

The Role of Atypical Antipsychotics in Glucose/Insulin Dysregulation and the Evolving Role of the Psychiatrist in a New Era of Drug Treatment Options

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FOCUS POINTS

- Psychiatric patients tend to have higher baseline risk for cardiovascular disease and tend to be less likely to receive adequate general medical health care.
- The field of psychiatry is expanding to include concerns traditionally reserved for other medical specialties such as endocrinology and cardiology.
- In order to provide the best care of our patients, we must address not only the primary psychiatric symptoms but we must also try to minimize iatrogenic risk of cardiovascular disease by considering both patient risk factors as well as relative drug risks, using the literature as a guideline.
- Psychiatrists must follow a rational monitoring protocol when prescribing atypical antipsychotics and must encourage proper diet, exercise, and general medical care in all of our patients.
- Mechanisms of atypical antipsychotic-induced metabolic disturbances are an important area of current research and likely involve various overlapping pathways as well as individual genetic differences.

ABSTRACT

This article examines the issue of atypical antipsychotics, glucose/insulin, and other metabolic derangements (ie, metabolic syndrome), including a general introduction to the health concerns of our patients, a review of the

literature, possible mechanisms of antipsychotic induced glucose dysregulation, monitoring approaches, and management and prevention of metabolic syndrome. Literature review leads to mechanism hypotheses and risk estimations, leading to guidelines for monitoring and treatment. The patient population suffers from a higher degree of baseline metabolic dysregulation resulting in cardiovascular disease through components of the metabolic syndrome, and this risk increases with administration of atypical antipsychotic medication at different rates, depending on both drug and patient risk factors. The growing knowledge of mechanisms behind drug induced glucose/insulin and other metabolic dysregulation, as well as advances in pharmacogenomics, will help refine drug selection and monitoring for adverse, life-threatening metabolic effects.

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INTRODUCTION:

HEALTH CONCERNS OF OUR PATIENTS

There is a growing body of literature on metabolic derangements in patients treated with atypical antipsychotics. These metabolic derangements include diabetes mellitus, obesity, and hyperlipidemia, with sequelae including, but not limited to, cardiovascular, renal, and retinal disease. As psychotropic medications continue to become more effective, the overall care of our patients is becoming increasingly complex, with greater overlap developing between psychiatry and other specialties. And as the scope of indications for psychotropic use widens, so too does the num-

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ber and variety of people who will derive relief from them. We attempt here, through a review of the literature, to examine the association between atypical antipsychotics and glucose/insulin dysregulation, which will include an examination of possible risk factors and mechanisms of action for this growing problem, as well as proposed guidelines for monitoring and a look at management.

In keeping with this continuum of health care concerns is the need for an increased awareness of the concept of “metabolic syndrome,” also known as “insulin resistance syndrome.”¹ This cluster of metabolic abnormalities consists of ~10 signs that are associated with increased risk of cardiovascular disease, and includes dyslipidemia, insulin resistance, central obesity, hypertension, and procoagulant state. It is notable that this risk begins whether or not there is a diagnosis of type 2 diabetes,² and it may help explain the increased rates of cardiac mortality observed in patients with schizophrenia.³ Melkersoson and colleagues⁴ showed that 71% of patients who had been on olanzapine for a median treatment period of 5 months had signs of metabolic syndrome, including insulin resistance, hyperinsulinemia, central obesity, and hyperlipidemia. These were patients diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder, equally distributed by gender, and 43% had a family history of diabetes. Though the authors admit that some of the signs of metabolic syndrome may have already been present at the beginning of the study, we are struck by the possibility that they may not have been as prominent, or even present at all, 5 months earlier.⁴ At the same time, we must also consider what this means regarding the increased level of monitoring responsibility we have for these patients. In a recent Veterans Affairs-based study,⁵ nearly a quarter of all nondiabetic clozapine-treated patients in 8 medical centers had undiagnosed hyperglycemia.

This brings to the fore the issue of increased baseline prevalence of several of the signs of metabolic syndrome in our patient population. A recent study involving almost 40,000 patients⁶ with schizophrenia noted a baseline 6–7 times higher rate of diabetes in these patients versus age-matched controls.⁷ Furthermore, we are beginning to suspect that there may be other baseline metabolic derangements in the patient population we treat, including impaired lipid metabolism, and even increased risk for some forms of cancer and autoimmune disorders.⁸ These considerations, coupled with other risk factors our patients may already have, such as smoking, sedentary lifestyle, and poor nutrition habits, suggest to us more clearly the order of complexity we are dealing with in caring for patients. Of course, this picture becomes even more

complex when we consider more acute and potentially lethal outcomes such as diabetic ketoacidosis and acute myocardial infarction, forcing us to realize that any routine screening matrix we develop will need to reflect a keen vigilance regarding these complications.

ATYPICAL ANTIPSYCHOTICS AND GLUCOSE/INSULIN HOMEOSTASIS

There is a surprisingly limited number of controlled studies concerning the possible contribution of the atypical antipsychotics to the development or worsening of glucose/insulin dysregulation. However, there seem to be an increasing amount of open studies and numerous recent case reports. Of those that have been published,^{4,6,9-13} the majority have shown at least an association between components of metabolic syndrome, such as hyperglycemia and hyperlipidemia, and various atypical antipsychotics, if not a more intimate connection. Regarding hyperglycemia, the relationship between gluoregulatory abnormalities and the atypical antipsychotics seems thus far to be more along the lines of an insulin resistance phenomenon seen typically in type 2 diabetes, rather than the beta cell destruction which is classically indicative of type 1 diabetes.²

