-evaluation of risk factor profiles of patients with treatment-emergent diabetes (TED) is warranted. In this retrospective analysis of a large clinical trials database, our objectives were: (a) to identify patients with schizophrenia who exhibited TED; (b) to compare the entry characteristics, including pre-randomisation risk factor profiles, of
TED patients with those who maintained normal glucose tolerance during treatment; and (c) to examine the influence of treatment-emergent weight gain or therapy assignment on the development of TED.

**METHOD**

**Patient population and study designs**

Twenty-four studies were identified from the olanzapine clinical trial database in which patient weight and post-randomisation plasma glucose measurements were available at multiple time points. For many of the studies, the details of the study designs, patient characteristics (age, gender, race, illness characteristics), and efficacy and safety results have been previously published (Beasley et al., 1999, 2001; Tolleson et al., 1997, 1999, 2001; Tran et al., 1997). Briefly, study participants were in-patients or out-patients, aged 18–65 years, diagnosed with DSM-III-R or DSM-IV schizophrenia or related disorders (American Psychiatric Association, 1987, 1994), and had provided written informed consent after the study design and possible adverse events were described. Participation criteria were similar among the pooled trials, except that studies examining clozapine were limited to patients with treatment-refractory disease (Tolleson et al., 1999, 2001) and, in several studies comparing olanzapine with risperidone, entry criteria excluded patients with cardiovascular disease from participation in the original trial (Tran et al., 1997). All studies included a medication wash-out period of 2–9 days and a double-masked treatment period of 6–52 weeks, followed by an olanzapine open-label extension phase in some cases. For studies with medication crossover, only the initial monotherapy treatment period was included in the analyses. During the double-masked treatment period, all patients received therapeutic doses of a single antipsychotic medication (olanzapine 5–25 mg/day, haloperidol 5–20 mg/day, risperidone 4–12 mg/day, clozapine 200–600 mg/day) or placebo.

**Non-fasting glucose measurements**

Non-fasting glucose levels were analysed by Covance Inc. using a photometric chemistry analyser (Hitachi 747–20b; Roche Diagnostics, Indianapolis, Indiana, USA). The frequency of sample collection was specified by each study protocol. In general, two samples were obtained pre-randomisation and after that, samples were usually obtained weekly for the first 6 weeks and monthly or bi-weekly thereafter. In case of multiple glucose measurements for the same visit, only the maximum observation was considered. The analyses included all measurements up to and including the day after the last day of treatment.

**Classification of patients**

Patients with only baseline glucose values and those with pre-existing diabetes at entry (clinical diagnosis of diabetes, such as taking antidiabetic medications at baseline such as insulin, sulphonylureas, metformin, thiazolidinediones or α-glucosidase inhibitor) or two pre-randomisation glucose values of ≥11.1 mmol/l were excluded from the analyses. Patients (n = 27) with a single glucose measurement ≥11.1 mmol/l at entry were not excluded because these individuals lacked a confirmatory second value prior to drug assignment. A single glucose value of ≥11.1 mmol/l at entry was, however, considered suggestive of underlying dysglycaemia in the assessment of pre-existing risk factors for diabetes (see Categorical risk factors, below).

Post-baseline non-fasting glucose values were used to classify or categorise patients as exhibiting:

(a) treatment emergent diabetes (TED), defined as two non-fasting glucose values of ≥11.1 mmol/l at any time after baseline, final glucose ≥11.1 mmol/l, initiation of antidiabetic medication, or a new clinical diagnosis of diabetes;

(b) uncertain glucose tolerance (UGT), defined as two or more glucose values ≥7.8 mmol/l but one or no glucose value ≥11.1 mmol/l at any time prior to end-point;

(c) normal glucose tolerance (NGT).

A non-fasting glucose value of ≥7.8 mmol/l was chosen as the threshold for UGT based on several lines of evidence:

(a) post-prandial glucose levels of individuals with normal glucose tolerance rarely exceed 7.8 mmol/l (American Diabetes Association, 2001);

(b) individuals with glucose values of 7.8 mmol/l or greater in a standard 2h oral glucose tolerance test (OGTT) are considered to have impaired glucose tolerance (American Diabetes Association, 2002);

(c) non-fasting capillary glucose values 7.8 mmol/l or higher have reasonable sensitivity (62–65%) and specificity (95–96%) for identifying individuals with diabetes subsequently confirmed by OGTT or fasting blood sugar (Rolka et al., 2001).

