Patients on Atypical Antipsychotic Drugs

Another high-risk group for type 2 diabetes

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ABSTRACT — Patients with schizophrenia are more likely than the general population to develop diabetes, which contributes to a high risk of cardiovascular complications; individuals with schizophrenia are two to three times more likely to die from cardiovascular disease than the general population. The risk of diabetes, and hence cardiovascular disease, is particularly increased by some of the new atypical antipsychotic drugs. Individuals taking an atypical antipsychotic drug, particularly younger patients under 40 years of age (odds ratio 1.63, 95% CI 1.23–2.16), represent an underrecognized group at high risk of type 2 diabetes. The mechanisms responsible for antipsychotic-induced diabetes remain unclear. Hypotheses include these drugs' potential to cause weight gain, possibly through antagonism at the H_1, 5-HT_{2A}, or 5-HT_{2C} receptors. Other mechanisms independent of weight gain lead to elevation of serum leptin and insulin resistance. Patients with psychoses have difficulties with diet and lifestyle interventions for diabetes and weight management. If hyperglycemia develops, withdrawal from antipsychotic medication will often be inappropriate, and a change to an atypical antipsychotic drug with lower diabetogenic potential should be considered, especially in younger patients. Management of psychoses should routinely include body weight and blood glucose monitoring and steps to promote exercise and minimize weight gain. Careful collaboration between the psychiatric and diabetology teams is essential to minimize the risk of diabetes in patients taking atypical antipsychotic medication and for effective management when it develops. This collaboration will also help minimize the already high risk of cardiovascular disease in individuals with schizophrenia.

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The number of individuals in the population receiving antipsychotic drugs is surprisingly high. The most common reason is schizophrenia, although antipsychotic drugs are widely used in other psychiatric conditions (e.g., bipolar disorder and Alzheimer's disease). Schizophrenia is far more common than is generally appreciated. For example, as many as 1 in 100 individuals in the population will suffer one or more episodes of schizophrenia in a lifetime, and for at least half of these individuals, the illness will be lifelong, probably requiring long-term medication. Schizophrenia causes social disability and also carries a high mortality—approximately twice as high as in the general population (1). It has a strikingly high suicide rate of 10% (2,3), but the most common cause of death is accelerated heart disease (two to three times that in the general population) (4). Despite its relatively low prevalence, the early age at onset and its chronic nature means that schizophrenia is an expensive medical condition to health care systems and to society in general (5,6).

The introduction of chlorpromazine after 1956 transformed the lives of many sufferers. Several major chemical classes of antipsychotic drugs were developed, principally the phenothiazines (including chlorpromazine itself), the butyrophenones (e.g., haloperidol), and the thioxanthines (e.g., flupenthixol). All these "conventional neuroleptics" are effective because they are dopamine D_2 antagonists (7), but they all have major drawbacks and contribute their own stigmata to schizophrenia. These drugs share a set of Parkinsonian-like movement-disorder side effects, the "extrapyramidal side effects" (EPSs), resulting from antagonism at dopamine D_2 receptors in the basal ganglia.

Many conventional neuroleptics cause excessive daytime sedation, and many are muscarinic antagonists, causing dry mouth, blurred vision, and constipation, and may precipitate glaucoma in older patients.

Newer drugs with lower EPS liability, the "atypical antipsychotics," are increasingly replacing the conventional neuroleptics. The reason why these drugs have better efficacy and side-effect profiles is not fully understood. One suggestion for their lower EPS liability is lower occupancy of dopamine D_2 receptors in the striatum, but the evidence for this is conflicting. However, it is widely accepted that antipsychotic activity depends on antagonism at central D_2 receptors and that the threshold for antipsychotic activity is ~65% occupancy of D_2 receptors for both conventional neuroleptics and atypical antipsychotics (8).

As early as the mid-1960s, associations between diabetes and conventional neuroleptic treatment were reported (9–18), but evidence has accumulated that the risk is even higher for some of the atypical antipsychotics. This review summarizes the evidence for a causal link, discusses some possible mechanisms, and concludes by reviewing some of the spe-

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Abbreviations: EPS, extrapyramidal side effect; FDA, Food and Drug Administration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Diabetogenic potential of atypical antipsychotic drugs*

	Date introduced	Reports of diabetes (by January 2002)	Reported cases of ketoacidosis	Diabetes resolved when drug stopped or switched	Diabetes improved when drug stopped or switched‡
Clozapine	1989†	26	10	8‡	10 (5)
Risperidone	1994	3	1§	3	—
Olanzapine	1996	21	8	10	7 (3)
Quetiapine	1998	2	1	1	1
Ziprasidone	2001	0	0	—	—

Data were compiled from surveys (29–32) plus other case reports found in Medline using the search terms "diabetes" and "antipsychotic or clozapine or olanzapine or quetiapine or risperidone or ziprasidone" published between January 1999 and January 2002 (33–42). Data in parentheses indicate cases where the dose of antipsychotic was reduced and/or diabetes was controlled with drugs and/or diet. †Reintroduced with safeguards to detect potential agranulocytosis. ‡In one of these patients, diabetes resolved completely but recurred when clozapine was restarted and did not resolve when clozapine was subsequently.stopped §Patient was HIV positive and taking a protease inhibitor concomitantly with risperidone; protease inhibitors are known to cause diabetes.

cial problems associated with management in this patient population.

