# Atypical Antipsychotics and Glucose Homeostasis

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***Objectives:*** Persistent reports have linked atypical antipsychotics with diabetes, yet causative mechanisms responsible for this linkage are unclear. Goals of this review are to outline the pathogenesis of nonimmune diabetes and to survey the available literature related to why antipsychotics may lead to this disease.

***Data Sources:*** We accessed the literature regarding atypical antipsychotics and glucose homeostasis using PubMed. The search included English-language publications from 1990 through October 2004. Keywords used included *atypical antipsychotics* plus one of the following: *glucose*, *insulin*, *glucose tolerance*, *obesity*, or *diabetes*. In addition, we culled information from published abstracts from several national and international scientific meetings for the years 2001 through 2004, including the American Diabetes Association, the International Congress on Schizophrenia Research, and the American College of Neuropsychopharmacology. The latter search was necessary because of the paucity of well-controlled prospective studies.

***Study Selection:*** We examined publications with significant new data or publications that contributed to the overall comprehension of the impact of atypical antipsychotics on glucose metabolism. We favored original peer-reviewed articles and were less likely to cite single case studies and/or anecdotal information. Approximately 75% of the fewer than 150 identified articles were examined and included in this review.

***Data Extraction:*** Validity of data was evaluated using the existence of peer-review status as well as our own experience with methodology described in the specific articles.

***Data Synthesis:*** The metabolic profile caused by atypical antipsychotic treatment resembles type 2 diabetes. These agents cause weight gain in treated subjects and may induce obesity in both visceral and subcutaneous depots, as occurs in diabetes. Insulin resistance, usually associated with obesity, occurs to varying degrees with different antipsychotics, although more comparative studies with direct assessment of resistance are needed. A major problem in assessing drug effects is that psychiatric disease itself can cause many of the manifestations leading to diabetes, including weight gain and sedentary lifestyle. While studies in healthy subjects are limited and inconclusive, studies in animal models are more revealing. In the conscious canine model, some atypical antipsychotics cause adiposity, including visceral obesity, a strong risk factor for the metabolic syndrome. Furthermore, while few studies have examined effects of antipsychotics on pancreatic β-cell function, canine studies demonstrate that expected β-cell compensation for insulin resistance may be reduced or even eliminated with these agents.

***Conclusions:*** Atypical antipsychotics have been shown to contribute to weight gain, which may well reflect increased body fat deposition. Such increased fat is known to cause resistance to insulin action, although more information regarding effect on insulin action is needed. The effect of these drugs on fat distribution has been clearly shown in animal models. It is known that the normal response to insulin resistance is compensatory hyperinsulinemia, which may prevent diabetes. In animals, there is evidence that the hyperinsulinemic compensation is inadequate in the face of atypical antipsychotic agents. It remains to be examined whether failure of adequate pancreatic β-cell compensation for insulin resistance plays a central role in the pathogenesis of diabetes associated with this class of drugs.

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Diabetes is a major health problem in the United States and westernized societies, and the rate is increasing alarmingly throughout the world.[1] It is estimated that there are as many as 18 million individuals in the United States with diabetes and that half that number remains undiagnosed.[2] The increase in the rate of diabetes in this country is often explained by the so-called "obesity epidemic."[3] Obesity is a known and major risk factor for diabetes, and 80% of type 2 diabetics are overweight. The number of obese individuals has increased in virtually all parts of the United States, and it is now estimated that 56% of the population is obese. This is in contrast to 20 years ago, when the rate of obesity was 45%.[4] Reasons for the obesity epidemic are not entirely clear but have been linked to increased caloric intake due to high palatability of available foods, as well as reduced energy expenditure due to urbanization of the population.

Morbidity of obesity is related to increased risk of several diseases, of which diabetes is the most common. Obesity is a major cause of insulin resistance, and insulin resistance is an independent risk factor for type 2 diabe-

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tes. Thus, it is believed that if prevalence of obesity can be reversed in the U.S. population, the accelerating human, as well as financial, costs of diabetes could be slowed and suffering reduced. Complications of diabetes are severe and include blindness, renal failure, neuropathy, and cardiovascular disease. Unfortunately, obesity has proven difficult to treat, and most individuals revert to their pre–weight loss state. Thus, it remains a major public health goal to limit obesity and thereby slow the ascendance of diabetes in western societies.

The objective of this review is to outline the pathogenesis of nonimmune diabetes and to examine the available literature related to the relationship between atypical antipsychotics and glucose homeostasis.

## TYPES OF DIABETES

In normal individuals, the fasting glucose concentration ranges between 80 and 110 mg/dL (4.4 and 6.0 mmol/L). Overt diabetes mellitus is defined by the American Diabetes Association as fasting glucose concentration of 126 mg/dL (6.9 mmol/L) or greater.[5] There are several subgroups of diabetes types, and individual subgroups are defined on the basis of the mechanisms responsible for hyperglycemia (e.g., immune versus nonimmune causality).