**Categorical risk factors**

Patients possessing one or more of the following risk factors (American Diabetes Association, 2002) for diabetes at baseline were identified: age ≥45 years, baseline BMI ≥27 kg/m², non-White ethnicity, hypertension based on clinical diagnosis or use of antihypertensive medication, or non-fasting glucose levels suggestive of underlying dysglycaemia, e.g. a single pre-randomisation glucose value ≥11.1 mmol/l. Height was available for BMI calculation for approximately 80% of the patients. Where BMI could not be calculated, data from these patients were not included in these analyses. This analysis began before the BMI threshold as a risk factor for diabetes was lowered from 27 kg/m² to 25 kg/m² in the American Diabetes Association (ADA) Clinical Practice Recommendations (American Diabetes Association, 2002). Baseline glycaemic status of individual patients was based on the mean of two pre-randomisation measures for 4425 of the 5013 patients evaluated (88.3%).

**Statistical methods**

Data from 24 studies from the olanzapine clinical trial database were pooled for these analyses. The prevalence of baseline risk factors within the TED v. the NGT group or within the UGT v. the NGT group was compared by Fisher’s exact test. Imbalances in risk factors that are continuous variables (such as age, mean baseline glucose, maximum baseline glucose and baseline BMI) were tested by F-test. Weight gain was analysed by a last observation carried forward (LOCF) method.

To account for variation in observation times for individual therapy groups, a time-to-event analysis using the Cox proportional hazards model was employed to assess the risk of TED. Specifically, the Cox model assessed the impact of mean non-fasting glucose values or the presence of pre-existing risk factors for diabetes on the subsequent risk of being identified with
TED. The Cox proportional hazards model was also used to assess the impact of weight gain and therapy assignment on the risk of being identified with TED versus ‘not TED’ (UGT plus NGT cohorts). Because of the small number of events in individual therapy groups, treatment group results were compared between olanzapine and non-olanzapine groups (including haloperidol and placebo). Unless otherwise specified, the Cox proportional hazards model included a single test covariate (baseline mean non-fasting glucose concentration, baseline risk factors for diabetes, treatment-emergent weight gain, or therapy assignment) along with study protocol. The study protocol was also included as a stratification variable in the model to control for effects of pooling data from several clinical trials.

RESULTS

Categorisation of patients

Of the 5529 patients enrolled, 149 patients were identified with pre-existing diabetes and were excluded from the TED analysis. Post-randomisation glucose values were available for 5013 patients not known to be diabetic by diagnosis, use of antidiabetic medication, or pre-randomisation glucose values. The majority (60%) of these patients received olanzapine, followed by haloperidol (24%), risperidone (8%), placebo (4%) and clozapine (4%) (Table 1). After randomisation, most patients (n = 4637, 92.5%) appeared to maintain normoglycaemia and were considered to have NGT. Of the remaining patients, 94 (1.9%) were identified with TED and 282 (5.7%) exhibited an intermediate level of hyperglycaemia and, in the absence of more definitive testing, were considered to have UGT (Table 1). The mean post-randomisation observation time varied among the individual therapy assignments with a mean of 205 (s.d. 283) days (median 86 days), and a maximum observation time of 1775 days (Table 1). The mean weight gain for each therapy at endpoint (LOCF) is also presented in Table 1.

Risk factors for treatment-emergent diabetes

Risk factors at study entry

At study entry, mean non-fasting glucose levels for TED patients were significantly higher than for NGT patients (Table 2). Over half (61%) of the patients subsequently identified with TED had mean glucose values ≥ 6.1 mmol/l and over 30% had values ≥ 7.8 mmol/l at entry (Fig. 1). In comparison, 13% of NGT patients had mean glucose values ≥ 6.1 mmol/l and only 1.5% had values ≥ 7.8 mmol/l at entry. After randomisation of the patients with a single glucose measurement ≥ 11.1 mmol/l at entry (n = 27) who were not excluded from the analysis, 9 were categorised in the TED group, 3 were categorised in the UGT group, and 13 were categorised in the NGT group.