IS THERE A LINK BETWEEN SCHIZOPHRENIA AND DIABETES?

— Even before antipsychotic drugs appeared, there was evidence that diabetes was more common in patients with schizophrenia (17,19–26). A more recent study of patients with schizophrenia in the U.S. Veterans Administration health care system found that the rate of diabetes was 6.2–8.7% (27), compared with 1.1% in U.S. men aged 20–39 years without schizophrenia (28). These figures probably overestimate the incidence because most patients had already been exposed to antipsychotic medication. Nevertheless, the rate is strikingly high.

DIABETES AND ATYPICAL ANTIPSYCHOTIC MEDICATION

— We carried out a search in January 2002 in Medline using the terms "diabetes" and "antipsychotic" and identified four recent systematic reviews (29–32). We then compiled a table (Table 1) summarizing the cases contained in these reports, to which we added the results of a further search using the terms "diabetes" and "antipsychotic or clozapine or olanzapine or risperidone or quetiapine or ziprasidone" for publications between January 1999 and January 2002 that had not been cited by the four reviews listed above (33–42). We included all reported cases in which sufficient detail was given for us to determine that patients had developed either clinically relevant hyperglycemia or diabetes according to internationally recognized criteria. It is worth noting that in psychiatric circles, it is now generally recognized that diabetes is a risk in patients treated with antipsychotics, particularly clozapine. This means that the number of published case reports probably underrepresents the true prevalence of antipsychotic-associated diabetes. After our survey was completed, other publications on the subject have appeared, most notably those by Koller and her colleagues, which include results from the U.S. Food and Drug Administration's (FDA) MedWatch Drug Surveillance System (43,44). We have not included their data into our analysis because the new analyses cover different periods from our analysis, use different criteria for inclusion, and give insufficient information for us to determine which cases we have already incorporated and which are new. We therefore comment on these new analyses separately.

Clozapine

Clozapine (available on a limited basis since the 1980s) was associated with 26 published case reports of diabetes. Approximately one-third of cases were reported as diabetic ketoacidosis, although not all reports give detailed values for pH, blood glucose, blood gases, bicarbonate, and ketones and may therefore not strictly fulfil the criteria for full-blown ketoacidosis. It is also worth noting that patients taking clozapine are very prone to gain weight (see WEIGHT GAIN below).

Mahmoud et al. (45) calculated that the odds of developing type 2 diabetes during the first year of treatment with clozapine are 7.44 (95% CI 1.603–34.751) compared with patients with psychosis not receiving antipsychotics. In a 5-year naturalistic study of 82 patients being treated with clozapine, 52% experienced one or more and 23% two or more episodes of hyperglycemia; 30% were diagnosed as having type 2 diabetes (46). Koller et al. (43) analyzed the U.S. FDA's MedWatch surveillance program for the period of January 1990–February 2001 and pooled these data with published cases. They found 384 cases of clozapine-associated hyperglycemia, with 242 cases of confirmed diabetes. Of these, 80 had ketosis or acidosis, and 25 patients died during hyperglycemic episodes. On the other hand, Wang et al. (47) carried out a case-control study in patients taking "psychiatric drugs" in the government-sponsored drug benefit program in New Jersey (7,227 case subjects with newly treated diabetes and 6,780 control subjects). They reported that 1.3% of individuals who developed diabetes took clozapine versus 1.7% of control subjects. Considering that the minimum age for inclusion was >20 years, the mean age of individuals in their study was 63.6 years for diabetes case subjects and 61.9 years for control subjects, marking the population as highly unusual. Nevertheless, they found no significant association between clozapine use and developing diabetes, whereas use of "nonclozapine antipsychotic medication" was significantly associated with diabetes. In addition, less than half of patients had "psychotic disorders" (rather than "affective disorders," "anxiety disorders," or "other psychiatric disorders"), and the analysis did not look for any association between diagnosis, antipsychotic use, and diabetes. This study is interesting, but more work is needed to exclude the many potential confounding factors.

Risperidone

We found three published cases of new-onset diabetes associated with risperidone since 1993 (35,41). Mahmoud et al. (45) estimated that the odds of type 2 diabetes in a patient treated with risperidone are 0.88 (95% CI 0.372–2.070) compared with patients not receiving antipsychotic drugs during the first year of treatment (i.e., not significantly different from the risk in an untreated comparable population). Switching to risperidone

may also restore near-normal glycemic control in patients who develop hyperglycemia on other atypical antipsychotic drugs (48). Risperidone tends to cause weight gain, but less so than either clozapine or olanzapine (see WEIGHT GAIN below).