### Type 1 Diabetes

Type 1 diabetes is caused by autoimmune destruction of the β-cells of the pancreatic islets. Approximately 0.5% of the U.S. population is diagnosed with type 1 diabetes, which has a rapid onset and must be treated by insulin therapy. Inappropriate therapy can result in diabetic ketoacidosis, which is associated with overproduction of ketoacids by the liver in the absence of sufficient insulin.

While insulin injection is by far the most common therapy for type 1 diabetes, recent advances in islet transplantation have proven conceptually promising.[6] The number of available human islets for transplantation appears to limit the overall application of this approach, and efforts continue to design an "artificial" pancreas in which insulin is administered automatically in proportion to need. The criterion for diagnosis of type 1 diabetes is detection of circulating antibodies, which are markers for the autoimmune process involved in β-cell destruction. Thus, antibodies to insulin, to islet cell membrane proteins, and to the protein glutamic acid decarboxylase are usually observed in the blood as the disease progresses and the β-cells are slowly destroyed.[7] The appearance of fasting hyperglycemia is associated with destruction of 80% to 90% of the β-cell mass.[8]

Prevalence of type 1 diabetes differs substantially among different countries, with very high rates in Finland and Sardinia, for example, and low rates in Italy and Japan.[1] These differences have led to the suggestion that type 1 diabetes may be an infectious disease,[9] but the role of infection remains to be proven.

### Type 2 Diabetes

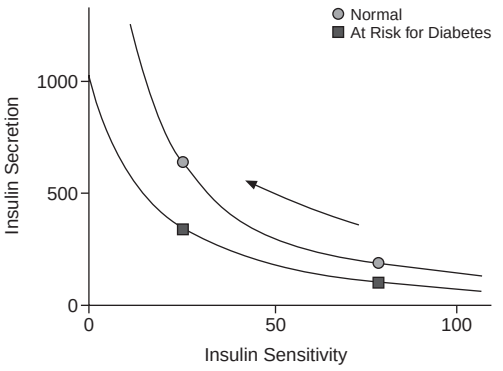
Much more prevalent in western societies is type 2 diabetes. This disease is thought by most investigators to be independent of autoimmunity, although cases of type 2 diabetes in the presence of autoimmunity have been reported.[10,11] While type 2 diabetes was previously known as "adult-onset," because of diagnosis after the age of 30, this moniker is no longer appropriate. Type 2 diabetes in prepubertal children is a frequent diagnosis, and as many as 50% of the children diagnosed with diabetes mellitus in large medical centers are free of autoimmunity and suffer from type 2 diabetes.[12]

The precise causality of type 2 diabetes is considerably less clear than for type 1. Most patients are obese, but obesity is not necessary to have this disease, and in some populations, lean type 2 diabetes is commonly observed.[13,14] Obesity is a major cause of resistance to the hormone insulin, and it has long been held that insulin resistance may in turn cause type 2 diabetes.[15] In fact, extensive resources have been expended to understand mechanisms of insulin resistance. The exact causal relationship between obesity and insulin resistance, however, has not been elucidated. Many factors may be important, including possible effects on insulin sensitive tissues (liver and muscle) of proteins secreted by adipocytes, including adiponectin, resistin, interleukin-6, and tumor necrosis factor-α.[16–19] Also potentially important are the effects of free fatty acids (FFA), which are released by adipose cells under fasting conditions and which have a higher turnover in diabetic patients.[20] FFA are known to induce insulin resistance of liver as well as skeletal muscle,[21,22] and it is plausible that the release of FFA from adipocytes, which themselves are particularly insulin resistant, may cause accumulation of triglycerides in liver and skeletal muscle and result in whole-body insulin resistance.

Which factors may be most important in the pathogenesis of obesity-induced insulin resistance is a subject of intense investigation. Is insulin resistance sufficient, however, to explain type 2 diabetes? While some investigators may still support this position,[23] the preponderance of evidence indicates that a second and possibly more important factor is critical to the development of overt type 2 diabetes. In fact, pathogenesis of type 2 diabetes has more in common with type 1 diabetes than was previously understood.[24]

Unlike in type 1 diabetes, insulin levels and the concentration of the co-secreted protein fragment C-peptide are not zero in type 2 diabetes but in fact are similar to those seen in normal subjects. The condition known as impaired glucose tolerance, in which fasting blood glucose is normal but 2-hour glucose following a standardized glucose ingestion is between 140 and 199 mg/dL, is

**Figure 1. Hyperbolic Relationship Between Insulin Sensitivity and Insulin Secretion**




often associated with insulin levels that are above normal values. Yet it has become clear to most investigators that people at risk for type 2 diabetes have a defect in their pancreatic β-cells.[25] To understand why insulin levels can be normal or even elevated in subjects at risk for diabetes who have a β-cell defect, it is important to consider the stereotypic relationship between insulin secretion and insulin action.