Patients subsequently identified as having TED were significantly older, more obese and more likely to be hypertensive, non-White, female, or have baseline dysglycaemia than NGT patients (Table 2). Sixty-four per cent of TED patients possessed multiple risk factors for diabetes compared with 21% of NGT patients (Fig. 2). Baseline characteristics of patients subsequently identified with TED demonstrated that substantial numbers had baseline non-fasting glucose levels ≥ 7.8 mmol/l or multiple pre-existing risk factors for diabetes in each of the individual treatment groups (Table 2). Approximately half of the cases of TED were identified within 3 months of trial entry. For these ‘early’ TED patients, the entry glucose was 7.9 (s.d. 2.2) mmol/l and 71% possessed at least two risk factors for diabetes at entry.

As expected, entry non-fasting glucose had a highly significant impact on the risk of TED. The risk of being identified with TED was substantially greater for patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients randomised</th>
<th>Post-randomisation glycaemic category</th>
<th>Median observation time (days (max.))</th>
<th>Weight gain at end-point (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N)</td>
<td>NGT n (%)</td>
<td>UGT n (%)</td>
<td>TED n (%)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3068</td>
<td>2799 (92.1)</td>
<td>198 (6.4)</td>
<td>19 (0.6)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1164</td>
<td>1122 (96.4)</td>
<td>33 (2.8)</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>364</td>
<td>346 (95.0)</td>
<td>13 (3.6)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>211</td>
<td>172 (81.5)</td>
<td>33 (15.6)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>206</td>
<td>198 (96.1)</td>
<td>5 (2.4)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>5013</td>
<td>4637 (92.5)</td>
<td>282 (5.6)</td>
<td>94 (1.9)</td>
</tr>
</tbody>
</table>

NA, not available; NGT, normal glucose tolerance; TED, treatment-emergent diabetes; UGT, uncertain glucose tolerance.

1. Results are shown as the number (n) and percentage (n/N) of patients within each treatment group where N = number of patients randomised.
2. Last observation carried forward.

Table 2 Comparison of entry characteristics of patients with treatment-emergent diabetes, uncertain glucose tolerance and normal glucose tolerance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TED (n=94)</th>
<th>UGT (n=282)</th>
<th>NGT (n=4637)</th>
<th>P value: TED v. NGT</th>
<th>P value: UGT v. NGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline non-fasting glucose, mmol/l (mean (s.d.))</td>
<td>7.1 (2.0)</td>
<td>6.0 (1.3)</td>
<td>5.2 (0.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years (mean (s.d.))</td>
<td>44.4 (10.3)</td>
<td>42.4 (11.4)</td>
<td>37.1 (10.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>53.2</td>
<td>65.6</td>
<td>63.7</td>
<td>0.040</td>
<td>0.566</td>
</tr>
<tr>
<td>BMI, kg/m² (mean (s.d.))</td>
<td>31.5 (6.4)</td>
<td>28.1 (5.6)</td>
<td>25.8 (5.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (% patients)</td>
<td>23</td>
<td>15</td>
<td>9</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-White ethnicity (% patients)</td>
<td>38</td>
<td>21</td>
<td>27</td>
<td>0.026</td>
<td>0.027</td>
</tr>
<tr>
<td>Baseline dysglycaemia (% patients)</td>
<td>10</td>
<td>2</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BMI, body mass index; NGT, normal glucose tolerance; TED, treatment-emergent diabetes; UGT, uncertain glucose tolerance.
with non-fasting glucose of 5.2 mmol/l; hazard ratio (HR) 31.9; 95% CI 19.6–52.0; P<0.001. Even at lower entry glucose levels, the risk of TED was still markedly elevated. For example, in patients with non-fasting glucose of ≥6.7 mmol/l, the risk of TED was elevated (HR 11.85, 95% CI 7.7–18.3; P<0.001) (Fig. 3). Further, the risk for TED was 9 times greater for patients with baseline random plasma glucose ≥6.7 mmol/l (HR 9.6, 95% CI 6.2–14.8; P<0.001).

The presence of multiple baseline risk factors for diabetes (age, BMI, non-White ethnicity, hypertension and dysglycaemia) also had a highly significant impact on the risk of being identified with TED. Without adjusting for entry non-fasting glucose in the Cox proportional hazards model, patients with two or more risk factors at entry were nearly 6 times more likely to be identified with TED (HR 5.70, 95% CI 3.6–9.0; P<0.001) than patients with one or no risk factor.

