Do Atypical Antipsychotics Cause Diabetes?

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Dr. Wyne has disclosed that she has no conflict of interest regarding any of the therapies discussed in the presentation. There will not be any discussion of off-label uses of medications. Her research interests include understanding the progression from "prediabetes" to type 2 diabetes, especially in the context of the use of atypical antipsychotics, in women with PCOS, and the risk for CVD. She is involved with the Texas Diabetes Council in updating the guidelines for the management of diabetes in the state of Texas.

Case 1

"A 15-year-old woman with paranoid schizophrenia, no past medical problems, eating disorders, or history of obesity did not improve with conventional antipsychotics. The patient was admitted to a day treatment facility where weights were recorded by the same clinician who used identical protocol and the same calibrated scale each time. There were no changes in dietary intake, eating, or exercise patterns. The patient's height was 163.8 cm, and admission weight was 77.2 kg (ideal body weight = 55.6 kg +/- 10%). The patient was begun on risperidone, 2 mg daily. After 4 weeks, the risperidone was increased to 5 mg daily, and the patient had gained 7.16 kg. The risperidone was decreased to 4 mg daily. After 12 weeks on risperidone alone, the patient had gained 17.16 kg. There was no clinical improvement, and thus clozapine was added, 400 mg daily. After 38 weeks of risperidone and 24 weeks of concomitant clozapine, the patient's weight had reached 102.3 kg, for a total increase of 25.1 kg from admission weight."[1]

This case has raised considerable discussion regarding the following questions:

Is this person now going to have the Metabolic Syndrome?
Is she at increased risk of developing CVD?
Is she at increased risk of developing type 2 diabetes mellitus?

One would say yes, maybe and maybe if she did not have schizophrenia. Does this change since she has schizophrenia?

Introduction

Studies by Malzberg in 1934 demonstrated early mortality in people with schizophrenia in the US.[2] This was confirmed in 1936 in studies from Norway.[3] This excess mortality has often been attributed to suicide and accidents. This question was revisited by Tsuang and Woolson in the 1970s with a longitudinal study of the four-decade period beginning with 1934–1944 in the state of Iowa.[4] They reported that excess mortality was found starting in the first decade of follow-up for schizophrenia and that death due to suicides and accidental deaths is not the sole cause for the excess mortality. While risk of death related to suicide was increased by a factor of twenty, there was still an increased mortality risk from natural causes. Subsequent studies have examined the causes of death on cohorts of people with schizophrenia.[5-8] The excess mortality is due to an increase in conditions seen in the general population, namely smoking related disease, cardiovascular disease, diabetes and hypertension.

These data are not a surprise to the health care practitioners who are involved in the ongoing care of patients with schizophrenia. It is not uncommon for these patients to not be available in their hospital rooms during daily ward rounds because they are downstairs smoking and/or trying to obtain illicit fast food. Prior to the conversion to nonsmoking hospitals, when seeing these patients in consultation as an outpatient, we would often only be able to interview

the patient while smoking. In one of the few descriptive studies examining the health of those with schizophrenia, Brown and colleagues measured the diet, cigarette and alcohol use, exercise and obesity of a cohort of people with schizophrenia and compared results to general population rates. They found that, on average, individuals with schizophrenia eat a diet high in fat, smoke heavily, and get very little exercise.[9] Thus, individuals with schizophrenia have all the risk factors for obesity, the metabolic syndrome and its complications. In fact, for many health care practitioners, their mental image of a patient with schizophrenia that is controlled by medication is an overweight person who is smoking cigarettes.

Antipsychotic Therapy and Weight Gain

Obesity has been a problem for individuals with schizophrenia long before the advent of the atypical antipsychotic agents. The prevalence of obesity in individuals with schizophrenia has been reported to range between 40%-60%.[10, 11] Weight gain has been a recognized side effect of treatment of schizophrenia however, prior to the introduction of the atypical antipsychotics, the benefit of clinical improvement was felt to outweigh the risk of modest weight gain.[10, 12] Due to poor efficacy and intolerable side effects, primarily tardive dyskinesia, the newer generation of antipsychotic agents were introduced in about 1990. Table 1 lists the antipsychotic agents commonly in use. The approximate date of FDA approval in the US is listed for the atypical antipsychotics as it sets stage for the emergence of the reports of weight gain and diabetes.