Insulin sensitivity is determined by a variety of genetic and environmental factors. There is strong evidence that this physiologic function is heritable.[26,27] Additionally, as discussed, obesity is a strong determinant,[28–32] and obesity itself is heritable.[33,34] However, many factors in the environment change insulin sensitivity during the normal vicissitudes of life, including those that reduce it (puberty, pregnancy, infection, sloth, aging) and those that increase it (exercise, weight loss, parturition). Despite these changes, the ability to dispose of a carbohydrate challenge and maintain tolerance to glucose is usually preserved. It is in those at risk for type 2 diabetes that tolerance may not be preserved. To understand type 2 diabetes, we must understand how normal glucose tolerance is maintained in nondiabetic individuals in the face of changes in insulin sensitivity.

Reduction in insulin sensitivity in normal individuals elicits a compensatory increase in insulin secretion. In fact, a hyperbolic relationship exists between insulin sensitivity and the sensitivity of the β-cell to stimulation by glucose, as illustrated in Figure 1. Thus, a given reduction in insulin sensitivity elicits a proportionately equal but opposite change in insulin secretory function; in fact, the product of insulin secretion times insulin sensitivity is constant for any normal healthy individual. We defined this product as the parameter *disposition index* (DI).[35] Because the DI is a measure of the ability of the β-cells to compensate for insulin resistance, and thus maintain glucose tolerance within normal bounds, it is an appropriate designation for β-cell health. In fact, there is strong evidence that insulin resistance by itself will not cause diabetes, provided that an adequate β-cell response can be mounted.[36]

On the other hand, it has been shown in a large group of studies that reduction in the DI is associated with risk for type 2 diabetes mellitus. Thus, subjects with impaired glucose tolerance have a 50% to 60% reduction in DI compared to individuals with normal glucose tolerance.[35,37,38] Likewise, women with so-called gestational diabetes, which normalizes at parturition but still represents a sizable risk factor for type 2 diabetes, have a 68% reduction in DI compared to normal women.[39]

Thus, it has been clearly demonstrated that individuals who are at risk for type 2 diabetes have a reduced DI, which is representative of a latent β-cell defect. The defect is not reflected in fasting plasma insulin values, which are often close to normal. This defect becomes increasingly profound, until it results in the development of hyperglycemia. The DI is progressively decreasing during this phase. Thus, type 2 diabetes can be understood as a disease in which insulin resistance is associated with a subtle latent β-cell defect, which only becomes obvious after β-cell function diminishes to approximately 20% of normal. At that juncture, the β-cell is no longer able to compensate at all for progressive insulin resistance, and hyperglycemia ensues. Therefore, it is generally understood that most cases of type 2 diabetes reflect a "2-hit" phenomenon: insulin resistance plus progressive β-cell defect.[36,40–42] That the insulin resistance itself contributes to the demise of the β-cell is evidenced by studies in which prevention of the progression of insulin resistance by thiazolidinediones also prevented the death march of the β-cells.[43]

## METHOD

***Data sources.*** We accessed the literature regarding atypical antipsychotics and glucose homeostasis using PubMed. The search included English-language publications from 1990 through October 2004. Keywords used included *atypical antipsychotics* plus one of the following: *glucose*, *insulin*, *glucose tolerance*, *obesity*, or *diabetes*. In addition, we culled information from published abstracts from several national and international scientific meetings for the years 2001 through 2004, including the American Diabetes Association, the International Congress on Schizophrenia Research, and the American College of Neuropsychopharmacology.

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***Data extraction.*** Validity of data was evaluated using the existence of peer-review status as well as our own experience with methodology described in the specific articles. The available studies in human subjects and animal models are reviewed to describe the current understanding of the effects of atypical antipsychotics on glucose metabolism.

## ATYPICAL ANTIPSYCHOTICS AND METABOLIC PROFILE

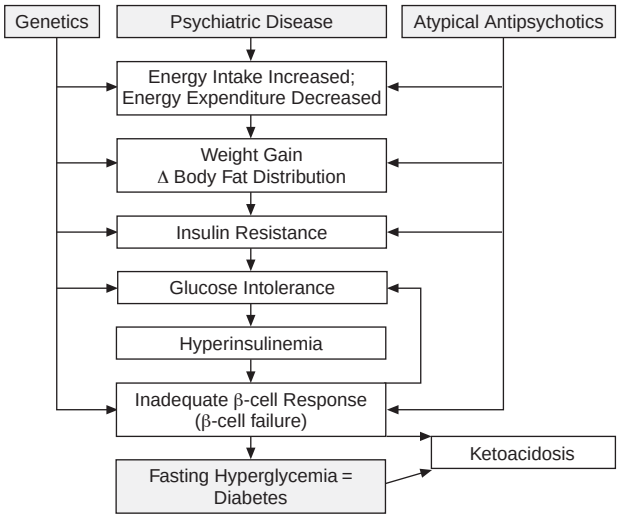
As will become clear, events occurring during the use of atypical antipsychotic therapy cause a metabolic profile with many characteristics in common with type 2 diabetes. Yet, there are important differences, not the least of which is the presence of diabetic ketoacidosis, which is very rare in cases of type 2 diabetes. Thus, the glucose intolerance that has been associated with atypical antipsychotic therapy should be understood in the context of the pathogenesis of type 1 and type 2 diabetes, as the syndrome associated with this therapy has elements of both.