An interaction between entry non-fasting glucose value and number of pre-existing diabetes risk factors would be expected. Among patients with entry glucose values ≥7.8 mmol/l and two or more baseline risk factors for diabetes, 40% (26 of 64 patients) were identified with TED. In contrast, less than 1% (26 of 3795) of patients with ≤1 risk factor and an entry glucose <7.8 mmol/l were identified with TED. Furthermore, for patients with entry glucose <7.8 mmol/l, the likelihood of being identified with TED was greater if multiple (two or more) baseline risk factors were present: 3.2% (34 out of 1068) of patients with normal glucose and multiple risk factors were identified with TED.

Of the 94 TED patients, nine appeared to lack risk factors for diabetes at study entry. However, within this subgroup, detailed review revealed that seven patients were overweight (BMI 26.5 to 26.9 kg/m² or weight >118 kg), over 35 years of age, or had questionable entry non-fasting glucose levels (range 7.8–10 mmol/l). The two remaining patients experienced substantial weight gain (>13 kg) prior to identification of TED.

A subset of patients (n=282) with repeated post-randomisation glucose levels ≥7.8 mmol/l, but an insufficient hyperglycaemia to meet criteria for TED were identified. This appeared to be a heterogeneous group in terms of glycaemic control and because confirmatory testing data (e.g. fasting plasma glucose or OGTT) were not available to define glycaemic status more precisely, these patients were considered to have UGT and were analysed separately. Overall, this group possessed entry characteristics (Table 2) and risk factor profiles (Fig. 2) intermediate to those of the TED and NGT groups. At study entry, the mean non-fasting glucose for patients identified as possessing UGT was significantly higher than NGT patients and 37% of the UGT patients had entry glucose values ≥6.1 mmol/l, with 7% ≥7.8 mmol/l (Table 2 and Fig. 1). The number and percentage of patients identified with UGT in individual therapy groups with baseline mean non-fasting glucose ≥7.8 mmol/l or with 2 or more baseline risk factors for diabetes are presented in Table 3.

**Post-randomisation risk factors**

Patients identified as having TED gained slightly more weight than NGT patients (3.9 kg v. 2.7 kg, baseline to end-point, LOCF). However, observation times were longer for TED patients compared with the overall NGT group (data not shown). To adjust for differences in observation time, a time-to-event analysis was performed using a Cox proportional hazards
model. In this analysis, the impact of weight gain (7% or more of the patient’s initial body weight) as a categorical covariate on the risk of being identified with TED did not achieve statistical significance (HR 1.21, 95% CI 0.77–1.90, P=0.414; Fig. 3), without adjusting for baseline glucose concentration or number of pre-existing risk factors.

The risk of TED for patients receiving olanzapine vs. non-olanzapine interventions (risperidone, haloperidol and placebo) was also assessed using the Cox proportional hazards model. As there were relatively few TED events in individual non-olanzapine treatment groups, the risk of TED was evaluated between patients receiving olanzapine and a pooled cohort of patients receiving the other non-olanzapine interventions (Table 1). Because clozapine, like olanzapine, has been suggested to be more closely associated with treatment-emergent diabetes than other antipsychotic medications, clozapine was omitted from the non-olanzapine group to avoid the potential for increasing the risk of diabetes in the non-olanzapine group. Using the Cox proportional hazards model, without adjusting for baseline random plasma glucose level, baseline number of risk factors or weight gain, the short-term risk for TED patients treated with olanzapine was not significantly greater than in a pooled cohort of patients receiving risperidone, haloperidol and placebo (HR 1.46, 95% CI 0.83–2.57, P=0.186; Fig. 3). In a separate analysis that included baseline glucose concentration, number of baseline risk factors and weight gain as continuous covariates, the risk for TED was also not significantly different between the olanzapine and non-olanzapine treatment groups (P=0.220). In this multivariate analysis, both baseline glucose values and number of pre-existing risk factors remained highly significant (P<0.001) covariates, whereas treatment-emergent weight gain was not significant (P=0.311).