In 1990, eight months after the approval of clozapine, the first atypical antipsychotic available in the US, Cohen and colleagues from the University of Washington reported that six of seven patients treated with clozapine gained 6-69 lb.[13, 14] The authors felt this report was important as the use of clozapine was anticipated to increase dramatically in the US. This was rapidly followed by another report of significant average weight gain of 16.0 lb over 6 months with 75.0% of the patients gained at least 10 lb.[15] A subsequent report in 1992 included 21 patients with a mean weight gain over 16 weeks of 13.9 lb, or 8.9% of body weight. The patients who gained the most weight also had the most improvement in their psychiatric symptoms as assessed with a modified version of the Brief Psychiatric Rating Scale (BPRS).[16] A longer term retrospective study in 1994 evaluated weight gain in 82 patients who received clozapine treatment for up to 90 months and did not show a correlation between BPRS response and weight gain.[17] They did report that being underweight at baseline correlated with maximum amount gained thus suggesting that weight gain is not necessarily an issue of concern, given the clinical benefits with the lesser risk of tardive dyskinesia. A double blind controlled trial was ultimately done in 39 patients comparing weight gain in clozapine vs. haldol treated subjects. The patients treated with clozapine gained significantly more weight over baseline (7%) than the haloperidol-treated patients (1%). and continued to gain more weight through the next year.[18]

Table 1 Antipsychotic Agents

Drug	Class	Brand Name(s)	FDA approval
Phenothiazines			
Chlorpromazine	Phenothiazine	Thorazine	
Thioridazine/mesoridazine	Phenothiazine	Mellaril, Serentil	
Fluphenazine	Phenothiazine	Prolixin	
Perphenazine	Phenothiazine	Trilafon, Triavil	
Trifluoperazine	Phenothiazine	Stelazine	
Prochlorperazine	Piperazine phenothiazine	Compazine	
Non-Phenothiazine Typicals			
Thiothixene	Thioxanthene	Navane	
Loxapine	Dibenzodiazepine	Loxitane	
Haloperidol	Butyrophenone	Haldol	
Molindone	Dihydroindolone	Moban	
Pimozide	Diphenylbutylpiperidine	Orap	
Chlorprothixene	Thioxanthene	Taractan	
Atypicals			
Risperidone	Benzisoxazole	Risperdal*	12/29/1993
Clozapine	Dibenzodiazepine	Clozaril *	9/26/1989
Olanzapine	Thienobenzodiazepine	Zyprexa	9/30/1996
Olanzapine/Fluoxetine		Symbyax	12/24/2003
Quetiapine	Dibenzothiazepine	Seroquel	9/26/1997
Sertindole	Phenylindole derivative	Serlect	**
Ziprasidone	Benzisothiazolylpiperazine	Geodon*, Zeldox	2/5/2001
Aripiprazole	Piperazine-quinolinone	Abilify	11/15/2002

*available as a generic in the US
** not FDA approved in the US

Reports then began to emerge of significant weight gain with other atypical antipsychotics. One was a case report of two individuals who gained 25 and 46 kg (not pounds) after combination therapy which involved risperidone.[1] At this point in time attention became focused on the weight gain to the point that it has been termed "tardive dyskinesia" for the new millennium in the field of schizophrenia. David Allison completed a review of the available data on the typicals and atypicals and concluded that most neuroleptic drugs were associated with weight gain (Figure 1).[19] He found that some compounds produced as much as 5 kg weight gain at 10 weeks. He then proposed that since this may represent more than 5% of initial body weight then it should be considered a health risk, in the context of recommendations that obese people lose at least 5% of their body weight to obtain clinically meaningful reductions in

morbidity and risk of early mortality. [20] Subsequent data has shown that a 5% increase in weight over the re ported weight at age 20 was associated with nearly a 20% greater risk of insulin resistance syndrome by middle age, suggesting that Dr. Allison was correct to raise the caution that this weight gain could contribute to increased morbidity and mortality.[21]