### Effects of Atypical Antipsychotics on Glucose Homeostasis: Statement of the Problem

Given the complexity of the pathogenesis of nonimmune diabetes, it is a daunting challenge to understand the role that antipsychotics may play in the development of fasting hyperglycemia. It is even more difficult to accurately assess differences among the atypical agents in terms of their individual effects. The nature of the problem is illustrated in Figure 2.

Psychiatric disease itself can lead to changes in energy intake and expenditure; for example, changes in patterns of food intake and/or day-to-day activities or sleep patterns will contribute to increased storage of fat. There is some evidence that subjects with schizophrenia have greater visceral adiposity than healthy individuals,[44] although this is not a universal observation.[45] A significant body of evidence supports the visceral fat depot as being particularly well correlated with insulin resistance.[29,31] Additionally, cigarette smoking, which is almost universal in individuals with schizophrenia,[46] will exacerbate the increased resistance[47] even though smoking may reduce body weight due to reductions in appetite and increased energy expenditure.[48–50] Insulin resistance in turn will reduce glucose tolerance, which is defined as the integrated glucose concentration pattern seen after a carbohydrate meal.[36,51] The elevated glucose, and/or other factors,[52,53] provoke the β-cells to mount a greater insulin response, and insulin clearance by the liver is reduced in the insulin-resistant state. Thus, elevated fasting insulin concentrations and postload hyperinsulinemia result. As discussed, failure of β-cells to respond adequately will result in fasting hyperglycemia.

**Figure 2. Possible Pathways by Which Atypical Antipsychotic Treatment May Result in Diabetes**




Prevalence of diabetes overall has been estimated to be 2 to 3 times higher in subjects with schizophrenia.[54] Clearly obesity and psychotropic therapy may have contributed to the increased diabetes risk. Nevertheless, there could also be a component of inadequate compensation by the β-cells. Thus, even in the absence of treatment with antipsychotic medication, there must be a wide distribution in metabolic regulation among subjects with schizophrenia. Against this heterogeneous background, these pharmacologic agents can affect energy intake and/or expenditure; insulin resistance, directly or via changes in body fat distribution; and/or β-cell function. Thus, the response of any individual is determined not only by the environmental factors previously alluded to (i.e., food intake, smoking, etc.) but also by the genetic predisposition for weight maintenance,[33,34] insulin resistance,[26,27] and pancreatic function.[37,55,56]

These complex interacting factors confound the ability to assess the effects of specific treatments except in carefully controlled clinical trials. Even then, the outcome will be highly dependent on the psychiatric disease itself and its metabolic effects. It is even more challenging to evaluate potential differences among the currently available atypical antipsychotics. It is important, however, to evaluate differences because there is strong evidence that these agents differ substantially in their potential metabolic effects.

### Pathways to Diabetes With Antipsychotic Medication

It is universally agreed that many atypical antipsychotic drugs lead to increased body weight.[57] Of the commonly used agents, clozapine, olanzapine, and quetiapine appear to have the greatest effect. Less effect has been

reported overall for risperidone, with aripiprazole and ziprasidone having apparently little overall effect on body weight.[57,58] The relationship between body weight per se and specific body compartments is less clear. Even with increased food intake, which leads to increased weight, there are differential effects on the visceral adipose depot versus subcutaneous fat and lean body mass. All 3 depots increase in obese subjects but to varying degrees.[59] To compare the mechanisms of action of different atypical antipsychotics, it is important to establish the relative contributions of changes in food intake versus energy expenditure to increased caloric storage. Additionally, to evaluate risk for diabetes, it is important to establish where additional adiposity is deposited—in the intra-abdominal area or subcutaneously. A significant body of evidence has implicated the visceral or intra-abdominal fat depot as being a greater contributor not only to insulin resistance, but also to risk for cardiovascular disease, hypertension, and dyslipidemia.