### DISCUSSION

In this retrospective analysis of a large clinical trial database of patients with schizophrenia, 94 cases of treatment-emergent diabetes (about 2% of the patient population) were identified. The annualised rates of TED were about 3% for patients treated with olanzapine, haloperidol and risperidone. The patients in the placebo group had an annualised TED rate of about 5%, which was not statistically different from the rate in the olanzapine treatment group. Only the patients treated with clozapine had a significantly greater rate (about 11% per year; P=0.022 vs. olanzapine). Assuming that the definition of TED used in this study truly reflects more conventional definitions of diabetes, the rates of new diabetes seen were significantly greater than the rate that would be expected in the general population (about 0.3% per year in US adults, with a peak incidence of about 1% per year in the elderly; Harris et al., 1998). Although it is possible that the definition of TED used for these analyses might have led us to underestimate the actual incidence of diabetes (see the paragraph discussing study limitations, below), the rates seen in our study are consistent with those reported in other studies of patients with schizophrenia. Annualised rates of diabetes of 1–7% have been reported in several epidemiology studies (Caro et al., 2002; Lee et al., 2002; Buse et al., 2003). The increased incidence of diabetes relative to the general population seen in these studies is present regardless of the type of antipsychotic drug.
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prescribed. In addition, the elevated rate of diabetes seen in the placebo group in our study is consistent with the significantly increased risk of diabetes in patients with mental illness (Tabata et al., 1987; Mukherjee et al., 1996; Dixon et al., 2000).

At entry into the clinical trials, patients in this study subsequently identified with TED had significantly higher non-fasting glucose levels and were much more likely to have multiple risk factors for diabetes than patients who maintained NGT. In general, TED patients were significantly older, more obese and more likely to be non-White, hypertensive or have non-fasting glucose levels suggestive of pre-existing dysglycaemia (e.g., single pre-randomisation glucose value greater than 11.1 mmol/l) at study entry than patients who appeared to maintain normal glucose levels (NGT patients). Overall, results of this analysis suggest that the majority of patients who were identified with TED were likely to have pre-existing, unrecognised glycaemic abnormalities or to have had a greater burden of pre-existing risk factors for diabetes than patients who appeared to maintain normoglycaemia.

Weight gain has been established as a risk factor for diabetes (Chan et al., 1994; Colditz et al., 1995), and weight gain has been observed during treatment with many antipsychotics (Allison et al., 1999). However, some reports have failed to demonstrate a relationship between weight gain and new-onset diabetes temporally associated with atypical antipsychotic treatment (Koller et al., 2001, 2003; Henderson, 2002; Koller & Doraiswamy, 2002). A direct effect of atypical antipsychotic medications to promote dysglycaemia has been postulated (Koller et al., 2001, 2003; Henderson, 2002); however, in a prospective randomised study of healthy volunteers (n=48) treated for approximately 2.5 weeks with olanzapine or risperidone, there was no significant change in insulin secretion or insulin sensitivity in the active therapy groups after adjusting for the impact of weight gain (Sowell et al., 2002). In the current analysis, weight gain during the trials did not have a statistically significant effect on the risk of TED, although patients with TED gained slightly more weight than those who maintained NGT. Evaluation of the relationship between weight gain and risk of diabetes might be confounded if significant numbers of individuals with unrecognised pre-existing diabetes were present or if the population was already at high risk of diabetes (Wannamethee & Shaper, 1999). Even among individuals without pre-existing diabetes but who are at high risk for the disorder, it may be difficult to measure a significant impact of further weight gain (Wannamethee & Shaper, 1999).

In our analysis, a substantial number of TED patients appeared to have a high likelihood of underlying glycaemic abnormalities or possess multiple risk factors for diabetes at baseline (for example, about a third of patients in the TED group had entry non-fasting glucose values ≥7.8 mmol/l and about two-thirds had two or more baseline risk factors). This, coupled with the relatively short duration of observation, might have contributed to the non-significant impact of weight gain in the Cox proportional hazards analysis.