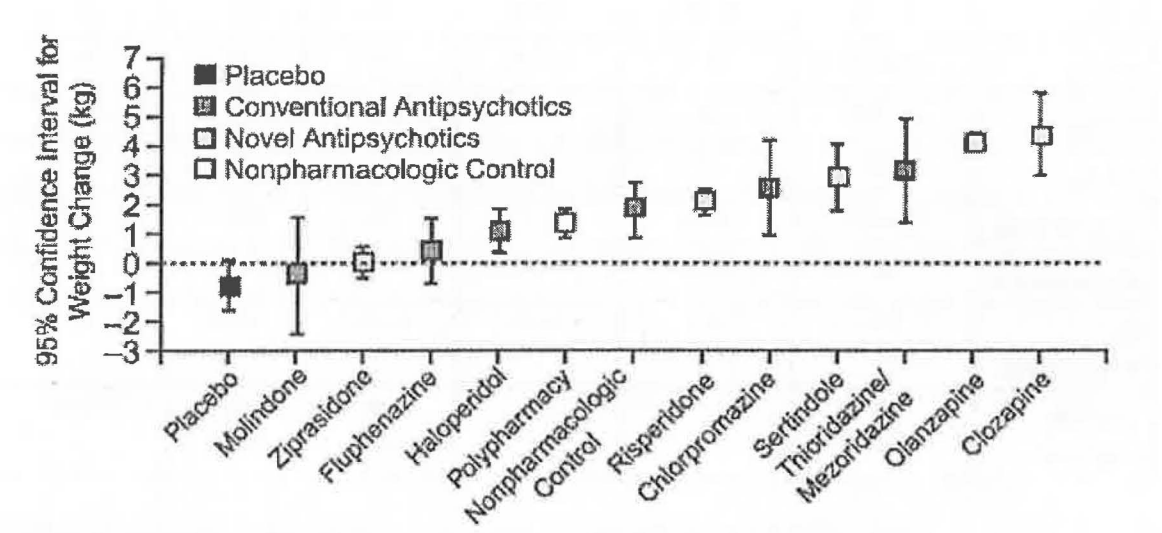

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random-Effects Model

The conclusions from his review have been supported by other studies.[22] In data from preclinical trials with ziprasidone, as compared with the mental health supplement of the 1989 National Health Interview Survey (NHIS) and NHANES III, showed that the excess weight that was present in noninstitutionalized women with schizophrenia was not exacerbated by the addition of this new atypical antipsychotic.[11] In 2005 the CATIE study, a prospective project funded by the NIH, reported that 30% of olanzapine treated schizophrenic patients gained 7% or more of their baseline body weight.[23]

The weight gain that occurs in people with controlled schizophrenia has been postulated to be a function of the mechanism of action of the neuroleptic agent. The extent of weight gain apparently varies by differing degrees of action on the serotonergic, dopaminergic, cholinergic, histaminergic, and other neurotransmitter systems. The data has shown that the affinity if the antipsychotics for the H_1 histamine receptor affinity predicts short term weight gain.[24] Table 2 shows the relative receptor binding affinities of the atypical antipsychotics which supports the H1 receptor as the primary receptor with respect to Dr. Allison's observations.

Table 2. Relative Receptor-Binding Affinities of Atypical Antipsychotics

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Aripiprazole
D_2	++++	++++	++	+	+	++++‡
5-HT_{2A}	+++++	+++++	++++	+	++++	++++
5-HT_{2C}	+++++	++++	++++	–	++	++
5-HT_{1A}	++++‡	+	–	+	+	++++‡
5-HT_{1D}*	++++	+	+	–	–	–
α_1 adrenergic	++++	++++	++	++	++++	++
M_1 muscarinic	–	–	++++	++	++++	–
H_1 histaminergic	++	++	++++	++++	++++	++
5-HT/NE reuptake†	++	–	–	– 5-HT + NE	– 5-HT + NE	++ 5-HT

It is certainly possible that effects on other receptors may still have a role in the net effect on feeding behavior and/or weight gain. For example, increasing serotonin (whether by increasing production or decreasing reuptake) has been shown to decrease carbohydrate hunger, reduce consumption of carbohydrate-rich foods, and inhibit weight gain in humans and animals. Such compounds actually have the potential to decrease carbohydrate craving and facilitate weight loss. In contrast, agents that produce antagonistic effects at serotonin receptor sites are likely to stimulate appetite, carbohydrate craving, and weight gain. Chlorpromazine, for example, is thought to be weight neutral as it inhibits serotonin reuptake mechanisms and may simultaneously block serotonin receptor sites. One other consideration must be the impact of side effects on feeding behavior. For example, the production of dry mouth and thirst by psychotropic drugs may contribute to weight gain through consumption of high-calorie beverages. The cause of the weight gain is not completely clear as even with depot preparations of compounds thought to not cause weight gain, the prevalence of obesity remains elevated as compared with that of the general non-psychiatric population.[10]

Since the publication of Dr. Allison's review in 1999 the issue of weight gain has come under intense scrutiny. Factors proposed to be associated with weight gain include choice of atypical antipsychotic, better clinical outcome, increased appetite, and low baseline body mass index.[25] In general, the weight gain tends to occur early in therapy and does not continue to accumulate over time. For example, in patients treated with olanzapine for up to 3 years, weight gain trended toward a plateau at approximately 36 weeks. The newest atypical

antipsychotics, ziprasidone and aripiprazole, appear to have the least weight gain although the amount gained with these agents is not trivial

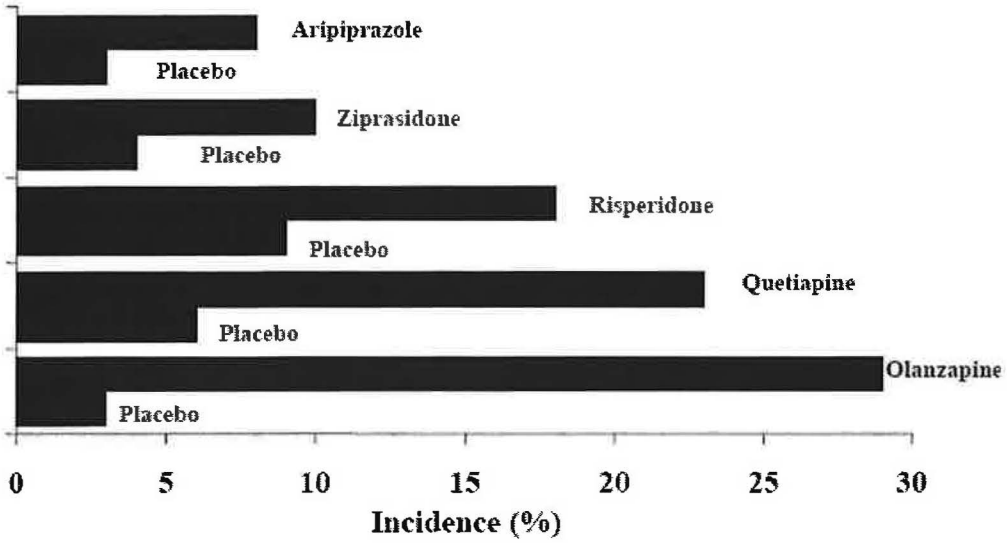

Figure 2. Clinically Significant Weight Gain in Short-term Clinical Trials (source: package inserts).