Olanzapine

We found 21 case reports between 1996 and 2002 of new-onset diabetes in patients taking olanzapine, with 8 described as presenting with diabetic ketoacidosis. Mahmoud et al. (45) estimated that the odds of type 2 diabetes in the first year of treatment with olanzapine are 3.10 (95% CI 1.620–5.934) compared with the risk in patients with psychosis not receiving antipsychotics. Olanzapine is similar to clozapine in its high weight gain potential (see WEIGHT GAIN below). In 2002, the Committee on the Safety of Medicines reported a number of diabetic case subjects presenting with ketoacidosis or coma from "yellow card" reporting in the U.K. Most, but not all, also experienced weight gain. In their search of the literature up to May 2001 and from the U.S. FDA MedWatch surveillance program for the period of January 1994–May 2001, Koller and Doraiswamy (44) found 237 cases of olanzapine-associated hyperglycemia. Of these cases, 188 were new-onset diabetes, 80 involved metabolic ketosis or acidosis, and 15 patients died.

Quetiapine

We found three cases of quetiapine-associated diabetes reported since 1998, one of these presenting as diabetic ketoacidosis (Table 1). Quetiapine is intermediate between risperidone and olanzapine in weight gain potential (see WEIGHT GAIN below).

Ziprasidone

Ziprasidone was introduced in 2001, and there have not been any reports of diabetes, but its introduction is probably too recent for any drug-associated cases to have appeared in the literature. Ziprasidone has a relatively low weight gain potential (see WEIGHT GAIN below).

Comparison studies

These published reports of diabetes must be considered in relation to the relative numbers of patients treated with each of the agents. In the U.S., it has been estimated that in 2001, there were 10,547,000 prescriptions for risperidone (31.4%), 8,788,000 for olanzapine (26.2%), 4,184,000 for quetiapine (12.5%), 2,222,000 for clozapine (6.6%), and 491,000 for ziprasidone (1.5%) (49). A study of the U.S. Veterans Administration health care system analyzed the records of individuals diagnosed as having schizophrenia over a 4-month period (27). Of the 38,632 patients, 1,207 were prescribed clozapine, 10,970 olanzapine, 9,903 risperidone, and 955 quetiapine. Overall, there was a significant association between the development of diabetes and prescription of quetiapine, clozapine, and olanzapine, but not risperidone. Odds ratios (and 95% CIs) for the development of diabetes for quetiapine, clozapine, olanzapine, and risperidone were 1.31 (1.11–1.55; $P < 0.002$), 1.25 (1.07–1.46; $P < 0.005$), 1.11 (1.04–1.18; $P < 0.002$), and 1.05 (0.98–1.12; $P = 0.15$), respectively (Table 2). The strongest effect was in patients aged <40 years. In this group, the odds ratios (and 95% CIs) for the development of diabetes for clozapine, quetiapine, olanzapine, and risperidone were 2.13 (1.36–3.35; $P < 0.002$), 1.64 (1.23–2.21; $P = 0.0009$), 1.51 (1.12–2.04; $P < 0.008$), and 1.82 (1.05–3.15; $P < 0.04$), respectively.

Retrospective analyses are complicated by the possibility that duration of treatment will affect the risk of developing diabetes and that diabetes may persist after a switch to an antipsychotic drug with low diabetes-inducing liability, thus assigning an inappropriately high risk to the "benign" antipsychotic. To deal with these problems, Chue and Welch (50) controlled for duration of therapy, the reason for any switches to current therapy (e.g., weight gain), age, and concomitant medication. They looked at the effect of clozapine, olanzapine, risperidone, and conventional neuroleptic on a variety of metabolic risk factors. Although they did not give actual prevalence values, they concluded that the prevalence of diabetes was highest with clozapine, lower for olanzapine (which had a higher prevalence than conventional antipsychotics), and lowest with risperidone. Clozapine and olanzapine were associated with the

Table 2—*Logistic regression analysis of the association between atypical and conventional neuroleptics and diabetes in patients of all ages with schizophrenia with reference to diabetes in a nonschizophrenic population*

	n	Odds ratio	Rank order	95% CI	*P*
Any atypical	22,648	1.09	—	1.03–1.15	0.002
Clozapine	1,207	1.25	2	1.07–1.46	<0.005
Risperidone	9,903	1.05	4	0.98–1.12	0.15
Olanzapine	10,970	1.11	3	1.04–1.18	<0.002
Quetiapine	955	1.31	1	1.11–1.55	<0.002

Data are from Sernyak et al. (27). Low rank order equates high risk.