There has been increasing interest in a possible differential risk for diabetes among patients taking different antipsychotic medications. When considering case reports involving patients treated with atypical antipsychotics, the largest number are for patients using olanzapine and clozapine (Henderson, 2002; Jin et al., 2002). However, there are now reports of hyperglycaemia or diabetes during treatment with risperidone (Melamed et al., 1998; Croarkin et al., 2000; Wirshing et al., 2001), quetiapine (Sobel et al., 1999; Procshyn et al., 2000) and ziprasidone (Yang et al., 2002). However, because case reports often lack information on family history and additional factors that might affect glucose regulation, are subject to reporting bias and do not have a reference or control group, causal relationships between individual antipsychotics and treatment-emergent diabetes cannot be determined from case reports. Although numbers of case reports regarding specific agents differ, results from several large retrospective cohort analyses have been inconsistent regarding differences in risk of diabetes among users of various antipsychotic medications (Gianfrancesco et al., 2002; Kornegay et al., 2002; Koro et al., 2002; Lage & Kemner, 2002; Sernyak et al., 2002; Wang et al., 2002b; Buse et al., 2003). This retrospective analysis of data from olanzapine clinical trials found that patients treated with olanzapine did not have a significantly greater risk of TED compared with a non-olanzapine cohort whose treatment did not include clozapine. This result is consistent with some reports comparing the relative risk of developing diabetes during treatment with olanzapine vs. other antipsychotics (Lage & Kemner, 2002; Smith et al., 2002; Buse et al., 2003), but not with other reports (Caro et al., 2002; Gianfrancesco et al., 2002; Koro et al., 2002; Meyer, 2002; Newcomer et al., 2002; Sernyak et al., 2002).

All retrospective analyses have inherent limitations, and several limitations specific to the current study warrant discussion. Non-fasting glucose measurements have limited sensitivity for detecting diabetes (American Diabetes Association, 2002; Rolka et al., 2001). Consequently, the current analysis probably represents a minimal estimate of the number of cases of TED. Inclusion of the NGT post-randomisation category may ameliorate this limitation to some extent in terms of the descriptive findings; however, without definitive diagnostic testing, limited conclusions regarding the true frequency of abnormal glycaemic events can be drawn from this heterogeneous group. It must also be acknowledged that reasonable alternative classification paradigms for identifying patients with TED or NGT could be employed: for example, use of 6.7 mmol/l glucose as the lower limit for UGT (Rolka et al., 2001), or exclusion of 27 patients with a single glucose value >11.1 mmol/l at study entry. In addition, alternative terminology could be applied to the post-randomisation glycaemic categories, as our TED criteria do not strictly meet ADA criteria for diabetes in absence of reported symptoms (American Diabetes Association, 2002). The clinical trials database also lacked information on prior antipsychotic treatment history and a number of important risk factors for diabetes (family history, previous history of impaired glucose tolerance or lipid profile) as these data were not collected in a systematic fashion. Therefore, the risk factor assessment may well represent an underestimate of the true pre-existing risk burden. Furthermore, some of the between-group comparisons for patients receiving different treatments were limited by differences in sample sizes and duration of observation. Finally, a major limitation is that the clinical trials used in this analysis were not intended to assess risk factors for diabetes or to look for treatment-emergent diabetes, and caution is warranted when extrapolating results of this analysis to a more general practice setting. Nevertheless, the clinical trials were randomised and masked, and unlike a number of the retrospective cohort

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studies noted above, more detailed baseline risk factor information was available for study participants. Retrospective analyses cannot definitively answer all questions regarding a potential link between schizophrenia and diabetes, nor can this type of analysis resolve whether there are subtle differences in risk for diabetes among users of different antipsychotic medications. We hope, however, that the results of this analysis may provide important preliminary information regarding antipsychotic therapy and the relative impact of pre-existing risk factors for diabetes, short-term weight gain and use of olanzapine on the short-term risk of marked glycaemic abnormalities or diabetes.

In summary, results of this retrospective analysis suggest that over the short term (generally less than 1 year’s exposure, with a median exposure time of less than 6 months), elevated baseline non-fasting glucose level and presence of multiple risk factors for diabetes appear to have a major impact on the risk of being identified with TED, whereas the impact of treatment-emergent weight gain on short-term TED risk was relatively small and was not statistically significant. Patients treated with olanzapine did not have a significantly greater risk of short-term TED compared with a pooled cohort of patients receiving risperidone, haloperidol and placebo. Overall, the risk factors for diabetes in patients with schizophrenia overlap those in the general population.