There are several classes of glucose intolerance, updated in 1997 by the Expert Committee,¹⁴ which now include impaired fasting glucose, the newest category, as well as the previous ones (ie, impaired glucose tolerance [IGT] and frank diabetes). It is notable that diabetes is now diagnosable with a fasting plasma glucose ≥ 126 mg/dL (lowered from the original 140 mg/dL) or by a 2-hour post 75 g oral glucose load plasma glucose level (2hPG) of ≥ 200 mg/dL. Impaired glucose tolerance is classified as a 2hPG ≥ 140 mg/dL, and impaired fasting glucose as a fasting plasma glucose ≥ 110 mg/dL. Increased risk of both development of diabetes, as well as cardiovascular disease, occurs at the level of impaired glucose tolerance, which is diagnosed based upon 2hPG, and not fasting plasma glucose. This tells us that our patients are at risk even if they are not formally diagnosable with diabetes mellitus and that further study design should perhaps be geared towards accurate measurements of 2hPG in our patients. This data may actually be easier to obtain than are accurate measurements of fasting plasma glucose in our patient population and will help identify patients with impaired glucose tolerance. What follows is a review of the literature regarding glucose/insulin dysregulation in connection with the atypical antipsychotics, with a further attempt to explore these issues within the context of other factors, such as age, weight gain, dyslipidemia, and family history, among others.

Age as a Risk Factor

Several studies have noted correlations between age and the development or worsening of glucoregulatory problems with the atypical antipsychotics. A main area of interest is whether these drugs contribute to the incidence of these problems *de novo* versus playing a role in hastening a predetermined genetic disposition to them, perhaps as modifiers of other risk factors. Sernyak and colleagues⁶ found that the strongest association between diabetes and the atypical antipsychotics was in patients <40 years of age, where the odds of having diabetes was significantly higher for all four of the atypical antipsychotics studied (clozapine, olanzapine, risperidone, and quetiapine) versus typical antipsychotics. In fact, when the notably large number of patients in that study (N=38,600) was divided into five age groups, they found that patients in the three youngest groups (<40 years of age, 40–49 years of age, and 50–59 years of age) who were treated with atypical antipsychotics had a significantly higher rate of diabetes when compared to those treated with typical antipsychotics. They found no significant association in the two older age groups (60–69 years of age, ≥70 years of age), which might suggest that older people who have not yet developed diabetes may lack the genetic predisposition for its development, regardless of other potential risk factors such as use of these medications.

Similarly, Lund and colleagues⁹ found, when comparing patients treated with clozapine to those treated with typical antipsychotics, that in patients 20–34 years of age the incidence was ~5% in the clozapine group, versus 2% in the typical antipsychotics group, which made for a relative risk of 2.5. Hagg and colleagues¹⁰ also compared clozapine with typical antipsychotics and found that the patients in the clozapine group were significantly younger and had a higher incidence of hyperglycemia (33% versus 19%), impaired glucose tolerance (10% versus 3%), and diabetes (12% versus 6%). Although the study failed to show significance in these areas, this may have been partially due to the small sample number. Overall, these younger patients in the clozapine group were more than twice as likely to develop either impaired glucose tolerance or frank diabetes than were the patients on typical antipsychotics (22% versus 10%), and, notably, had significantly shorter durations of both disease and treatment than patients in the typicals group.

Koller and colleagues,¹⁵ using data from the Food and Drug Administration MedWatch surveillance program, found that patients with new onset, clozapine-associated diabetes had a mean age of 39 years

and that at least 40% of them were in the fourth decade of life. Similarly, in a different study,¹⁶ also using MedWatch but this time searching for olanzapine-associated diabetes, positive cases had a mean age of 39.8 years. In a study using data derived from a large health plan database¹⁷ comparing the relative association of diabetes with several atypicals versus conventionals, found that, though patients on both olanzapine and risperidone were of similar age, those on olanzapine were 2.5 times more likely to develop diabetes than those on risperidone. Results for clozapine, even more remarkable, involved a younger subgroup of patients.

Weight Gain as a Risk Factor

Another area of increasing interest is the relationship of weight gain to the development of glucoregulatory problems during treatment with atypical antipsychotics. Though it is generally well understood that there is a correlation between obesity and insulin resistance, especially abdominal visceral adiposity, (even with as little as 4 lbs of weight gain),² we are beginning to see that the story is not so simple with regards to atypical antipsychotic induced problems. In fact, we see in the literature evidence that weight gain and atypical use may be independent, or at least semi-independent risk factors for the development of glucoregulatory problems.

Newcomer and colleagues¹³ studied modified oral glucose tolerance test results in patients who were matched for body mass index (BMI) and found that the association between glucose dysregulation and use of atypical antipsychotics can vary independently of adiposity. In this study, patients treated with olanzapine had significant glucose elevations at all post-glucose load time points (ie, 0 minutes, 15 minutes, 45 minutes, 75 minutes) compared with patients taking typical antipsychotics and to untreated healthy controls. Clozapine-treated patients had significant elevations at fasting and 75 minutes post-load, and risperidone-treated patients had elevations in fasting and post-load levels 45 minutes and 75 minutes only when compared with untreated healthy controls. Similarly, Hagg and colleagues,¹⁰ when comparing clozapine to typical antipsychotics, found that the body weights of patients with impaired glucose tolerance or diabetes in the clozapine group were not higher than those with normal glucose metabolism. Henderson and colleagues¹¹ found that, over the 5-year study period, 67% of clozapine-treated patients had diabetes by the revised criteria of the Expert Committee,¹⁴ and that weight gain was not a significant risk factor for its development. However,

they did find that patients on clozapine had significant weight gain and it continued for ~46 months into the study period. Melkersson and colleagues,⁴ in studying patients on olanzapine for a median treatment period of 5 months, found elevated fasting glucose even in patients with normal BMI. This would suggest mechanism(s) other than being obese for the insulin resistance seen in these patients. At the same time, change in weight did have a positive correlation to overall blood glucose levels as would be expected. In an earlier study, comparing clozapine with the typical antipsychotics, Melkersson and colleagues¹² found no significant difference in BMI between the two groups, yet more patients in the clozapine group had elevated insulin levels compared to the typicals group (46% versus 21%).