Table 3—*Rank order of risk of antipsychotic drugs for diabetes-related factors (in order of decreasing value), adjusted for diagnosis, duration of antipsychotic treatment, other medications, family history of diabetes, ethnicity, and smoking habits*

	Clozapine	Olanzapine	Risperidone	Conventional neuroleptics
Prevalence of diabetes	1	2	4	3
Hyperglycemia (fasting)	1	2	3	4
Hyperinsulinemia (fasting)	2	1	3	4
Elevated total cholesterol	1	3	4	2
Elevated triglycerides	1	2	4	3
Elevated BMI	2	1	3	4
Elevated plasma uric acid	1	3	2	4
Sum of ranks*	9	14	23	24

Data are from Chue and Welch (50). *The parameters assessed are not equivalent in their contribution to the pathology of diabetes or its cardiovascular complications. However, no attempt has been made to weight the sums of rank orders. Low rank order or rank sum equates high prevalence or risk.

Table 4—*Weight gain liabilities for atypical antipsychotic drugs*

	Clozapine	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Haloperidol
Wirshing et al. (59)*	6.9 ± 0.8†	6.8 ± 1.0**	5.0 ± 0.6	—	—	3.7 ± 0.6
Meyer (53)‡	5.3–6.3	6.8–11.8	2.0–2.3	2.77–5.6	0.23	—
Czobor et al. (52)§	4.2 ± 4.7‖¶	5.4 ± 4.6*†	2.3 ± 2.8‖#	—	—	0.2 ± 0.2

Data are in kilograms.*Maximal weight gain ± SE. Maximal weight gains were adjusted by controlling for age, treatment duration, and initial body weight. These weight gains occurred over treatment periods of 24–73 months, and the corrected values are adjusted for duration of treatment. The expected weight gain for the normal population not receiving antipsychotic drugs over this period would be ~2–3 kg. For clozapine, weight gain ceased at 25 months, compared with 21 months for olanzapine, 15 months for risperidone, and 18 months for haloperidol. Patients in this study were counselled about diet and exercise and were referred to a clinical nutritionist if their weights increased by >4.5 kg. †$P \leq 0.01$ vs. haloperidol (pairwise comparison, controlled for age, treatment duration, and initial weight). ‡Range of weight gain over 1 year (6 months for ziprasidone). §Mean weight gain ± SD after 14 weeks' treatment; ‖$P < 0.05$ vs. baseline; ¶$P < 0.05$ vs. haloperidol; #no significant difference from haloperidol.

greatest increase in insulin resistance, BMI, and lipids. By assigning a rank order to each of the agents and summing these ranks for all the risk factors examined (the lower the rank sum, the higher the risk), it can be concluded that the overall risk was highest for clozapine and slightly less for olanzapine. The overall risk was almost the same for risperidone and conventional neuroleptics (Table 3).

Koro et al. (51) used a population-based nested case-control design to examine the data held on >3.5 million patients in England and Wales over a 13-year period. Olanzapine significantly increased the risk of diabetes compared with no antipsychotic (adjusted odds ratio 5.8 [95% CI 2.0–16.7]). The risk associated with risperidone was less (2.2 [0.9–5.2]). They also found a small increase in risk associated with conventional neuroleptics (1.4 [1.1–1.7]). The risk associated with olanzapine was also significantly increased compared with conventional neuroleptics (4.2 [1.5–12.2]), whereas the risk with risperidone was not significantly greater than that with conventional neuroleptics (1.6 [0.7–3.8]).

MECHANISMS FOR ANTIPSYCHOTIC-ASSOCIATED DIABETES

Weight gain

Weight gain is common with conventional neuroleptics and atypical antipsychotics (52,53), and excessive body weight is a clearly established risk factor for type 2 diabetes (54–56). It is tempting to think that antipsychotic-induced diabetes is a consequence of weight gain. For example, clozapine and olanzapine have the highest propensity to cause both weight gain and diabetes (Table 4) (52,53,57,59). However, patients taking antipsychotic drugs can develop diabetes without significant weight gain (60) or can lose weight (61). Furthermore, their diabetes usually improves rapidly when the antipsychotic drug is withdrawn, without significant reduction in body weight, and often recurs rapidly if the drug is started again.

Cagliero et al. (62) used a frequently sampled intravenous tolerance test to investigate the acute effect of clozapine, olanzapine, and risperidone on insulin resistance in a small group of nonobese patients (BMI <30 kg/m^2 at baseline) with schizophrenia. Clozapine produced significantly higher 20-min glucose levels than risperidone, and individuals taking risperidone had a significantly higher insulin sensitivity than those taking olanzapine or clozapine. Newcomer et al. (63) performed modified oral glucose tolerance tests in patients with schizophrenia and healthy control subjects matched for BMI and age. Compared with patients taking conventional neuroleptics or untreated normal control subjects, olanzapine and clozapine produced significant elevations in plasma glucose. Risperidone, however, only produced significant elevations when compared with untreated control subjects.