ACKNOWLEDGEMENTS

Appreciation is expressed to Drs Margaret Sowell and Cindy Coe Taylor for assistance with prepara-
tion of the manuscript. Dr Buse has received honor-
aria, consulting fees and research grants from Eli Lilly and Novartis. Since October 2001, by
institutional policy aimed at minimising potential du-
ities of interest in the conduct of clinical trials, these funds are received under contract with the Univer-
sity of North Carolina School of Medicine and are not of direct financial benefit to Dr Buse. In 2002, abstracts of this study were presented at the American Diabetes Association, the Collegium International Neuro-Psychopharmacologicum, and the Institute on Psychiatric Services annual meetings.

REFERENCES


Summary Description of Errors and Corrections

Br J Psychiatry 2004;47:S94-S101 (TED Manuscript)

Retrospective Analysis of Risk Factors in Patients with Treatment-Emergent Diabetes during Clinical Trials of Antipsychotic Medications

During further investigation of the data set post-publication, an error was observed in the treatment-emergent diabetes (TED) manuscript that led to a thorough data review. Additional errors were discovered. Despite these errors, conclusions from a reanalysis about the impact of pre-existing risk factors on TED are largely unchanged; however, the interpretation of the impact of weight gain on TED has been refined. Four errors had the most impact on the TED analyses.

First, for calculation of the categorical weight gain risk factor, three programming syntax errors were found. The syntax incorrectly used a >7% criterion as opposed to the appropriate ≥7% criterion for categorical weight gain, it incorrectly grouped patients with weight loss together with patients with weight gain as risk present, and it incorrectly set the value of the weight gain risk variable backwards (ie, if weight gain >7% then weight gain risk = 0 should have been = 1).

Second, for calculation of the overweight risk factor (body mass index [BMI] ≥27 kg/m²), the programming syntax assigned patients to the risk-absent condition if their BMI was incalculable due to missing height data. Therefore, some patients who were overweight were categorized as risk absent. This error also affected the assessment of total number of risk factors, since being overweight was one of the included factors.

Third, a placebo-like 1-mg dose group was used in the analyses when only patients with standard olanzapine dosing (5-20 mg/day) were to be included.

Fourth, when serial glucose values were examined to identify confirmatory results for identification of TED cases, laboratory data were processed based upon highest glucose value across time between visits (from 1 to 8 weeks of time) rather than using each individual actual sample, resulting in a less sensitive process for identification of TED cases.

These errors were corrected in a reanalysis of the data following the approach described in the TED Manuscript. Patients without height data were excluded for analyses that included BMI.

The main findings in the original TED manuscript were incidence of TED and risk factor impact on the risk of developing TED (hazard ratios [HR]). These TED incidence and risk factor results for the “original analysis” and “reanalysis” are summarized below (Table 1 includes full summary of incidence rates). The original analysis included 5,013 patients. The reanalysis included 4,820 patients, largely due to exclusion of the 1-mg dose group (error 3, above). The crude TED incidence for olanzapine- versus placebo-treated patients in the original analysis (2.3% vs. 1.4%, p=0.626) was similar to the incidence of TED in the reanalysis (2.3% vs. 1.0%, p=0.321).

The incidence of TED after adjusting for exposure was not statistically significantly different for olanzapine-treated patients compared to haloperidol-, risperidone-, or placebo-treated patients.
when these treatment groups were combined or when treated as separate treatment groups in either the original analysis or reanalysis. Patients treated with olanzapine had a statistically significantly lower rate of TED (after adjusting for exposure time) than clozapine-treated patients in both the original analysis (HR not reported in the original analysis, HR = 1.467, p=0.022) and in the reanalysis (HR = 1.387, p=0.018).

As reported in the original analysis, patients with baseline non-fasting glucose ≥6.7 mmol/L were at a greater risk of TED (HR = 11.85, p<0.001) than normoglycaemic patients. The reanalysis provided a similar result (HR = 12.70, p<0.0001). In patients with ≥2 baseline risk factors, the likelihood of TED was also similar between the original analysis (HR = 5.70, p<0.001) and reanalysis (HR = 7.35, p<0.0001). The risk of TED for olanzapine- vs. non-olanzapine-treated (risperidone, haloperidol, and placebo) patients was similar between the original analysis (HR = 1.46, p=0.186) and reanalysis (HR = 1.49, p=0.228), with the risk of TED for olanzapine-treated patients not statistically significantly greater than that of the non-olanzapine-treated patients.