Weight gain alone is not sufficient to cause metabolic syndrome, CVD and/or diabetes. Where the person puts the weight is potentially more important than how much weight has been gained. There is very little data looking at weight distribution in people with schizophrenia. Hopefully such data will be forthcoming despite the barriers to completing such studies in this population. There is some preliminary data from abdominal CT scans in 15 people with schizophrenia who had a significant difference in visceral fat distribution, regardless of drug treatment, as compared with matched, non-schizophrenia controls.[26] This same group has done a preliminary study of 16 patients treated with either olanzapine or risperidone. After 6 months of therapy, they found no significant increase in intra-abdominal fat.[27] In a Chinese study of 10 weeks of therapy with risperidone there was also no increase in intra-abdominal fat.[28] It is important to raise the point that these are small studies and do not focus on the drugs that are known to cause the most weight. While these data are just preliminary pilot studies they do raise questions as to whether the atypical antipsychotics are increasing metabolic risk and remind us that further studies are needed.

An interesting question has been raised whether the weight gain with the atypical antipsychotics is specific to the population of people with schizophrenia, This is due to reports such as one report which evaluated weight gain in nursing home residents with Alzheimer's disease. They found the 36 of the 99 subjects evaluated who were treated with risperidone, olanzapine or quetiapine over a 12 month period had no significant weight gain. [29] This is a small study thus this question needs to be evaluated in a larger population.

Antipsychotics and Dyslipidemia

One approach to examining the metabolic risk of the weight gain is to look at the lipid effects. Again, case reports began emerging documenting modest hypertriglyceridemia related to newer antipsychotics, including clozapine and olanzapine. A case series from Oregon reported in 14 cases of severe hypertriglyceridemia (>600 mg/dL) associated with olanzapine and quetiapine therapy. Seven of these 14 cases had triglyceride levels that exceeded 1,000 mg/ dL. Four of the 14 patients also developed new-onset diabetes. Nine cases occurred during the first 8 months of treatment, with three cases identified within 3 months of commencing olanzapine or quetiapine therapy. Weight gain was considered to be modest with each drug (12.3 lb and 8.5 lb, respectively) and did not correlate with the severity of hypertriglyceridemia. Subsequent reports have confirmed the emergence of the diabetic dyslipidemia in many people treated the antipsychotics and that it was more common with the use of atypical antipsychotics.[30-38] Aripiprazole and ziprasidone, which are associated with the least amount of weight gain, do not seem to be associated with a worsening of serum lipids. Risperidone and quetiapine appear to have intermediate effects on lipids. The appearance of hypertriglyceridemia may represent an impairment of insulin secretion and/or an increase in insulin resistance manifesting as ineffective insulin action on lipolysis of triglycerides. The authors then proposed that clinical monitoring of serum lipids must be added to the concerns about the metabolic consequences of therapy with certain newer antipsychotic agents.[39, 40]

Given that people with schizophrenia who are treated with atypical antipsychotics tend to gain weight and that may be accompanied by a pattern of dyslipidemia that is characteristic of insulin resistance, the question is then raised as to whether the use of the atypical antipsychotics increases the likelihood of developing diabetes in this population which already has a high prevalence of diabetes.

Antipsychotics and Diabetes

The most recent National Diabetes Fact Sheet, which represents the estimates for the year 2005 from the CDC projects that 9.6% of all people in the US age 20 years or older have diabetes. In contrast, the prevalence in the US adult population was 4.9% in 1990, which is around the time that the atypical antipsychotics were introduced in the US.[41] Studies on the prevalence of diabetes in people with schizophrenia are limited and typically do not differentiate between type 1 or type 2 diabetes. Additionally, they are limited by, until recently, a lack of standardization of diagnostic criteria. Furthermore, very few do comprehensive testing including FPG and an OGTT so there may be a lot of undiagnosed diabetes in these populations. One study from 1987 was conducted in Japan and used a standard glucose tolerance test and WHO criteria for diabetes. They found a 8.8% prevalence of diabetes among 248 people with schizophrenia with a 5% prevalence in matched office workers.[42] Another report from 1995 in the US evaluated community based schizophrenics

and found a 24.5% prevalence of diabetes.[43] A 1996 study in Italy found an intermediate prevalence of diabetes (15.9%) in 95 schizophrenic patients aged 45 to 74 years admitted to a long-term care facility.[44] Interestingly, they found that diabetes was more common in patients not receiving neuroleptics than in those who were receiving such treatment. The authors report the medication doses in chlorpromazine equivalents but do not report what neuroleptics were actually in use in this facility.