In studying both clozapine and olanzapine associated diabetes, Koller and colleagues¹⁵ and Koller and Doraiswamy¹⁶ found that the time to onset of diabetes or hyperglycemia varied greatly among patients, from immediately after one dose to >5 years with clozapine, and from 2 days to 45 months with olanzapine. Of the patients who developed gluoregulatory problems, the majority of cases occurred within 6 months of initiation of treatment, and 27% and 18%, respectively, were diagnosed with diabetes within the first month of treatment with clozapine and olanzapine. Furthermore, 63% of cases of primarily new onset diabetes with blood glucose ≥ 700 mg/dL occurred within 3 months of the start of clozapine therapy, with comparable numbers for olanzapine. The variable time to onset of problems, very early in many cases (ie, before weight gain) and years later in others, as well as the severity of these problems along that time range, point to a multifactorial mechanism or perhaps multiple separate mechanisms towards the onset gluoregulatory problems associated with these drugs. Underlining this point is a retrospective analysis of olanzapine-treated patients which did find a marginal association between median nonfasting glucose and weight gain over the longer term.¹⁸

Hyperlipidemia as a Risk Factor

Another theme of interest is the possible association between glucose dysregulation and hyperlipidemia in patients taking atypical antipsychotics. Several studies^{4,9,12} have demonstrated hyperlipidemia, especially hypertriglyceridemia, in patients who also showed glucose dysregulation during treatment with clozapine and olanzapine. Furthermore, hyperlipidemia, and especially hypertriglyceridemia, may itself be associated with insulin resistance (and secondary increased insulin secretion)^{19,20} In both

of the previously mentioned Melkersson and colleagues studies,^{4,12} which considered clozapine and olanzapine, respectively, patients on both of these medications demonstrated elevated insulin levels (71% of the patients in the olanzapine study and 46% in the clozapine study). Lipids were measured as part of the olanzapine study and it was found that 85% of patients had hypercholesterolemia and 62% had hypertriglyceridemia. Still not clear then is the nature of the relationship between hyperlipidemia and insulin resistance (ie, whether it is one of causality or whether these adverse effects are independent of one another, or maybe “relatively independent”).

Henderson and colleagues¹¹ noted a significant increase in serum triglycerides in patients treated with clozapine, and that this increase was nonsignificantly associated with the development of diabetes or nonconfirmed diabetes. They also found that total serum cholesterol was not associated with development of diabetes or nonconfirmed diabetes. Lund and colleagues⁹ observed an increased relative risk of hyperlipidemia (as for diabetes) only among younger patients on clozapine (20–34 years of age), but no significant difference in overall incidence rates when compared with patients on typical antipsychotics. This further suggests the possibility that atypical antipsychotics like clozapine may not be independent risk factors for hyperlipidemia and glucose/insulin dysregulation, but may instead be modifiers of other risk factors, such as family history, obesity, diet, age, etc.

Family History as a Risk Factor

Studies have thus far failed to show a significant correlation between family history and glucose/insulin dysregulation. In the latest Melkersson and colleagues⁴ study, six of the 14 patients on olanzapine gave a family history of type 2 diabetes, yet only two of these had elevated insulin levels (compared with eight who gave no family history of diabetes) and none had elevated fasting blood glucose levels. Hagg and colleagues¹⁰ showed that in those who had either diabetes or IGT, four out of 13 on clozapine gave a positive family history and in the control group, on conventional depot neuroleptics, three out of six gave a positive history. Henderson and colleagues¹¹ also failed to show a significant correlation between glucose/insulin dysregulation and family history of diabetes. In all of these studies, however, there remains the possibility that family history of diabetes was underreported, due to reasons ranging from study patients not knowing the status of their relatives, to undiagnosed problems in family members.

Ethnicity as a Risk Factor

In terms of ethnicity, case reports show that a majority of atypical antipsychotic associated diabetes involve non-caucasian patients (African American, Hispanic, Asian, and Pacific Islander), who seem to have a higher baseline risk^{10,11} for the components of the previously mentioned metabolic syndrome. Henderson and colleagues¹¹ noted that half of the patients who developed insulin dependent diabetes, were either African American or Hispanic. Notable is that all of these patients had also gained >40% of their body weight and had elevated triglycerides, abdominal obesity, and hypertension. However, the clozapine study by Hagg and colleagues¹⁰ involved only caucasian patients, almost all of whom were of Scandinavian descent, and those on clozapine still had higher rates of incidence of hyperglycemia, diabetes, and IGT than controls.

Lindenmayer and colleagues,²¹ in comparing changes in glucose and cholesterol levels in patients treated with clozapine, olanzapine, risperidone, and haloperidol, noted that, among patients with abnormally elevated glucose, there was a higher proportion of African American patients (18.6%) than white (10.3%) or Hispanic (0%) patients. However, at least one study¹⁶ had a higher proportion of Caucasian patients (56%) with newly diagnosed hyperglycemia while on an atypical (olanzapine), than patients of Hispanic, African, or Asian descent combined.¹⁶ Another study,¹⁵ using the same data source, but this time measuring clozapine-associated diabetes, found that African Americans represented almost three times the number of positive cases than did Caucasians.