As part of the original analyses, a multivariate analysis was performed, where the continuous variables baseline glucose, number of baseline risk factors, and weight change were included as covariates. As with the univariate analysis, the risk of TED was not statistically different between olanzapine- and non-olanzapine-treated patients (p=0.220). This finding was similar for the reanalysis (p=0.3956).

There was one analysis where the original results were not consistent with those of the reanalysis: impact of ≥7% weight gain on risk of TED. In the original analysis, ≥7% weight gain from baseline was a non-statistically significant risk factor (HR = 1.21, p=0.414). In contrast, in the reanalysis, a statistically significant temporal association was observed between >7% weight gain and a decreased risk of developing diabetes (HR = 0.538, p=0.0174). This finding does not intuitively make sense, given that being overweight is a known risk factor for diabetes.

Therefore, to further evaluate the potential contribution of treatment-emergent weight gain to the risk of TED, an alternative analysis was performed in which baseline weight was included as a fixed covariate and post-baseline weight change was utilized as a time-varying covariate. This methodology is considered to be more appropriate than the approach taken in the original analysis, which modeled weight change as a single post-baseline quantity measured up to the patient’s last observation. In this alternative analysis, a multivariate model was used that incorporated baseline weight, each of the five key risk factors for TED (age ≥45 years, baseline nonfasting glucose ≥6.7 mmol/L (120 mg/dL), non-Caucasian origin, baseline hypertension, and female gender), treatment group assignment, and time-varying weight change. In this alternative analysis, weight gain was found to be a statistically significant risk factor (HR = 1.05, p=0.0117). Baseline weight, baseline nonfasting glucose ≥6.7 mmol/L, ≥45 years of age, and non-Caucasian origin were also statistically significant risk factors. Hazard ratio estimates for female gender and hypertension at baseline did not achieve statistical significance but the hazard ratio estimates did exceed 1 (estimate is in the direction of a risk). The risk of TED for patients treated with olanzapine was not statistically significantly different from the non-olanzapine
Overall, results from the reanalysis and alternative analysis are consistent with the main conclusion from the original TED manuscript: “The majority of patients who were identified as TED were likely to have pre-existing, unrecognized glycaemic abnormalities or to have had a greater burden of pre-existing risk factors for diabetes than patients who appeared to maintain normoglycaemia.” and in addition, “…elevated baseline non-fasting glucose level and presence of multiple risk factors for diabetes appear to have a major impact on the risk of being identified with TED, whereas the impact of treatment-emergent weight gain on short-term [< 6-month median exposure] TED risk was relatively small.” The risk of TED for patients treated with olanzapine was not statistically significantly different from a pooled cohort of patients receiving comparator treatments, including placebo. Similar to the original analysis, the baseline characteristics of patients identified as UGT were intermediate to those of patients identified as TED or NGT. There is only one substantial difference from the original manuscript that should be noted. The manuscript stated that weight gain “did not have a statistically significant effect on the risk of TED.” When using a new, more appropriate characterization of weight gain as a time-varying covariate, weight gain was a statistically significant risk factor of TED.

**Table 1** Post-randomisation glycaemic categories and median observation time by therapy assignment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients Randomized (N)</th>
<th>Post-randomization glycaemic category</th>
<th>Median observation time days (max.)</th>
<th>Weight gain at end-point (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT (n (%))</td>
<td>UGT (n (%))</td>
<td>TED (n (%))</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2899</td>
<td>2650 (91.4)</td>
<td>183 (6.3)</td>
<td>66 (2.3)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1147</td>
<td>1109 (96.7)</td>
<td>31 (2.7)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>362</td>
<td>344 (95.0)</td>
<td>13 (3.6)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>208</td>
<td>170 (81.7)</td>
<td>32 (15.4)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Placebo</td>
<td>204</td>
<td>198 (97.1)</td>
<td>4 (2.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Total</td>
<td>4820</td>
<td>4471 (92.8)</td>
<td>263 (5.5)</td>
<td>86 (1.8)</td>
</tr>
</tbody>
</table>

NA, not available; NGT, normal glucose tolerance; TED, treatment-emergent diabetes; UGT, uncertain glucose tolerance.

1. Results are shown as the number (n) and percentage (n/N x 100%) of patients within each treatment group where N=number of patients randomized.

2. Last observation carried forward.
Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications

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Access the most recent version at DOI: 10.1192/bjp.184.47.s94