Intriguingly, a number of the reported cases of new-onset diabetes associated with atypical antipsychotic use are described as presenting with diabetic ketoacidosis, although most did not ultimately need insulin. Few of the reports give detailed clinical and laboratory information, but some of the patients were clearly very ill.

These observations suggest a direct metabolic effect rather than an indirect effect secondary to weight gain. It is possible that the apparent correlation between weight gain potential and diabetogenicity results from a common pharmacological action rather than diabetes being an indirect effect caused by weight gain.

Receptor antagonism

The antipsychotic activity of both atypical and conventional antipsychotics is mediated by antagonism at central dopamine D_2 receptors (7,8). Consequently, if diabetes were related only to antagonist potency at D_2 receptors, all antipsychotics would be expected to have similar diabetes-inducing potential. This is clearly not the case.

The dosages of antipsychotic drugs differ greatly, but the effective antipsychotic concentration in plasma or cerebrospinal fluid is closely correlated with their antagonist potency at D_2 receptors (8). To compare the receptor profiles of the different antipsychotic drugs, it is therefore necessary to examine their potencies at different receptors relative to their potencies at the receptors through which their antipsychotic effects are primarily mediated—namely D_2 receptors (8). No clear patterns emerge (Table 5).

Antagonism at 5-HT receptors. High antagonist potency at 5-hydroxytryptamine 5-HT_{2A} receptors combined with slightly lower potency at D_2 receptors may be one prerequisite for the low EPS liability and extra efficacy of the atypical antipsychotics (Table 5) (64). It is unlikely to be the reason for antipsychotic-induced diabetes, however, because risperidone has a 5-HT_{2A}/D_2 potency ratio similar to that of clozapine and olanzapine, but has lower propensity to cause diabetes.

5-HT_{2C} receptors are probably involved in the regulation of food intake

Table 5—*Potency of antipsychotic drugs at different receptors*

	Risperidone (1–5 mg/day)		Haloperidol (5–10 mg/day)		Olanzapine (5–15 mg/day)	
	K_i (mol/l)	Relative potency vs. D_2 receptors	K_i (mol/l)	Relative potency vs. D_2 receptors	K_i (mol/l)	Relative potency vs. D_2 receptors
D_2	4.07×10^{-9}	1	2.04×10^{-9}	1	63.10×10^{-9}	1
H_1	33.11×10^{-9}	0.123	$1{,}202.26 \times 10^{-9}$	0.0017	1.20×10^{-9}	52.5
5-HT_{1A}	426.58×10^{-9}	0.0096	$1{,}621.81 \times 10^{-9}$	0.0013	$3{,}235.94 \times 10^{-9}$	0.020
5-HT_{2A}	0.41×10^{-9}	10.0	302.00×10^{-9}	0.0068	2.34×10^{-9}	26.9
5-HT_{2C}	75.86×10^{-9}	0.054	*	*	18.20×10^{-9}	3.47
ACh_m	*	*	$3{,}467.37 \times 10^{-9}$	0.00059	54.95×10^{-9}	1.15
α_1-Adrenoceptors	2.45×10^{-9}	1.66	26.30×10^{-9}	0.078	57.54×10^{-9}	1.10
α_{2A}-Adrenoceptors	21.88×10^{-9}	0.19	$1{,}047.13 \times 10^{-9}$	0.0020	426.58×10^{-9}	0.15

Absolute values are given as K_i values (mol/l): the higher the K_i, the lower the potency. However, to take into account the different dosages, it is more useful to compare the potencies of these drugs in terms of their potency at the receptors through which their antipsychotic activity is mediated—namely D_2 receptors. Values of relative potency <1.0 therefore mean that the drug has lower potency at that receptor type than at D_2 receptors, and, conversely, values >1.0 mean that the drug is more potent at that receptor than at D_2 receptors. Typical daily doses are also included. Data are from Leysen et al. (64). *Potency at this receptor was too low to measure.

(65). Relative antagonist potency at 5-HT_{2C} receptors roughly matches weight gain potential, except perhaps for ziprasidone and quetiapine (Table 5). Antagonism at 5-HT_{2C} receptors is therefore an appealing explanation for clozapine- or olanzapine-induced weight gain and diabetes. However, two 5-HT_{2C}–selective agonists, (+/−)-2,5-dimethoxy-4-iodoamphetamine and α-methyl-5-HT, both cause hyperglycemia rather than hypoglycemia in rats (66). If antagonism at 5-HT_{2C} receptors is involved in antipsychotic-induced diabetes, it is probably not the only mechanism.

The role of 5-HT_{1A} receptors on glucose homeostasis is complex (67–70), but 5-HT_{1A} blockade is unlikely to be responsible for new-onset diabetes because the relative potencies of atypical antipsychotics at 5-HT_{1A} receptors do not match their diabetogenic potential (Table 5).