Little is known regarding the ultimate cause of increased weight with antipsychotics or the distribution of excess caloric stores in the body. In rodents, clozapine and olanzapine increase food intake,[60] with fewer data supporting risperidone in this regard.[61,62] Rodents, however, have been considered a poor model for antipsychotic-induced weight gain due to extensive sedation, which will affect food intake and expenditure, and because there is a less than 1:1 relationship between the effects of different agents in rats compared to human subjects.[63]

While it is widely held that atypical antipsychotic drugs increase food intake, the data regarding energy expenditure are less clear. It has proven difficult to measure food intake and energy expenditure accurately in subjects with schizophrenia due to changes in habitation and failure to match body mass appropriately. In a single subject, energy expenditure was measured before and after 1 month of olanzapine treatment. Energy expenditure decreased 4% measured under overnight fasting conditions and 11% during a 3-hour euglycemic clamp.[64] A rough calculation suggests that this decrease could account for up to one half of the drug-induced weight gain of 6 kg observed after treatment. Use of doubly labeled water allows for 24-hour energy expenditure measurements without confining subjects.[65] Thus it would be important to measure expenditure and weight changes under controlled conditions in which food intake could be estimated. Such careful studies remain to be conducted.

An important question is how the increased stored fat is distributed in patients taking atypical antipsychotics. Use of dual-energy x-ray absorptiometry (DEXA) allows for excellent estimate of total fat as a percentage of body weight.[66] Such an approach would allow for comparison of lean versus fat body mass in the presence of drug therapy. Possibly more revealing would be the use of imaging techniques such as computed tomography (CT) scans or magnetic resonance imaging (MRI) to quantify distribution of body fat between the visceral versus the subcutaneous compartments. Clearly, preferential distribution of fat in the visceral compartment could account for greater risk of insulin resistance and, hence, of diabetes itself.

Thakore and colleagues[44] report CT scans in subjects with schizophrenia not on drug therapy (drug-naive or drug-free) versus normal lean patients. Strikingly, individuals with schizophrenia exhibited a 3-fold greater volume of abdominal fat compared to healthy control subjects. Yet, further expansion of this already enlarged abdominal compartment was not observed after 6 months of treatment with either olanzapine or risperidone.[67] While Zhang and colleagues[45] did not observe greater adiposity using MRIs performed in patients with first-episode schizophrenia, they did report substantial increases in both visceral and subcutaneous adipose stores after treatment with antipsychotics (primarily risperidone or chlorpromazine) for only 10 weeks. These provocative results deserve to be further explored. It is possible that the use of state-of-the-art MRI measurements at appropriate landmarks on the body could resolve the question of whether drug-naive patients have increased adipose stores.

## INDICATORS OF GLUCOSE DYSREGULATION

### Fasting Values

Measurement of fat content alone does not reveal insulin resistance, as various other factors impact the degree of resistance. Thus, to assess the effects of atypical antipsychotics on insulin action, some direct or indirect measure of insulin resistance must be used. Insulin resistance is often estimated from fasting glucose and insulin concentrations. Many reports have indicated fasting insulin levels in obese patients taking atypical antipsychotics that are above levels in lean normal subjects, which is not unexpected since the obese patients can be expected to be insulin resistant. For example, Melkersson and Dahl[68] report that hyperinsulinemia was recorded in over half of obese subjects taking clozapine or olanzapine. In contrast, subjects taking risperidone did not display elevated fasting insulin levels.[69] These data suggest that an elevated insulin level, which is indicative of insulin resistance, may be secondary to obesity per se.

There are several indices of insulin resistance that are based on fasting insulin level alone.[70,71] One of the most widely used is the homeostasis model assessment (HOMA) index,[70] which is equal to fasting insulin concentration × fasting glucose concentration/22.5. For example, from the Melkersson and Dahl data,[68] the HOMA index for patients taking typical antipsychotics is 3.97 versus 4.26 for patients taking clozapine, suggesting more resistance associated with clozapine. A greater difference in the HOMA index was shown in a preliminary report by

Cohn et al.[72] They reported a HOMA index of 3.1 for patients taking clozapine or olanzapine but a lower index of 2.0 for those taking risperidone, quetiapine, or typical antipsychotics grouped together. In support of this finding, Berry et al.[73] reported a 43% decrease in HOMA index in patients switched from olanzapine to risperidone.

Taken together, these latter data suggest that clozapine and olanzapine may induce moderately greater insulin resistance than other agents. However, fasting insulin level is not a direct measure of insulin resistance, and using it in an index can be misleading (c.f., reference 28). Fasting insulin concentration is determined by fasting insulin secretion, as well as insulin clearance from the circulation. Fasting insulin level is elevated in insulin-resistant states because (as discussed previously) insulin resistance provokes a β-cell response in proportion to the degree of resistance, if β-cells are normally responsive. In this context, Ryan et al.[74] recently reported that fasting insulin levels were only slightly higher than normal in drug-naive subjects with schizophrenia: 7.7 to 9.8 μU/mL. However, despite near-normal insulin levels, 15% of the 26 patients studied had fasting glucose levels in the so-called "impaired fasting glucose" range. An elevated glucose level, despite a near-normal fasting insulin level, suggests a certain degree of β-cell impairment, as an elevated glucose level did not appear to elicit an expected hyperinsulinemia. Thus, there may be a latent β-cell defect—even in patients with schizophrenia not on antipsychotic therapy.