Gender as a Risk Factor

Another finding is the relationship between gender and glucose/insulin dysregulation in patients taking atypical antipsychotics. Hagg and colleagues¹⁰ found that women were more frequently diagnosed with diabetes or IGT when treated with clozapine than when treated with typical antipsychotics. Sernyak and colleagues⁶ noted an association between receiving a prescription for clozapine, olanzapine, and quetiapine, but not risperidone, and the diagnosis of diabetes. The patients receiving these prescriptions were significantly more likely to be female, of younger age, and to have psychiatric comorbidity). However, Lund and colleagues⁹ noted a significantly higher proportion of men in their clozapine group than in their typical antipsychotics group, with an effect of clozapine on diabetes incidence that was significant in younger patients. One large database study²² comparing the

risk of diabetes with olanzapine versus risperidone use, besides finding that the former was generally associated with a 20% greater risk than the latter, also found that in women the risk was even greater (30%).

In two FDA studies of olanzapine and clozapine associated diabetes, respectively,^{15,16} the authors found that the male-to-female ratio for all newly diagnosed cases of hyperglycemia was 2:1 and 2:9, both of which differed significantly from the expected ratio (incidence) of 0.7.²³ A study in the *British Medical Journal*,²⁴ which demonstrated that patients taking olanzapine had a significantly increased risk of diabetes than controls (no drug) and those on conventionals, also showed that women had a higher incidence rate of treatment-related diabetes than did men. Overall, however, there does not thus far appear to be a definitive trend regarding either gender as a risk factor or co-risk factor for the development of gluco-regulatory problems with the use of atypical antipsychotics.

Other Possible Factors

Other factors of interest include effects of regular exercise, duration of disease and treatment, psychiatric comorbidities, and other primary diagnoses besides schizophrenia (ie. schizoaffective disorder, bipolar disorder, personality disorder, and psychotic depression). Henderson and colleagues,¹¹ in their 5-year clozapine study, found that weight gain continued despite active weight-loss programs consisting of diet and exercise and 67% of the patients in this study qualified for diagnosis of diabetes. Hagg and colleagues¹⁰ point out that patients in their clozapine group, who had higher rates of hyperglycemia, diabetes, and IGT, also had significantly shorter duration of both disease and treatment (and were younger). Finally, several studies^{4,10-12} have involved patients with primary diagnoses other than schizophrenia or have included comorbidities such as substance abuse or other, previously mentioned disorders. How differences in baseline prevalence among these disorders might effect study outcomes has not yet been fully explored.

POSSIBLE MECHANISMS OF ANTIPSYCHOTIC INDUCED GLUCOSE DYSREGULATION

The causative factors behind glucose dysregulation appear complex and are not yet fully understood. Questions and themes which arise repeatedly in the literature point to the complexity and multi-organ system nature of glucose and insulin homeostasis. Authors have pondered the question of insulin resistance versus dysregulated insulin secretion, the

latter of which seems especially difficult to understand given our relatively limited knowledge of pancreatic beta cell function and factors that might influence it, such as leptin⁴ for example, which is discussed later. Another theme which arises involves the question of the direct versus indirect effects of atypical antipsychotics on metabolic homeostasis, including for example, the indirect effect of causing increased abdominal visceral adiposity leading to insulin resistance (even with increases as little as 4 lbs).² This would be in contrast to a direct effect on skeletal muscle cells, influencing their ability to absorb glucose in the periphery, or direct effects on hepatic glucose production, or even on glucose transporter function.²⁵ As already mentioned, other factors which are becoming areas of increasing interest include effects of age, ethnicity, and genetics on the adverse side effects of these medications.

Insulin Resistance versus Dysregulated Secretion

It has been shown in recent studies by Melkersson and colleagues^{4,12} that atypical antipsychotics such as clozapine and olanzapine may cause both insulin resistance as well as increased insulin secretion. The authors found that glucose levels remained high in the face of hyperinsulinemia, indicating insulin resistance, but they also found something else. These patients also showed low insulin-like growth factor binding protein-1 (IGFBP-1 levels [produced in the liver by an insulin regulated process]), at fasting insulin levels that were within normal limits. We would expect instead high levels since IGFBP-1 usually has an inverse correlation to insulin levels in healthy subjects. As they point out, this makes sense if we consider a high diurnal insulin secretion over a 24-hour period rather than just the low simple fasting insulin levels. In fact it is known that diurnal insulin secretion is reflected by IGFBP-1 better than by fasting morning insulin levels.^{26,27} This would lead to the possibility of either a direct or indirect effect of olanzapine and clozapine on the pancreatic beta cells, causing increased secretion of insulin.

Serotonin

Some consideration has to also be given to the potential direct effects of the atypical antipsychotics on serotonin (5-HT) receptors, which leads to complex and at times contradictory findings. It has been postulated that antagonism of 5-HT_{1A} receptors can cause decreased insulin levels by influencing β -cell function and also that agonism of 5-HT_{2A/C} receptors can cause hyperglycemia.^{28,29} It is also postulated that antagonism of 5-HT_{2C} receptors may play a role

in weight gain.³⁰ Patients on the atypicals have been shown to have increased insulin levels and hyperglycemia.^{4,12,13} This leads to the possibility that the net effect of serotonergic blockade by these drugs is to potentiate the overall clinical presentation of insulin resistance. We must also consider the issue of specific differences in metabolism of these drugs in different people, as we shall see later when we discuss the burgeoning field of pharmacogenomics. For example, it has been shown that blood glucose levels, as well as lipids, weight gain, and leptin levels, vary inversely with a major metabolite of olanzapine, *N*-desmethyloanzapine, but not with olanzapine itself.⁴ It is possible that patients who are more susceptible to these complications produce more of this metabolite via a genetically determined dominant pathway of metabolism of the parent drug. Similarly, it is possible that 5-HT receptor binding plays a different role in different people, depending on genetic predisposition, including quantity and distribution of particular 5-HT receptor subtypes.