Antagonism at histamine H_1 receptors. Antagonism at central histamine H_1 receptors has been suggested as the reason for antipsychotic-induced weight gain (59). However, quetiapine has relatively low weight gain potential (Table 4), yet is 87 times more potent at H_1 receptors than at D_2 receptors (Table 5).

Antagonism at muscarinic acetylcholine receptors. Although both clozapine and olanzapine produce significant blockade of muscarinic ACh receptors at antipsychotic doses, muscarinic ACh receptor blockade can be discounted as the cause of either weight gain or diabetes. Risperidone has no measurable affinity for muscarinic ACh receptors (Table 5) but causes some weight gain, and neither weight gain nor new-onset diabetes have been reported in psychiatric patients prescribed muscarinic antagonists for excessive EPS.

Acute pancreatitis

Several cases of new-onset diabetes attributed to clozapine and olanzapine were associated with acute pancreatitis (71). It is possible, therefore, that antipsychotic-induced diabetes results from chemical damage to the pancreas. However, diabetes associated with atypical antipsychotics is associated with hyperinsulinemia rather than failure of insulin release (46,72,73). Hyperlipidemia has been reported in several studies (46,73) and elevated serum triglycerides is an almost universal finding in type 2 diabetes (46), consistent with the view that diabetes is a complex metabolic disturbance involving carbohydrates, fats, and amino acids. Pancreatitis associated with antipsychotic use could therefore be an indirect effect caused by hyperlipidemia.

Insulin resistance

Dwyer et al. (74) have shown that some antipsychotics inhibit glucose transport into PC12 cells in culture and increase cellular levels of the glucose transporter isoforms GLUT1 and GLUT3. This scenario would lead to hyperglycemia, which in turn would cause a homeostatic increase in insulin release. Prolonged hyperinsulinemia could eventually lead to insulin resistance and further hyperglycemia as a result of downregulation of insulin receptors.

Leptin

Leptin levels are elevated in patients with antipsychotic-induced new-onset diabetes (75,76) and in many patients taking clozapine or olanzapine who have not been diagnosed with diabetes (72,77). Leptin is released from adipocytes and is believed to reduce appetite and stimulate catabolism of fat and/or inhibit fat synthesis in adipocytes, although serum levels are elevated in obese humans, indicating leptin resistance (78). However, the rapidity and the disproportionate magnitude of the increase in leptin levels when clozapine is started (75,76) suggest that it may be a direct effect and not a response to antipsychotic-induced weight gain. Raised leptin and subsequent downregulation of hypothalamic leptin receptors or altered transport dynamics could explain the weight gain and diabetes in patients taking certain antipsychotics (72). Against this are the results of a study comparing leptin levels in 59 patients with chronic schizophrenia with those from a group of healthy subjects matched for sex, age, and BMI (79). There was no difference between leptin levels in patients taking chronic antipsychotic medication (37 conventional and 17 atypical) and matched control subjects. The relevance of this is uncertain because of the small numbers of patients taking atypical antipsychotics. A definitive study of the putative correlation between antipsychotic intake and leptin would require an antipsychotic-naive population, a control group given placebo, and several test groups each given different antipsychotics with different diabetes-inducing

Table 5—*Continued*

Clozapine (200–450 mg/day)		Quetiapine (300–450 mg/day)		Ziprasidone (20–160 mg/day)	
K_i (mol/l)	Relative potency vs. D_2 receptors	K_i (mol/l)	Relative potency vs. D_2 receptors	K_i (mol/l)	Relative potency vs. D_2 receptors
177.82×10^{-9}	1	724.44×10^{-9}	1	6.76×10^{-9}	1
1.07×10^{-9}	166.0	8.32×10^{-9}	87.10	64.56×10^{-9}	0.11
190.55×10^{-9}	0.93	416.87×10^{-9}	1.74	5.50×10^{-9}	1.23
6.31×10^{-9}	28.2	275.42×10^{-9}	2.63	2.09×10^{-9}	3.24
12.59×10^{-9}	14.1	$2{,}454.71 \times 10^{-9}$	1.10	6.46×10^{-9}	1.05
33.11×10^{-9}	5.37	$1{,}071.52 \times 10^{-9}$	7.94	$2{,}454.71 \times 10^{-9}$	0.0028
22.39×10^{-9}	7.94	52.48×10^{-9}	13.8	13.18×10^{-9}	0.51
53.70×10^{-9}	3.31	$1{,}778.28 \times 10^{-9}$	0.41	186.21×10^{-9}	0.036

potentials. Nevertheless, although imperfect, the existing evidence does suggest that elevated leptin may play a part in the etiology of antipsychotic-induced diabetes (Fig. 1).