Reports of fasting-based measures of insulin resistance and/or insulin secretory function can only be regarded as suggestive of mechanistic changes. It is well accepted in the diabetes community that more direct, although complex, methodology must be used to accurately assess changes in insulin sensitivity and/or insulin secretion. Clearly, to truly be able to compare different antipsychotics, it is requisite to utilize direct measures of insulin action and secretion.

### Glucose Tolerance

The oral glucose tolerance test (OGTT) has long been available as a diagnostic test for various prediabetic states, although its use has fallen in and out of favor over the years.[75,76] The test, in which a known dose of glucose (usually 75 g) is given orally and glucose and insulin (and sometimes C-peptide) measurements are made over 2 or more hours, yields a qualitative measure of the holistic ability of the body to dispose of carbohydrate. Clearly, if the glucose pattern is elevated, this ability is diminished. If the glucose pattern is elevated and the insulin pattern is elevated, this is compelling evidence of the reduced ability of insulin to enhance glucose disposal, i.e., insulin resistance.

Newcomer et al.[77] provided evidence for insulin resistance using a modified oral glucose tolerance protocol in subjects taking atypical antipsychotics. Glucose dose was 50 g, as opposed to the usual 75 g. Fasting glucose and insulin levels were higher with olanzapine, risperidone, and clozapine compared to levels in psychiatric patients taking typical antipsychotics and normal volunteers. These data suggest insulin resistance. Also, the time course for plasma concentrations of glucose as well as insulin were higher for patients taking the atypical antipsychotics than for the control groups. These investigators reported the highest glucose and insulin levels in the clozapine-treated group, and a tendency for higher levels with other agents.[77] In contrast, Baptista et al.[78] failed to see an additive effect of typical antipsychotics in individuals with schizophrenia compared to healthy subjects beyond the reduced glucose tolerance due to obesity itself. OGTT data support reduced glucose tolerance as well as insulin resistance due to treatment with antipsychotic agents. However, the degree to which the insulin resistance is due to adiposity per se or additional effects of the drugs remains unclear with the atypical agents.

It is extremely difficult to understand mechanisms of decreased tolerance from the OGTT alone. After glucose ingestion, the rate of gastric emptying as well as the rate and the degree of absorption from the small bowel contribute to the flux of glucose into the bloodstream. Changes in these rates will have a profound effect on the glucose tolerance, even if insulin sensitivity and β-cell function are entirely normal.[79] The change in plasma insulin concentration depends not only on the prevailing glucose level, but also on stimuli to the β-cells other than glucose. Oral glucose elicits the response of the incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which magnify the insulin response.[52] Insulin clearance is also important,[30,32] as is the effect of glucose to enhance disposition independent of the change in insulin level ("glucose effectiveness").[80] Thus, if we see changes in glucose or insulin levels during the OGTT, these could be due to alterations in insulin sensitivity, β-cell function, or a plethora of other physiologic responses that are involved in the OGTT response. We have little information as to the effects of atypical antipsychotics on any or all of these physiologic processes, such as gastrointestinal function and incretin response, or on the pancreas itself. There are dopamine receptors in the gastrointestinal tract, and these receptors might be directly responsive to antipsychotics or responsive to the central effects of these drugs.[81]

The limitations of the OGTT are suggested by a case report from Avram et al.[82] on effects of clozapine treatment associated with ketoacidosis. Although other factors could have contributed to the diabetic ketoacidosis, clozapine was implicated by the fact that after cessation of clozapine treatment, glucose tolerance was normalized, despite continued insulin resistance and reduced first-phase β-cell responsiveness. Thus, atypical antipsychotics appear to reduce glucose tolerance and usually elevate

postload insulin levels. Qualitatively, this finding appears to suggest insulin resistance, which may be due to changes in body weight or body fat mass and distribution. However, other physiological changes could account for observed altered tolerance. As with other metabolic indices, tolerance data appear insufficient to infer mechanism and cry out for direct measures of body fat quantity and distribution as well as direct measures of insulin sensitivity, β-cell function, and glucose effectiveness.

### Direct Measures of Metabolic Processes of Those Using Atypical Antipsychotic Agents

There are 2 widely accepted methods for assessment of insulin resistance: the euglycemic clamp and the minimal model. In addition, there are a variety of methods for assessment of β-cell function. Very little data exist in which these accepted methods have been used to assess the effects of atypical antipsychotics, although it is expected that data will appear in the near future.