Leptin

Leptin has been particularly interesting as it is thought to be intimately involved in another important area seemingly effected by these medications, weight regulation, yet it may also play a more direct role in insulin homeostasis. It has been shown that the normal positive correlations between leptin levels and elevated BMI, as well as leptin levels and female gender do not hold for patients taking olanzapine, but that there is, however, a positive correlation between leptin levels and serum insulin levels.⁴ In their previously mentioned olanzapine study, Melkersson and colleagues⁴ found that 57% of patients had hyperleptinemia that was independent of BMI. It seems there are two sides to this coin however: insulin is known to stimulate leptin production in adipocytes,³¹ which might help explain higher leptin levels in patients taking this class of medication, however leptin is also thought to affect pancreatic β -cell function in as yet unclear ways.^{32,33} One might hypothesize a direct effect upon leptin levels by these medications which might lead to either increased or decreased insulin secretion.

Insulin Sensitivity

The nature of the decline in sensitivity of insulin-sensitive tissues, namely skeletal muscle, liver, and adipose tissue needs clarification. As touched upon earlier, patients taking olanzapine and clozapine have been shown to maintain appropriately low levels of IGFBP-1 in the face of high diurnal serum insulin levels.^{4,12} Since the production of

IGFBP-1 in the liver is regulated by insulin, it is suggested that the insulin resistance seen is likely not primarily hepatic in nature. This helps confirm that most of the problem is in adipose tissue and skeletal muscle, which is further determined by factors such as intrinsic tissue characteristics, direct drug effects on these tissues, and genetic predisposition to these variables. Furthermore, drugs can indirectly cause insulin resistance by other mechanisms, including increasing appetite, decreasing activity level, and decreasing oxidative metabolism in tissues, among others.²

Glucose Transporters

There has been some effort to clarify the effects of antipsychotic drugs on glucose transporters, and specifically transporters within the rat pheochromocytoma cell line, a neuronal cell line which participates in glucose uptake and transport via glucose transporter proteins (GLUTs) in the cells.^{25,34} The thought was that drugs such as olanzapine and clozapine might share an affinity for dopamine receptors in rat pheochromocytoma cells, and that upon binding to these dopamine receptors, interfere with glucose uptake, seen clinically as insulin resistance. The problem is that the results have been inconsistent with respect to the dopamine D₂ receptor, with some drugs, like haloperidol, that have a very high affinity for this receptor, having minimal effect on glucose uptake whereas others with high affinity, like fluphenazine, having strong inhibitory effects.²⁵ The atypical antipsychotic clozapine, which has a strong affinity for D₄ also affected glucose transport strongly. Whether the mechanism by which these medications affect these cells involves dopamine receptors or some other site (Calcium channels have also been proposed^{35,36}) requires further research. Meanwhile we are left with considering the various steps in the glucose metabolism signaling pathway which may be sensitive to adverse effects of these drugs, whether by directly affecting GLUTs or perhaps by somehow altering receptor binding characteristics in rat pheochromocytoma cells, among other possibilities. Given the complexity and interdependent nature of the mechanisms outlined above, it becomes clearer, as we explore these possibilities, that terms such as “direct” and “indirect” become relative. Perhaps even more interesting and exciting is the possibility that the way we conceptualize our understanding of illnesses like diabetes mellitus will itself derive benefit from this wave of exploration of metabolic derangements in the patients we treat, further broadening the potential rewards of our careful examinations.

EVOLVING APPROACH TO THE PSYCHIATRIC PATIENT WITH METABOLIC DISTURBANCES

Monitoring Parameters

We are beginning to see a paradigm shift in psychiatry and in the doctor patient relationship within psychiatry. The newer antipsychotic medications, which provide new levels of relief from symptoms, also challenge us to broaden our realm of responsibility to our patients. Perhaps now more than ever, our role as the sole physician for many of these patients comes to bear upon us. As we continue to design and carry out more controlled studies, we must concurrently bring together a practical set of guidelines for monitoring and treatment so that we can more safely utilize these beneficial medications.

Experts agree^{37,38} that the approach to monitoring must be customized based upon several factors, including the patient's own risk profile, which includes complete medical and family histories (including side effects to psychotropics in family members), along with the relative risk of metabolic syndrome of the various atypical antipsychotics (Table 1). For higher risk patients and/or higher risks medications, monitoring will be more intensive (Table 2). High risk factors for patients include: family history of diabetes either independent of or related to medications use; ethnicity (African American, Hispanic, Pacific Islander, and Asian patients seem to be at higher risk); obesity; smoking; hypertension; hypercholesterolemia; and sedentary lifestyle. Younger patients seem to also be at increased risk, as mentioned previously. The agents with highest risk include clozapine and olanzapine,³⁹ though it is important to keep in mind that quetiapine is related to these dibenzodiazepine derivatives.

In these higher risk cases, it would be ideal to begin with a baseline 2hPG level, which can be abnormal even with normal fasting plasma glucose and will help gauge future monitoring needs and latent diabetes in younger patients, and a complete lipid panel. Note that this goes a step further than does the screening algorithm outlined in the 2003 American Diabetes Association Clinical Practice Recommendations,⁴⁰ which starts with the fasting plasma glucose test. Measurement of weight and blood pressure is done at every visit and height is also recorded. Due to the possibility of ketoacidosis, and even death, within days of beginning treatment, fasting glucose should be measured 3–7 days after starting the atypical antipsychotic. Following this, fasting glucose should

be monitored every month for the first 6 months (within which time the majority of cases of diabetes occurs^{15,16}), then every 3 months for the second 6 months. Watch for a rise in levels, which might point to oncoming problems, or perhaps latent diabetes and the need for decision-making about the current treatment.¹ Regarding cholesterol, the Adult Treatment Panel III (ATP III) guidelines of the National Cholesterol Education Program⁴¹ recommends in general that all adults ≥ 20 years of age should have a fasting lipid profile every 5 years. In the higher-risk category of patients we are discussing, lipids should be monitored every 6 months for the first year that they are on antipsychotic medication. According to ATP III, even if the patient is non-fasting, it is still useful to draw a total cholesterol and high-density lipoprotein, which should measure < 200 mg/dL and ≥ 40 mg/dL, respectively, otherwise necessitating a follow-up fasting profile so that low-density lipoprotein can be accurately measured (management is based on low-density lipoprotein level.)