Given that a family history of type 2 diabetes is one of the strongest of the traditional risk factors for diabetes, it raises the question as to whether the population of patients with schizophrenia perhaps has a strong family history which would enrich the risk for diabetes. As one can imagine, doing family studies in this population is not easy thus there are not a lot of reports. One study did attempt to quantify the family history in a US population in 1989. They found that about one-third of the subjects reported a known family history of diabetes, which was comparable to estimates in people with diabetes in the US population at that time and lower than that found in the population without diabetes.[45, 46] The fact that the prevalence of diabetes in the US population has doubled and is increasing at 8% per year makes one wonder what the current prevalence in the schizophrenic population is at this time. The projection would be that if there is a similar rate of increase it would be more than 50%, and this is without taking in to account the introduction of the atypical antipsychotics.

The prevalence of diabetes in the population of people with schizophrenia was brought to the attention in the Endocrine Community in the early 1990s when case reports began to appear in the literature of people with an apparently sudden onset of hyperglycemia. The first was in 1994 and described a case of severe hyperglycemia associated with high doses of clozapine.[47] This was followed one month later by a case report of diabetic ketoacidosis as a side-effect of clozapine treatment.[48] Apparently there had not been any reports of hyperglycemia or ketoacidosis during the preclinical trials with clozapine. The next reports emerged in 1996 with cases of ketoacidosis followed by small case series of apparent sudden onset hyperglycemia.[49-53]

The first case series was a report of four cases in 1997 describing either a de novo onset or severe exacerbation of preexisting diabetes mellitus. The pertinent observation was that the change in glycemic control was not significantly related to weight gain. The authors suggested that patients with a family history of diabetes mellitus or preexisting diabetes should have their blood sugar monitored closely during initiation of clozapine treatment.[52] For some reason this observation was not widely disseminated thus most people assumed that the weight gain caused the decompensation in glucoregulatory status. Additionally, the cases of ketoacidosis were somewhat ignored as the assumption was that the atypical antipsychotics were causing weight gain and type 2 diabetes.

By 1998 the total number of cases reported in the literature was 15 but now included both clozapine and olanzapine.[53] Interestingly, there were no cases in the literature of risperidone related hyperglycemia or acidosis despite the fact that it was approved by the FDA in 1993.

The trends that had emerged to date were weight gain, male sex (14 of the 15 involved men) and ethnicity (11 of the 14 published cases in which the ethnicities of the patients were disclosed, had involved African-Americans). The challenge in analyzing these case reports is that there is rarely preceding analysis of glucose regulatory status. There are reports that specifically state that there was sudden onset hyperglycemia but very few of those actually have preceding data as to fasting plasma glucose. The hyperglycemia of sudden onset typically resolves after stopping the atypical antipsychotic.

Ultimately, there were cases of new onset diabetes and ketoacidosis reported with risperidone. As of 2003, the FDA's MedWatch surveillance program had received 131 reports of risperidone-associated hyperglycemia, 7 reports of hyperglycemia with combined risperidone-haloperidol therapy and 6 reports of acidosis that occurred in the absence of hyperglycemia.[54] 78 patients had newly diagnosed hyperglycemia, 46 had exacerbated preexisting diabetes, and 7 could not be classified. Overall, the age was young but with a very wide range: 39.8 +/- 17.4 years (range 8-96 yrs). Patients with new-onset diabetes were younger than those with preexisting diabetes and male. In most patients, the hyperglycemia appeared within 3 months of the start of risperidone therapy. Although more cases have been reported in association with clozapine or olanzapine, there are still cases associated with risperidone, and these are more than what has been observed with conventional neuroleptics such as haloperidol. It should be noted that there are cases of new onset diabetes during treatment with haloperidol. These cases had typically been attributed to the high risk of diabetes in this population but it does raise the question as to whether haloperidol may also increase insulin resistance and/or impair beta cell function. It is of interest to note that until recently, measuring glucose was not routine in psychiatry practice, despite the high prevalence of diabetes in the population of people with schizophrenia.

Most authors continued to attribute the hyperglycemia to weight gain as the majority, but not all, of the cases reported had gained weight. To further support this case characterization, studies of patients with hyperglycemia while taking an atypical antipsychotic typically showed an elevated glucose, insulin and c-peptide.[55] Thus it was presumed that the atypical antipsychotic was causing an increase in insulin resistance leading to new onset type 2 diabetes.

The oral glucose tolerance test has been used to evaluate glucoregulatory status in people treated with clozapine, olanzapine and risperidone, As compared to untreated healthy control subjects matched for adiposity and age.[56] It must be noted that most studies are compared to subjects without schizophrenia, which are not the ideal controls, because of the difficulties in doing baseline studies prior to initiating therapy with an antipsychotic. For similar reasons, it is also not possible to do randomized studies where patients switch between agents. For patients taking olanzapine, glucose elevations were present at all time points of the OGTT. For patients taking clozapine, glucose elevations were noted at fasting and at 75 minutes. Those taking risperidone had glucose elevations at the fasting and 2 hour post load glucose levels. There were no differences in glucose levels between the traditional drug and healthy controls but there were

significant increases in glucose, as compared to healthy controls, in the groups treated with clozapine or olanzapine. Henderson and colleagues also reported insulin resistance and impaired glucose effectiveness in olanzapine and clozapine vs. risperidone patients in normal weight subjects with schizophrenia.[57] An NIMH sponsored study is underway to identify the specific mechanisms discussed.