Henderson et al.[69] reported a cross-sectional study in nonobese subjects with schizophrenia treated with clozapine, olanzapine, or risperidone. Using the minimal model approach, they reported pronounced insulin resistance in nonobese patients taking clozapine, with less mean resistance in the olanzapine group (insulin sensitivity index, $S_I = 2.4 \pm 0.7$ vs. $4.2 \pm 0.8$ $min^{-1}$ per μUmL × $10^{-4}$). In contrast, risperidone was not associated with insulin resistance in the absence of obesity ($11.0 \pm 2.2$ $min^{-1}$ per μU/mL × $10^{-4}$). This preliminary report is one of the few available studies in which insulin resistance can be quantitatively compared among different atypical antipsychotic agents.[69] It suggests a substantial differential between drugs in terms of their relative effects on insulin resistance in a nonobese population of subjects with schizophrenia. Clearly, more information regarding the relationships among antipsychotic medication, obesity, and insulin resistance among subjects with schizophrenia is required. This information will be most useful if accepted methodology is used for assessment of risk factors for diabetes, i.e., for insulin sensitivity and β-cell function.

## EFFECTS OF ANTIPSYCHOTICS IN NONPSYCHOTIC INDIVIDUALS

The possible confounding effects of schizophrenia and other disorders per se on glucose tolerance make it problematic to separate the effects of the disease from the effects of treatments. Therefore, a few groups have examined the metabolic effects in individuals or in animals without psychiatric illness.[83–85] One group is that of Steinberg and Breier and colleagues in Indianapolis, Ind., and the second is our group in Los Angeles, Calif.

Sowell et al.,[83] of the Indianapolis group, performed euglycemic clamps in normal human volunteers tested at baseline and after administration of olanzapine, risperidone, or placebo. The study was performed on an inpatient basis over 3 weeks. The normal-weight volunteers were allowed up to three 72-hour passes out of the clinical center. Substantial weight gain was reported for olanzapine and risperidone over the 3-week period (~ 1.5 kg), but no change in weight occurred in the placebo group. No difference between agents was reported in whole body insulin sensitivity (glucose infusion rate during clamps/change in insulin concentration) at low or high insulin infusion rates. It was curious that no change in glucose infusion during clamps was reported, despite the substantial weight gain, as there is a known strong correlation between body mass index (BMI) and insulin resistance from clamps in normal-weight individuals.[86] It is possible (see Mechanistic Studies in Dogs) that specific changes in insulin sensitivity of muscle or liver may have occurred, but were masked because the specific effects of insulin on these separate components were not assessed.

The same group published a complete study of the effects of the same agents on normal individuals[84] in whom the hyperglycemic clamp was used to measure β-cell function as well as an index of insulin resistance. After diet stabilization, hyperglycemic clamps were performed. Following this, subjects were put on either olanzapine or risperidone treatment. Subjects were counseled to maintain an isocaloric diet throughout the 15 to 17 days they were kept on therapy.

In that report, absolute values of glucose infusion during clamps at baseline were not reported, nor were initial values of incremental insulin at steady state during baseline clamps. What was reported includes changes in weight during therapy and changes in glucose infusion rates, as well as changes in basal insulin levels and changes in incremental insulin levels. The absence of reported initial values of glucose infusion rate or incremental insulin during clamps in that article makes it problematic to calculate the specific effects of different agents. However, with reasonable assumptions of basal values, it is possible to infer the effects of the agents on the nonobese volunteers. Using such assumptions, we have estimated the following results from the Sowell et al. study: insulin sensitivity appeared to drop about 25% in both the olanzapine and the risperidone groups, while in the placebo group, insulin sensitivity increased 64%. This apparent increase in insulin sensitivity in the placebo group is not explained.

It was also possible to estimate β-cell function from our estimates of steady-state insulin secretion during clamps, before and after therapy. It appeared that both olanzapine and risperidone groups increased steady-state secretion appropriately to compensate for their degree of insulin resistance, and the DI did not change. There was an inexplicable increase in insulin sensitivity in the placebo group (from 0.22 to 0.36 mL/min per μU/mL). The increased sensitivity was reflected in a decrease in insulin

secretory function, so that the DI also remained normal in the placebo group.

Results from the Sowell et al. article[84] must be taken as inconclusive in that necessary numbers are not available to calculate actual insulin action and β-cell responsiveness before and after medication. It does appear, however, that in nonobese volunteers, in whom caloric restriction will minimize drug-induced obesity (provided the subjects are compliant), minimal effects of the drug on insulin sensitivity or insulin secretion were obvious. However, such a study does not represent the bona fide response to the drug, as greatly increased food intake and possibly reduced energy expenditure would be expected, at least with some drugs. What is not known from this study is whether the β-cells would have the *capacity* to upregulate in the presence of insulin resistance, which would most likely have occurred if food intake were not regulated at predrug values.

What is abundantly clear from the previous analysis is that carefully wrought information regarding the effects of atypical antipsychotics on glucose homeostasis is limited, and much more needs to be done to understand the mechanism of action of these agents. For example:

We do not know the primary site of action of the agents—whether they act centrally on the central nervous system, or peripherally, and which peripheral tissues may be most affected (muscle, liver, fat).