After the first year, fasting plasma glucose should be monitored every 6 months and lipids yearly. Should any of these indicators be abnormal or worsen over time, then the psychiatrist needs to decide whether to make a medication change and continue to monitor, or begin consultation with an endocrinologist and begin instituting an appropriate diet and exercise and/or medication program. (It would be ideal if patients

were given appropriate diet and exercise programs regardless of other factors, given their already increased risk of cardiovascular problems). In terms of length of time needed for monitoring, we must keep in mind the previously discussed results of Henderson and colleagues¹¹ that show continued significant weight gain through 46 months, and increasing incidence of diabetes through all 5 years of the study.

Lower-risk patients, or patients on lower risk medications (Table 1),³⁷⁻³⁹ would benefit from the same initial screening tests, that can then be repeated annually. Newer agents, such as ziprasidone and aripiprazole, will likely be included in future studies, with current clinical evidence suggesting they may also carry lower risk of metabolic syndrome complications. It is important for us to remember that our patients already have a higher risk of these complications, regardless of medications, and that, as it stands, they are not likely to have adequate general medical care.

It will likely take some time for psychiatrists to adopt the kind of monitoring outlined here, especially while such monitoring is still largely voluntary. The FDA is currently involved in having pharmaceutical companies give a class warn-

TABLE 1. EVALUATING RISK*^{37,39}

1. Complete medical and family history (high risk if positive for diabetes mellitus)
2. Ethnicity: high-risk groups—African American, Pacific Islander, Hispanic, Asian
3. Obesity
4. Smoking
5. Hypertension
6. Hypercholesterolemia
7. Sedentary lifestyle
8. Higher risk drugs: clozapine and olanzapine
9. Moderate risk drugs: risperidone and quetiapine
10. Lower risk drugs: haloperidol and other typicals, ziprasidone, and aripiprazole

* Note also that younger patients may also be at increased risk.

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TABLE 2. MONITORING PARAMETERS

1. Evaluate the risk of patient and drug
2. Baseline serum glucose level (2hPG for higher-risk cases would be ideal)
3. Baseline lipid panel
4. Weight and blood pressure at every visit and height at initial visit (for BMI)
5. Fasting serum glucose 3–7 days after starting medication (higher-risk cases)
6. Fasting serum glucose monthly for the first 6 months then every 3 months for the second 6 months (annually for lower-risk cases)
7. Lipid panel every 6 months for the first year (annually for lower risk cases)
8. After the first year, fasting glucose every 6 months and lipids annually (higher risk)
9. Emphasize proper diet and exercise regardless of risk (baseline higher risk of metabolic syndrome)
10. Maintain good communication with PCPs and endocrinologists

2hPG=2-hour postglucose; BMI=body mass index; PCPs=primary care physicians.

Ferraioli A, Shirley KL, David P. *CNS Spectr*. Vol. 9, No. 11. 2004.

ing regarding diabetes in their information about these medications, and we might predict that rigorous monitoring as well as prudent medication choices will be more common among psychiatrists in future months. Until then, physicians should strive to watch for signs of metabolic dysregulation in patients on atypical antipsychotics, especially the higher risk drugs and patients, in the manner we have discussed herein.

Of course, any program is better than none, and one might argue that a “bare bones” approach may serve as a more gradual introduction to the average practicing psychiatrist looking to incorporate some of these ideas into his/her practice. With this in mind, a minimalist introductory monitoring approach is included in Table 3. As is evident, this falls considerably short of the 10 steps we have derived from the literature in terms of completeness; however, it is certainly better than nothing, and involves very little in the way of the limited resources of time and money.

PHARMACOLOGIC MANAGEMENT/ PREVENTION OF METABOLIC SYNDROME AND PHARMACOGENOMIC INSIGHTS

Weight Gain and Impaired Glucose Tolerance

According to currently published literature, clozapine and olanzapine cause substantial weight gain more frequently than most conventional and atypical agents such as risperidone, quetiapine, ziprasidone, and aripiprazole.⁴² As stated previously weight gain can effect self-esteem, and patients have indicated this side effect is the most distressing surpassing both sedation and sexual dysfunction.³⁷ Weight-gain is often treated pharmacologically in addition to exercise and dietary

interventions, in order to induce weight loss thereby increasing self-esteem and compliance.⁴² Though a detailed review of the treatment of obesity and diabetes is beyond the scope of this article, we will touch upon some possibilities for management and prevention of these problems. Of course, it is important to emphasize the need for regular consultation with endocrinologists, internists, or family physicians, rather than an ad hoc approach to general medical care in the psychiatric setting. Some psychiatric clinics are beginning to employ these other specialists on a part-time, consultation basis where they are on-site ≥ 1 days/week and working in collaboration with psychiatrists.

Orlistat, a lipase inhibitor, and sibutramine, a selective serotonin-noradrenaline inhibitor (SNRI), are both FDA labeled for the treatment of obesity.⁴² They have both been shown to be effective for weight reduction and maintenance of weight loss in placebo-controlled, randomized clinical trials.⁴² They provide additional benefits in patients with metabolic syndrome, since both improve glycemic control and lipid profile.⁴² All published clinical trials reported significant weight loss in the range of 7–10 kg, however control groups also lost between 3–6 kg from concomitant behavioral interventions.⁴² Clearly, the evidence suggests that these agents are of greater value in prevention of weight regain than in promotion of weight loss. However, both agents have their therapeutic limitations for our patients with chronic mental illnesses such as schizophrenia.