Subsequent studies have used the frequently sampled intravenous glucose tolerance test (FSIVGTT) to evaluate whole body insulin sensitivity in chronically treated patients with schizophrenia. What they have found is that BMI and waist circumference predict insulin sensitivity and acute insulin response to glucose (AIR) and not medication except that there was no effect of ziprasidone and risperidone on thse parameters. In these studies there were no consistent effects of medication group on either insulin sensitivity or secretion, independent of adiposity. Henderson and colleagues have used the FSIVGTT to show significant changes in insulin sensitivity in non-obese subjects, primarily white and male, among those taking clozapine and olanzapine.[58] There is no data on insulin sensitivities in non-obese women of differing ethnic or racial backgrounds. Studies in rats have shown an acute effect of olanzapine and clozapine on insulin resistance thus supporting these data which suggest that the drugs are merely bringing out the diabetes sooner.[59]

There have not been studies looking at hepatic glucose production or hepatic insulin resistance in these patients. For logistical reasons it is not easy to perform glucose clamp studies in this population of patients. There is data showing an increase in hepatic insulin resistance in dogs treated with olanzapine. Similarly, acute treatment of rats with olanzapine and clozapine led to an increase in hepatic glucose production.[59] It is very likely that the increase in hepatic glucose production precedes the peripheral insulin resistance.

Measurements of adipocytokines suggest that there are alterations in adipocyte biology. Treatment with atypical antipsychotics has been shown to be associated with increases in leptin and decreases in adiponectin. While these could be dismissed as being secondary to weight gain, this pattern has been seen in conjunction with risperidone and chlorpromazine therapy, which are associated with lesser amounts of weight gain.[60] Studies of primary adipocytes in culture have demonstrated that clozapine and risperidone decreased glucose uptake.[61] These same investigators also found that clozapine and olanzapine, but not risperidone, were able to impair insulin-stimulated glucose transport in 3T3-L1 adipocytes. They then looked at lipogenesis which also showed some discrepant data. Olanzapine, clozapine, and quetiapine, but not risperidone decreased the basal lipolytic rate suggesting that they are keeping the fat stored in the adipocyte. All four drugs showed a decrease in insulin stimulated lipolysis, although the effect was the least with risperidone. Although this is just one study of adipocytes in culture it does suggest that these agents have direct cellular effects that can increase insulin resistance. They also suggest that there may be an impairment in the ability to mobilize free fatty acids which could compromise insulin secretion as a minimal amount of free fatty acids are necessary for basal insulin secretion.[62]

Based on the available data, most authors have come to what appears to be a reasonable conclusion that weight gain caused an increase in insulin resistance, thus bringing out the diabetes sooner.

Antipsychotics and Hyperglycemia

It was at this time that the hyperglycemia came to my attention as a result of some patients admitted to the University Diabetes Treatment Center in Parkland Memorial Hospital. The following case reports are the first two that raised the perplexing question as to what was causing the hyperglycemia.

Case 2

A 42 year old man with a history of stable schizophrenia was admitted to the hospital for management of community acquired pneumonia. He was overweight but not obese and did not have hypertension. That evening the cross cover was called for evaluation of confusion. After approximately 2 hours of evaluation he was found to have a plasma glucose of 29 mg/dL. Insulin, proinsulin, c-peptide and glucose were drawn but never received in the lab. He responded to a continuous intravenous glucose infusion.
On review, we found that he had not had his medication for two days and had been taking a high dose of olanzapine for about 5 years. He did have a family history of diabetes. He had not had significant weight gain over the previous 5 years.

Case 3

A 47 year old woman with type 1 diabetes and schizophrenia was admitted to the UDTC for management of uncontrolled hyperglycemia. After stabilization of her glucose she was transferred to the psychiatry unit for management of her schizophrenia. Approximately 24 hours after the transfer, the diabetes fellow was called to assist with management of uncontrolled hyperglycemia. The only change in her regimen and/or diet was the addition of an atypical antipsychotic. She required about a 50% increase in her total daily dose of insulin (which was not high to begin with) before her glucose stabilized at near normal levels. She did not have DKA during the admission.

Case 4

A 35 year old man was admitted from the ED for management of uncontrolled hyperglycemia, DKA and new onset diabetes. He was found to have triglycerides of 3,000. He had no history of diabetes or dyslipidemia. He had recently been started on clozapine. He reports that six months ago he had a routine physical at which time he was told his glucose and cholesterol were normal. It is not known if there are any lipid disorders in his family.