We do not know the molecular mechanisms by which the agents act on metabolism. Knowledge of the mechanisms could lead to new generations of better agents.

We do not know whether the primary effects of these drugs are on adiposity per se or whether there are other metabolic effects of the drugs.

The role of disease per se, versus effects of the drugs themselves, has not been sorted out.

We have not been able to discern effects on insulin-sensitive tissues from effects on insulin-secreting cells (i.e., β-cells of the pancreas). The surprising emergence of diabetic ketoacidosis in treated patients strongly suggests that there are effects on the insulin secretory mechanisms.

If there are effects on secretion, we do not know if these are mediated by central or peripheral mechanisms.

## MECHANISTIC STUDIES IN DOGS

To attempt to address some of the previous concerns, in our laboratory we have mounted a physiologically-based study to understand and compare the effects of 2 commonly used atypical antipsychotic agents—olanzapine and risperidone—and compare their effects with placebo control. Some of the principles of design of our studies are described in this section.

Longitudinal studies were performed in the conscious canine model. This model was used because the dog tolerates the antipsychotics well at clinically relevant doses with a minimum of sedation. Of course, the dog model allows us to examine the effects of the agents in the absence of associated psychiatric disease. We were able to measure effects of each agent not only on body weight, but also on distribution of fat tissue with MRI. We easily applied tracer dilution methods to assess insulin sensitivity directly in skeletal muscle versus liver. We were able to assess relative effects of the agents on insulin secretion and insulin action, and the relationship between them, expressed as the DI (explained earlier). The overall summary of our results is as follows:[85]

Atypical antipsychotics have profound effects on glucose metabolism, independent of psychiatric disease.

We did not observe fasting hyperglycemia, the hallmark of type 2 diabetes, in our treated animals.

The agents differ substantially in their metabolic effects. Specifically,

- Olanzapine caused substantial increases in adiposity—both in visceral and subcutaneous fat depots. In contrast, risperidone did not increase adiposity beyond that observed in placebo-treated animals on ad lib diet.
- Observed changes in adiposity were not proportional to the effects on body weight.
- Changes in body weight result from differential effects of agents on food intake and energy expenditure.
- The 2 agents had very different effects on insulin action. Olanzapine caused a highly significant reduction in hepatic insulin sensitivity—after drug treatment for 1 month, hyperinsulinemia during euglycemic glucose clamps no longer suppressed glucose production. Little net effect of risperidone on hepatic insulin sensitivity was observed.

Finally, and most significantly, the normal compensatory increase in insulin secretion elicited during obesity-induced insulin resistance was completely prevented by olanzapine. These results were obtained by comparing the β-cell response to insulin resistance induced by olanzapine with that observed in dogs with matched insulin resistance and obesity induced by moderate dietary fat supplementation.[85] Risperidone induced less adiposity than did fat supplementation, so drug effects on compensation could not be directly compared with fat feeding.

## CONCLUSIONS

Examination of the uses of antipsychotics on glucose metabolism represents the intersection of 2 disparate fields of research: psychiatry and diabetology. Much of the work that has been done is wanting in one or both of these fields, and state-of-the-art approaches have not generally been utilized. The sophisticated and well-validated tools available to the clinical investigator such as the glucose clamp, the minimal model, C-peptide deconvolution, and imaging techniques have hardly been applied in this field. Many investigators have used nonquantitative measures such as body weight or BMI (as opposed to adiposity itself) and fasting values or the OGTT, rather than validated assessments of insulin sensitivity and β-cell function and measures of energy expenditure such as the doubly labeled water method. There is only a modicum of studies of atypical antipsychotic use in normal individuals, making it difficult to separate effects of disease versus therapy. It is not possible at this juncture to make definitive statements regarding the primary versus secondary effects of these agents. It is clear that some agents are more adipogenic than others. However, because their mechanisms of action are not clear, it is not yet possible to distinguish among the agents in terms of their effects on physiologic risk factors for diabetes other than adiposity itself. There is provocative evidence, including our studies in the dog model, that some or all of these agents might affect β-cell function. Whether results from the dog can be extrapolated to man is not yet known, and it is likely that agents will differ in their physiologic actions as well as mechanisms of action.

It is our view that the canine studies we have performed might represent a template for the types of studies that must be performed before firm conclusions can be drawn regarding mechanisms of action and variations in efficacy as well as deleterious effects. Similar studies must also be performed in patients as well as (if possible) in healthy human volunteers. It is critical that quantitative methods that have been used to differentiate a variety of pharmacologic agents in the diabetes and obesity fields be used for evaluation of atypical antipsychotics. A similar point of view was clearly espoused in the recent consensus report on the metabolic effects of antipsychotics.[87] The prevalent use of atypical antipsychotics cries out for such an approach.

*Drug names:* aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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