

## 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 as 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 antidiabetic 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 uncompromising 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%, 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 medications. In his retrospective epidemiological 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 psychiatrists 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 screening 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 epidemiological 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 prevalence 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 represent 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 parameters of insulin resistance (Shiloah *et al*, 2003).

## Importance of an appropriate placebo group

Design difficulties encountered with retrospective database analyses are further compounded because it is almost impossible to obtain a valid placebo group for comparative 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 schizophrenia 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 psychosis 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 homeostasis. Data are available from diabetes studies in the general population and from schizophrenia clinical trials that support the concept of expecting a gradual worsening in glucose 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 (HbA<sub>1c</sub>) 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 common 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 testing. 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 prospective RCTs, where most recognised confounders can be eliminated, is clear. Patients entering 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 confounders and reduces bias. True incidence figures for both type 2 diabetes and impaired glucose tolerance in a particular trial can thus be established, allowing robust comparisons 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*, 2003); one of them (study 5) lasted 6 weeks. Unfortunately, because of the way the data are presented, it is not always possible to identify the individual study being referred to. However, all the blood glucose data available from the aripiprazole studies with placebo comparators are summarised in Table 1.

Fasting blood glucose levels are reported from only one RCT (Marder *et al*, 2003). The remainder of the glucose data is limited to random blood glucose levels. Fasting blood glucose data from one short-term RCT comparing aripiprazole and placebo show similar rates of glucose abnormalities (defined as a treatment-emergent glucose level that rose to above normal limits) in the placebo group (10%, 3/29) and the aripiprazole group (6%; 6/109). The data appear to derive

**Table 1** Summary of placebo-controlled, randomised prospective studies with aripiprazole (Food and Drug Administration, 2003; Marder *et al*, 2003)

Glucose parameter	Aripiprazole	Placebo
Patients with fasting blood glucose values above upper limit of normal during study, normal at baseline (% (n/N))	5.5 (6/109)	10.3 (3/29)
Patients with random blood glucose abnormalities <sup>1</sup> (% (n/N))	1.4 (9/648)	1.3 (4/309)
Patients with treatment-emergent diabetes as an adverse event (% (n/N))	0.2 (2/926)	0.5 (2/413)
Decrease in mean fasting blood glucose values from baseline (mg/dl (mmol/l))	0.37 (0.021) (n=120)	5.03 (0.279) (n=34)

1. Increase from <160 mg/dl to 200 mg/dl (<8.8 mmol/l to ≥11.1 mmol/l).

from a partial selection of patients participating in the only 6-week study (study 5) in which fasting blood glucose data were collected on 'a limited number of patients' (Marder *et al*, 2003). No demographic data were given for the chosen population, and no explanation was offered about the choice of patients to include. From the original 420 patients randomised to receive various doses of aripiprazole (10 mg, 15 mg or 20 mg) or placebo, fasting blood glucose levels are reported for 138 patients (33%). This equates to tests on only 27% of the placebo cohorts and 35% of the patients given aripiprazole. From almost the same cohort, mean fasting blood glucose levels showed similar changes from baseline for the aripiprazole (−0.37 mg/dl (0.021 mmol/l); n=120) and placebo groups (−5.03 mg/dl (0.279 mmol/l); n=34). It is not clear at which time points the glucose measurements were taken in this study, although in study 3 blood samples were collected at baseline and on days 14 and 28 (Kane *et al*, 2002; Marder *et al*, 2003).

Random blood glucose test data are also reported from these five short-term RCTs, with abnormalities reported in 9 of 648 (1.4%) patients taking aripiprazole and 4 of 309 (1.3%) participants given the placebo. Abnormal glucose level was defined as an increase during the study from an initial value of <160 mg/dl (8.8 mmol/l) (considered a normal baseline value) to >200 mg/dl (11.1 mmol/l) (Marder *et al*, 2003). No information is given to explain why random glucose testing data were unavailable for the remaining members of the aripiprazole and placebo cohorts, or how the cohorts were selected. Demographic data for included and excluded patients are also missing.

The numbers of diabetes adverse events reported in the short-term RCTs *v.* placebo

are presented. For aripiprazole, 2 of 926 (0.2%) patients developed type 2 diabetes, and for placebo, 2 of 413 (0.5%) patients developed diabetes (Food and Drug Administration, 2003). Marder *et al* (2003) report that 932 patients were originally randomised to treatment with aripiprazole, and it is unclear why this figure falls to 926 patients later in the paper.

Although several different definitions 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 HbA<sub>1c</sub> levels were not available in any of these study groups. Sowell

*et al* (2003) amalgamated the prospectively collected random blood glucose test data from a series of 5013 patients who participated in 24 RCTs comparing olanzapine, haloperidol, risperidone and clozapine (Table 2). They reported an overall incidence rate of glucose abnormalities of 1.9% for the whole group, which is similar to the rate reported by Citrome (2003) in his retrospective review.

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 antipsychotic drugs. 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-naïve 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-naïve 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).

**Table 2** Summary of prospective randomised controlled trials with antipsychotic drug comparators: incidence of glucose abnormalities

Study	Treatment	Duration of observation (weeks)	Incidence (%)	Definition of glucose abnormality
Sowell <i>et al</i> (2003)	Olanzapine (n=3068)			Two random blood glucose values $\geq 11.1$ mmol/l at any time after baseline, final blood glucose $\geq 11.1$ mmol/l, initiation of anti-diabetic medication or new clinical diagnosis of diabetes
	Haloperidol (n=1164)			
	Risperidone (n=364)			
	Clozapine (n=211)			
	Placebo (n=206)			
	Total (n=5013)		1.9	
Lindenmayer <i>et al</i> (2003)	Clozapine (n=28)	14	21	Fasting blood glucose $> 7.0$ mmol/l
	Haloperidol (n=25)	14	4	
	Olanzapine (n=26)	14	15	
	Risperidone (n=22)	14	14	
	Total (n=101)	14	14	
Food and Drug Administration (2003)	Olanzapine (n=127)	26	4.5	Increase from baseline random blood glucose value of $< 8.8$ mmol/l to $> 11.1$ mmol/l
	Aripiprazole (n=128)	26	47	
	Total (n=255)	26		

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.

### Prospective 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.

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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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