These cases highlight the fact that we do not know if the atypical antipsychotic is causing insulin resistance, with compensatory hyperinsulinemia, and/or acute insulin deficiency. It is likely that the metabolic changes that occur depend upon the person's underlying glucoregulatory status. Perhaps some of

the "new-onset diabetes" is actually people at high risk for diabetes in whom the weight gain precipitated the decompensation of the ability to make insulin. To date, studies in people without schizophrenia but at risk for diabetes have not been able to identify what actually precipitates the decompensation in beta cell function such that the insulin secretion is not adequate for their level of insulin resistance.[63] In the case of the antipsychotics, the general argument has been that the histaminic and, possibly the serotonergic, antagonism induces weight gain, which in turn leads to insulin resistance and the diabetic dyslipidemia. When the beta cell is no longer able to compensate, hyperglycemia appear. The question is then whether the data actually supports this sequence of events.

These cases actually draw a parallel to patients that we see at Parkland which Dr. Raskin calls Idiopathic Type 1 Diabetes.[64] They present with DKA, are very insulin resistant then have a dramatic decrease in their insulin needs such that their insulin is often stopped 6-12 months later. However, stopping medication may ultimately lead to further episodes of DKA thus his recommendation is that insulin remain a component of their regimen for the rest of their life. Although there has not been any long term management reports of the atypical antipsychotic induced diabetes other than that the hyperglycemia usually resolves when stopping the atypical antipsychotic one can not help but wonder if it is a similar scenario whereby the pancreatic beta cells are overwhelmed and temporarily stop producing insulin leading to DKA.

The apparent sudden onset of hyperglycemia in some patient has been proposed to be due to serotonin1A receptor antagonism which could decrease pancreatic beta-cell responsiveness, resulting in inappropriately low insulin and hyperglycemia. There is data showing an impairment of insulin secretion in the presence of olanzapine treatment in dogs.[65] The possibility of an insulin secretory defect has been examined in some detail in isolated rat islets comparing cholinergic- and glucose-stimulated insulin secretion from isolated rat islets. At concentrations encompassing therapeutically relevant levels, olanzapine and clozapine reduced insulin secretion stimulated by carbachol plus glucose but had no effect on glucose stimulated insulin secretion. In contrast, risperidone or ziprasidone had no adverse effect on cholinergic-induced insulin secretion or inositol phosphate accumulation. In vitro binding and functional data have shown that olanzapine and clozapine but not risperidone, ziprasidone, or haloperidol are potent muscarinic M3 antagonists. These findings demonstrate that olanzapine and clozapine can selectively impair cholinergic-stimulated insulin secretion by blocking muscarinic M3 receptors, thus providing a plausible explanation for the sudden inset of hyperglycemia in some patients.[66] These data suggest that insulin therapy would be a rational approach to managing the patients who present with sudden onset of hyperglycemia and/or DKA. There is no reported data using this approach in this population of patients.

Antipsychotics & Prevention and Management of Hyperglycemia

The reports of new onset diabetes have continued to accumulate. The question is now pertinent as to whether diabetes screening should be part of the management of patients taking the atypical antipsychotics or perhaps any

antipsychotic? Prevention is also an issue which needs further attention. The Diabetes Prevention Project (DPP) showed that lifestyle intervention in the US could prevent the progression by 58% from "prediabetes" to diabetes.[67] The incidence of diabetes was also reduced by 31% in the metformin group compared to placebo. Lifestyle intervention would be the ideal approach to prevent the weight gain and the diabetes in the population of patients with schizophrenia. We have completed a pilot study using cognitive behavioral therapy to show that such interventions can have an impact on weight in this population.[68] Ideally, in the future, a large study such as the LOOK AHEAD trial would need to be undertaken in this specific population.[69] There are also small studies suggesting that compounds such as tamoxifen and naltrexone may have a beneficial effect on preventing the weight gain associated with the antipsychotics. [70, 71] There is a lot of interest in using metformin to prevent the weight gain and the diabetes. Since the action of metformin is to increase insulin sensitivity in the liver and to reduce release of glucose from the liver it would only address part of the metabolic defect. Nonetheless, treatment with metformin has shown good success in weight reduction among small numbers of patients with hyperinsulinemia, obese adolescents and in pediatric patients taking antipsychotic drugs.[72-79] Other pharmacologic interventions for antipsychotic medication-induced weight gain (topiramate, sibutramine, orlistat, and nizatidine) yield modest weight loss (about 8 pounds in short-term trials) but raise concerns about potential exacerbation of psychosis.[80-82] Unfortunately, none of these studies have been randomized controlled trials with sufficient evidence to demonstrate efficacy similar to metformin or lifestyle intervention to prevent weight gain from the atypical agents.

Given that the ADA, in a joint statement with the EASD, has recommended that all patients with type 2 diabetes be treated with lifestyle intervention and metformin (unless the person has a contraindication to metformin), the use of metformin is likely to increase in this population.[83] This will not preclude the completion of trials comparing metformin and lifestyle interventions in the prevention of diabetes in this population. It is important that such studies be completed to show safety and efficacy rather than just treating all patients with metformin in addition to the antipsychotic agent. Additionally, until we are able to identify who is likely to develop the sudden onset of hyperglycemia and DKA, metformin should not be started at the time of starting the antipsychotic agent to "prevent" the diabetes and/or weight gain due to the risk of acidosis and death if the person develops DKA.