Orlistat is indicated in combination with a diet of <30% fat content.⁴² It is FDA labeled for the treatment of obese patients with a BMI ≥ 30 kg/m² or patients with additional risk factors such as metabolic syndrome with a BMI 28 kg/m².⁴² According to Allison and colleagues,⁴⁵ men with schizophrenia have an average BMI of 26–26.5 kg/m² and women with schizophrenia have an average BMI of 27–27.5 kg/m². Therefore, many of our schizophrenia patients may qualify for orlistat pharmacotherapy. However, orlistat pharmacotherapy without a fat-restricted diet will lead to unpleasant side effects, such as flatulence, oily stools, and fecal incontinence.⁴² Potential drug-drug interactions include warfarin and the oral antidiabetics acarbose and metformin as well as low absorption of fat-soluble vitamins of which vitamin E coadministration maybe necessary.⁴²

Sibutramine is pharmacologically similar to venlafaxine and was initially developed as an SNRI, but in clinical studies it did not produce a significant antidepressant effect.⁴² Sibutramine works through several mechanisms: increasing satiety and decreas-

**TABLE 3. MONITORING: “BARE BONES”
INTRODUCTORY APPROACH**

1. Weigh patients each visit
2. Educate patients re: symptoms of DKA/DM, as well as diet and exercise; instruct them to stop the medication and go to ER if they experience polyuria/nausea/vomiting/GI pain
3. Baseline FBG and cholesterol (at the very least a HbA1C)
4. Refer for high blood glucose/cholesterol

DKA=diabetic ketoacidosis; DM=diabetes mellitus; ER=emergency room; GI=gastrointestinal; FBG=fasting blood glucose; HbA1C=hemoglobin A1C.

Ferraioli A, Shirley KL, David P. *CNS Spectr*. Vol. 9, No. 11. 2004.

ing hunger as well as preventing the energy decline that follows weight loss.⁴² Due to its pharmacologic activity as an SNRI, sibutramine administration is contraindicated in patients who are also on serotonergic antidepressants, those patients with hypertension and/or seizure disorders.⁴² Unfortunately, many of our patients who need atypical antipsychotic pharmacotherapy, are also treated with SSRIs (in 75% of patients), excluding the possibility of sibutramine administration. Other potential adverse reactions include: insomnia, dry mouth, headache, tachycardia, and potentially serious complications in overdose.⁴² Potential drug-drug interactions include potential decrease of antipsychotic effect due to small agonistic activity on D₁ and D₂.⁴²

Topiramate is a second-generation anticonvulsant agent with γ -aminobutyric acid-ergic and anti-glutamatergic action.⁴² Topiramate also has carbonic anhydrase activity and was potentially developed as an oral antihyperglycemic agent for diabetes mellitus. It has been associated with dose-related weight loss between 1–8 kg in patients without mental illness.⁴² There are several smaller studies suggesting that topiramate may result in substantial weight loss in patients with bipolar disorder and schizophrenia (some report ≤ 21 kg weight loss over 5 months) however current evidence is limited to non-randomized and observational research.⁴² In any case, slow upward titration of topiramate is strongly recommended due to worsening of potential cognitive adverse reactions, especially in patients who already maybe afflicted with predominate negative symptomatology. Other potential adverse reactions include sedation, confusion, cognitive impairment (>5%), impaired performance of skilled tasks, psychosis (3%), depression, tinnitus, and nephrolithiasis.⁴² Potential drug-drug interactions include potentiation of neuroleptic-induced sedation, cytochrome P450 (CYP) interactions with phenytoin, carbamazepine, and decreased efficacy of oral contraceptives.⁴²

Nizatidine and cimetidine are histaminergic H₂ blockers that may be effective for weight control, as well as improved glycemic control and lipid profile. Nizatidine in particular has been studied for weight control in patients who are being treated with the atypical antipsychotic olanzapine, with reported of weight loss up to 4 kg over 2 months of treatment.⁴² However, any long-term effect of these agents (>6 months) is yet to be demonstrated in published research.⁴² Potential adverse reactions of cimetidine and nizatidine are rare but include renal and liver toxicity, hypotension, bradycardia, hyperprolactinemia and gynecomastia.⁴² Potential cimetidine-

drug interactions include CYP inhibition thereby increasing antidepressant, antipsychotic, benzodiazepine, and anticonvulsant levels.⁴²

Metformin, an oral antidiabetic biguanide, has proven beneficial effects on glucose plasma concentration and serum lipids. However, its potential as a weight-loss agent currently appears to be weak and dependent upon a hypocaloric diet.⁴² A small crossover placebo-controlled study was conducted in five schizophrenic women; metformin did not result in significant weight loss or improvement of glycemic control.⁴² Potential adverse reactions include decreased folate and B12 absorption, hypoglycemia and lactic acidosis thereby contraindicating its use in impaired renal and liver function.⁴² Potential metformin-drug interactions include an enhanced hypoglycemic effect with monoamine oxidase inhibitors, fluoxetine, testosterone, and an increased risk of lactic acidosis with alcohol consumption.⁴²

Thiazolidinediones are oral antidiabetic agents⁴³⁻⁴⁵ that have been shown not only to improve glucose sensitivity but also to delay and prevent the onset of diabetes mellitus. Currently, there are no published studies of thiazolidinedione (troglitazone, pioglitazone, rosiglitazone) pharmacotherapy within a mentally ill population. Their therapeutic benefit of true diabetes mellitus prevention is very enticing for our patients who develop atypical-induced metabolic syndrome. However their use is limited by potential liver enzyme elevation and toxicity,^{46,47} resulting in requirements for frequent monitoring for pioglitazone and rosiglitazone during the first year of therapy (baseline, then every 2 months). Unfortunately, some patients who took troglitazone developed idiosyncratic liver toxicity and some died from complete liver failure, thus resulting in complete FDA withdrawal of its approval.