REVERSIBILITY OF ANTIPSYCHOTIC-INDUCED DIABETES

— In most reported cases of hyperglycemia or diabetes associated with antipsychotics, the antipsychotic (usually clozapine or olanzapine) was either stopped completely or substituted with another antipsychotic. The speed with which blood glucose concentrations returned to normal is not always clear in these reports. In some cases, it was remarkably quickly—within 2–3 days of stopping or switching—although sometimes oral hypoglycemic agents or insulin were used. In nearly all the reports, blood glucose levels were normal when measured 2–3 weeks after stopping the antipsychotic drug. In a few cases, hyperglycemia persisted after stopping or switching but was usually less marked than before, or the blood glucose concentration became manageable with an oral hypoglycemic agent, when insulin was previously needed (Table 1). In a survey of the literature up to 2001, Cohen (61) found 22 cases of new-onset diabetes that resolved and 6 that did not when the antipsychotic was stopped. In a survey of diabetes associated with clozapine (43), glycemic control improved after clozapine was stopped in 78% of individuals who developed diabetes; 62% of these patients no longer required hypoglycemic drugs. Of 12 patients who were restarted on clozapine, 9 developed hyperglycemia again. For diabetes associated with olanzapine, Koller and Doraiswamy (44) reported that 78% of patients had improved glycemic control once olanzapine was

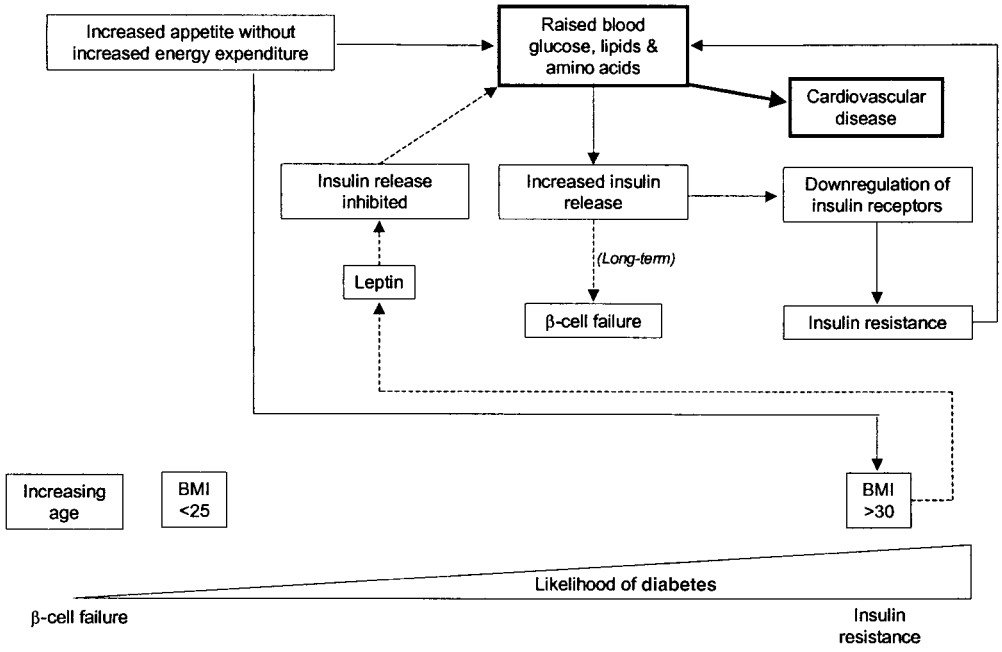

Figure 1—*Possible mechanisms for antipsychotic-induced new-onset diabetes. Possible sites of action for antipsychotics in causing diabetes include, among other possibilities, direct β-cell damage, appetite stimulation, or stimulation of leptin release.*

stopped or the dosage decreased; hyperglycemia recurred in 8 of 10 patients when olanzapine was restarted.

MANAGEMENT OF DIABETES IN PATIENTS WITH PSYCHOSIS

Relapse prevention and switching antipsychotic drugs

Diabetes is a serious medical development that requires immediate intervention and possibly lifelong management, often with increasing antidiabetic medication. However, schizophrenia is also a serious illness, the management of which usually requires continuation of antipsychotic drugs. The effective management of both conditions demands a careful and committed collaboration between the two medical teams—psychiatry and diabetology.

The course of schizophrenia is usually multiple acute episodes of frank psychosis and disability interspersed with periods of milder symptoms. Some patients may be essentially normal between acute episodes. Acute episodes tend to become more severe over time and the interval between episodes progressively shorter (80). The prognosis is definitely better in patients who continue to take antipsychotics between acute episodes, even when they are symptom free. Taken in this way, antipsychotics reduce both the frequency and intensity of relapses and therefore protect against the deterioration associated with repeated acute episodes (80,81).