Prevention of weight gain is important in this population as it impacts response to therapy, adherence and compliance. A review of twenty-six studies found that the noncompliance rate for oral antipsychotic medications ranged from 30% to 76% over a one-year period.[84] The reasons for medication non-adherence are complex and influenced by multiple factors which are patient related, medication related, environmental, and provider–related. Medication-related factors such as side effects are a major reason for non-adherence. Individuals with schizophrenia report that weight gain is a significant and

distressing side effect thus consideration must be given to use the antipsychotics which cause the least amount of weight gain.[85]

Given the fact that the excess of deaths in people with schizophrenia occurs from the usual causes (ie heart disease, stroke, diabetes and cancer) attention has now turned to screening this population for the Metabolic Syndrome and for diabetes. The Metabolic Syndrome is an excellent framework to use for increasing awareness of metabolic (ie CV & diabetes) risk in this population. The measurement of waist circumference has now been implemented in some psychiatry clinics. Recognition of the presence of the Metabolic Syndrome, or the risk for it, is not sufficient. One must also proceed with measuring the lipids and glucose in patients at risk. This becomes problematic as many of our patients attend the public mental health clinics and consider those clinics to be their primary clinic although these clinics are not in a position to function as PCPs. In fact, most of these clinics do not have the resources available to obtain glucose and lipid profiles. Given the high prevalence of diabetes and CVD in this population, provision of primary care services need to be coordinated with mental health care in the future.

These data, together with the other metabolic data, helped to set the stage for the Consensus Statement published jointly in 2004 by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.[86] They addressed the following questions:

1. What is the current use of antipsychotic drugs?
2. What is the prevalence of obesity, prediabetes, and type 2 diabetes in the populations in which the second-generation antipsychotics are used?
3. What is the relationship between the use of these drugs and the incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipedemia, and diabetes, and how should they be treated if diabetes develops?
5. What research is needed to better understand the relationship between these drugs and significant weight gain, dyslipidemia, and diabetes?

The panel recommended that baseline screening measures be obtained before, or as soon as clinically feasible after, the initiation of any antipsychotic medication (Table 3). These include personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease, weight and height (so that BMI can be calculated), waist circumference (at the level of the umbilicus), blood pressure, fasting plasma glucose and fasting lipid profile.

Table 3. Monitoring protocol for patients on second generation antipsychotics.

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

*More frequent assessments may be warranted based on clinical status

As seen in the Table, the patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing second-generation antipsychotic therapy and quarterly thereafter at the time of routine visits. If a patient gains 5% of his or her initial weight at any time during therapy, one should consider switching the second-generation antipsychotics, if possible. In such a situation, the panel recommended cross-titration to be the safest approach; abrupt discontinuation of an antipsychotic drug should generally be avoided. When switching from one antipsychotic drug to another, it is preferable to discontinue the current medication in a gradual fashion. The profile of the subsequent drug will determine the initial dose and escalation strategy. Particular consideration should be given before discontinuing clozapine because of the potential for serious psychiatric sequelae.

Fasting plasma glucose, lipid levels, and blood pressure should also be assessed 3 months after initiation of antipsychotic medications. Thereafter, blood pressure and plasma glucose values should be obtained annually or more frequently in those who have a higher baseline risk for the development of diabetes or hypertension. In those with a normal lipid profile, repeat testing should be performed at 5-year intervals or more frequently if clinically indicated. They also recognized that, although limited data are available in children and adolescents regarding the risks of diabetes when second-generation antipsychotics are given, these patients should have their height, in addition to weight, measured at regular intervals and their BMI calculated. BMI percentile adjusted for age and sex should be used to determine if excessive weight gain has occurred, and if present, a change in therapy should be considered.

For people who develop worsening glycemia or dyslipidemia while on antipsychotic therapy, the panel recommended considering switching to an S second-generation antipsychotic that has not been associated with significant weight gain or diabetes. All patients with diabetes should be referred to a diabetes self-management education program, if available. Referral to a clinician with experience treating people with diabetes was also recommended.

Summary

In summary, patients with schizophrenia have a very high prevalence of diabetes and of metabolic disorders. The introduction of the atypical antipsychotics has dramatically improved quality of life but at considerable metabolic cost. The weight gain appears to have a different mechanism than the sudden onset hyperglycemia. Measures must be taken to try to minimize the weight gain to prevent the early emergence of diabetes in the people who are at risk for diabetes. The sudden onset of hyperglycemia remains unexplained but possibly could be minimized by avoiding some of the antipsychotics such as clozapine and olanzapine. There are certain patients where it is not an option to treat with a different agent. In these cases, they should be treated with insulin. Other agents could be added to the regimen but insulin should be base of their regimen.

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