In conclusion, most of the currently available pharmacologic interventions do not provide as safe and effective a treatment option as we would like for atypical-induced metabolic dysregulation.⁴² On the other hand, H₂ antagonists, metformin, and perhaps thiazolidinediones may provide more acceptable benefit in the treatment and prevention of atypical-induced weight gain, impaired glucose tolerance, and hyperlipidemia. However, and especially with regards to management of diabetes, we must respect the complexity of these issues and the various side effects (eg, further weight gain in some instances) of the drugs used to treat them, including, for example, some of the antidiabetic agents.

We would also further refer the reader to the growing body of literature regarding treatment strat-

egies for these complications, including a succinct and accessible review by Vieweg and colleagues,⁴⁸ which discusses, among other strategies, combination therapies. Examples include adding a lower risk atypical to a higher risk one in order to reduce the dosage of the latter, combining a higher risk drug and a dopamine agonist, and using H₂ antagonists or the antiepileptic topiramate.

Finally, in addition to the collaboration with other specialists discussed above, another component to more complete and ethical care for patients on these medications is the provision of patient education and informed consent. This is an area which is ripe for further exploration and definition, which will not be attempted here. One major concern is the capacity of some of the more severely mentally ill patients to fully participate in such a process, so that a truly informed choice can be made.

Pharmacogenomics

Although there is an overwhelming burden of literature concerning clozapine and its association with the development of metabolic syndrome, clozapine has also demonstrated superior efficacy in patients with refractory schizophrenia, bipolar disorder, borderline personality disorder and in the prevention of suicide.⁴⁹⁻⁵³ Fontaine and colleagues estimated the deleterious effects of clozapine-induced weight gain (defined as 10 kg over a 10-year follow-up period) using clinical risk data from the Framingham Heart Study.⁵⁴ Clozapine prevented 492 suicide deaths/100,000 schizophrenia patients, however 416 deaths would be attributable to clozapine-induced weight gain and subsequent hypertension and impaired glucose tolerance.⁵⁴ In addition to these threats to health and longevity, weight gain from atypical antipsychotics can lead to psychological distress, poor self-esteem and noncompliance with pharmacotherapy.⁵⁴

The pharmacotherapy of schizophrenia is quite challenging, and until clinicians can apply evidence-based results from large-scale schizophrenia studies such as CATIE,⁵⁵ empirical approaches to medication selection are often used.⁵⁵ Pharmacogenomics is a term that embodies the concept of individualized and rational drug selection based on the genetic variations of a particular patient.⁵⁶ An understanding of these genetic variations or “polymorphisms” has the potential to enhance patient care by allowing prescribers to customize the selection of medication to meet individual patient needs.⁵⁶ Customization of atypical antipsychotic pharmacotherapy offers the potential for optimal safety and efficacy as well

as enhanced compliance in an individual patient. The foundation for psychiatric pharmacogenomic research regarding antipsychotics has been laid by clozapine response; perhaps in an effort to determine in which patients the therapeutic benefits outweigh morbidity or mortality of metabolic syndrome.

A large body of evidence supports a role for the 5-HT system in regulating feeding behavior.⁵⁵ It is not new information that studies in both animals and humans have shown that increasing 5-HT results in decreased feeding and decreasing 5-HT increases feeding. In light of these findings investigators have examined “polymorphisms” in 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{1C} receptors in patients on clozapine.^{55,57,58} Patients who respond to clozapine have been found to have the following 5-HT receptor genetic polymorphisms: 5-HT_{2A} (-1438G/A, His45Tyr), 5-HT_{2C} (-330GT/-244CT, Cys23ser, 5-HTTLPR) and as well as H₂ receptors (-1018 G/A).^{55,57,58} Clozapine responders have also been inconsistently found to have genetic polymorphisms in D₄ and D₃.^{51,54-55} D₃ and D₄ have been researched as possible targets, since clozapine has very high affinity for these receptors especially D₄.^{55,57,58} Based upon 5-HT and histamine genetic findings, investigators created a regression equation that correctly predicted clozapine responders 77% of the time. However, it was not specific enough to accurately predict all of the clozapine nonresponders at 38%.⁵⁹

The first step in endeavoring to genetically distinguish patients with the largest propensity for clozapine-induced weight gain and metabolic syndrome has been recently accomplished.

Patients who are more likely to gain weight (>7% total weight) on clozapine are associated with following genetic polymorphisms: β-3 receptors (Trp64Arg) and 5-HT_{2C} receptors (-759CT).⁵⁵ Previous investigations have shown β-3 receptors polymorphisms to be associated with predisposition to diabetes mellitus and the 5-HT_{2C} receptor polymorphism (-759CT) to be strongly associated with obesity and diabetes mellitus.^{55,60,61} Also, patients who are more likely have weight gain are associated with poor clozapine metabolism (via CYP 1A2 polymorphisms).⁵⁵ Lastly, patients who are less likely to gain weight possibly have a “protective” α₁ receptor polymorphism (Arg347Cys), thereby potentially gaining less weight than patients without this genetic variation.⁵⁵

CONCLUSION

There is a growing body of knowledge regarding atypical antipsychotic-induced metabolic derangements. This includes such issues as the general

health concerns of our patients and our responsibility to them, the metabolic syndrome, possible mechanisms of antipsychotic induced dysregulations, and an evolving approach to the psychiatric patient with metabolic disturbances. The latter includes both monitoring parameters as well as management and prevention of these disturbances. Finally, we have briefly touched upon the growing field of pharmacogenomics, which potentially holds promise to help avoid many of the problems we have discussed by customizing treatments even further. **CNS**

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