Therefore, although stopping an antipsychotic drug might resolve the diabetes it has triggered, effective antipsychotic therapy, preferably with a less diabetogenic drug, must be continued to prevent psychotic relapse and long-term deterioration. Some conventional neuroleptics have low potential to cause diabetes, but replacing an atypical with a conventional neuroleptic might reduce compliance and usually results in motor side effects and increasing severity of negative symptoms, such as social withdrawal, poverty of thought, and lack of initiative. Among the atypical antipsychotics, risperidone appears to have the least propensity to cause diabetes, and time will tell whether this also applies to quetiapine and ziprasidone.

Withdrawal from clozapine is particularly difficult because a so-called rebound effect may develop, in which the patient's condition becomes worse than before the drug was started. Withdrawal of clozapine must therefore be carried out slowly over a period of several weeks or months while replacement antipsychotic is slowly introduced. As patients with clozapine are usually severely ill and have usually failed to respond to other agents, it may be necessary to persist with clozapine and manage the diabetes.

Drug interactions: antipsychotic and oral hypoglycemic medications

Clozapine is metabolized mainly by CYP1A2 and CYP3A4, olanzapine mainly by CYP1A2 and CYP2D6, quetiapine and ziprasidone almost exclusively by CYP3A4, and risperidone by CYP2D6 (82,83). All are moderately protein bound, but this does not pose a significant interaction risk. Although all the sulfonylureas bind strongly to plasma protein and can displace weak acids, such as aspirin, they do not displace the atypical antipsychotics from their binding sites (82,83). The sulfonylureas tolbutamide, glipizide, and glibenclamide are metabolized by CYP2C9, so that there is no reason to expect hepatic interference (84). None of the oral hypoglycemic agents have been reported to interact with any of the atypical antipsychotics (82,83). Metformin is excreted largely unchanged and is therefore unlikely to cause pharmacokinetic interaction with any of the atypical antipsychotics.

Managing diabetes in patients with schizophrenia or taking atypical antipsychotics

A high-fat diet combined with physical inactivity contributes to weight gain and predisposes susceptible individuals to type 2 diabetes. Lifestyle management is therefore also central to long-term care. For patients with type 2 diabetes, the major pathological hazard is accelerated coronary heart disease and stroke. The frequent smoking habit of patients with schizophrenia greatly aggravates this problem (85). It is therefore important to monitor coronary risk factors, such as hypertension and dyslipidemia regularly.

Managing diabetes in patients with schizophrenia is complicated by their lack of insight, loss of initiative, and cognitive deficits that are central features of the illness. Even in the supervised environment of psychiatric units, it can be difficult to ensure that patients follow dietary advice. Patients with active psychosis are also unlikely to be able to monitor their own blood glucose concentrations, calculate insulin doses, manage their own food intake, or self-inject. Compliance with prescribed oral hypoglycemic drugs is also likely to be poor.

Unfortunately patients with schizophrenia often find it difficult to attend outpatient clinics regularly and frequently fail to adhere to treatments. The medical outlook for a schizophrenic patient with diabetes is therefore particularly bad and is reflected in their greatly increased rates of coronary heart disease (63). Management of diabetes therefore presents special problems requiring close supervision to avoid acute problems, such as hyper- or hypoglycemia and ketoacidosis.

Although their primary use is in schizophrenia, the atypical antipsychotics are used in a variety of other illnesses: behavioral and psychological symptoms of dementias (e.g., Alzheimer's disease and Lewy body disease), bipolar disorder, and a variety of psychiatric disorders with psychotic features. Patients with dementias are older and are therefore at much higher risk of developing diabetes than young patients with schizophrenia. Atypical antipsychotics with low diabetes-inducing liability should therefore be particularly preferred in this context.

CONCLUSIONS — Patients on atypical antipsychotic medication for schizophrenia or other illnesses should be considered a high-risk group for diabetes and vascular disease. Use of atypical antipsychotics is associated with a generally high risk of type 2 diabetes, but the risk is lower with some of these drugs than with others. The mechanisms include the drug-induced weight gain that is common with antipsychotics, but there is also evidence for a direct metabolic effect. This may be related to antagonism at the 5-HT_{2C} or histamine H_1 receptors or to elevation of serum leptin beyond that induced by increased body weight alone.

Stopping the antipsychotic commonly allows the diabetes to resolve. Given the compounding effects of weight gain and diabetes on coronary heart disease (the major cause of premature death in schizophrenia), aggravated by smoking and inactivity (frequent features of schizophrenia), antipsychotics with low potential for weight gain and diabetes should be preferred, provided their efficacy in schizophrenia is adequate. Among the atypical antipsychotics, risperidone has

been shown to reduce the long-term risk of relapse compared with the conventional neuroleptic haloperidol (81).

Diabetologists and psychiatrists need to work together to monitor patients prescribed atypical antipsychotics to detect impaired glucose tolerance and manage diabetes. This will help reduce the high risk of cardiovascular disease in patients with schizophrenia. Particular attention should be paid to patients taking clozapine or olanzapine. Management of schizophrenia in general should include a greater attention to medical risks, and effective diet and exercise programs are needed.

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