OBESITY, DIABETES, AND HYPERLIPIDEMIA: EXPLORING THE LINK TO ANTIPSYCHOTIC MEDICATIONS*

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ABSTRACT

The rates of overweight and obesity in the general population are of epidemic proportions. Only 39% of the US population is deemed to have a normal weight. An association between obesity and an array of illnesses is extremely well recognized. Featured prominently among these illnesses are the metabolic or insulin resistance syndrome and type 2 diabetes. People with major mental illness are at an increased risk for physical ill health and premature mortality. It was long thought that this was only because of the increased risk of suicide in the mentally ill; increasing evidence has shown that it is primarily from cardiovascular disease, although some other illnesses are also more common in the mentally ill. Many important factors are at play, including unhealthy lifestyles, poor access to healthcare, and insufficient screening. However, a key problem is the propensity of people with schizophrenia and bipolar disorder to gain excess weight and to develop insulin resistance and the metabolic syndrome, the likely precursors of type 2 diabetes and hyperlipidemia—all of which occur in the mentally ill at even higher rates than in the general population. From evidence collected during the pre-antipsychotic era, it appears that this may be in part disease related. However, some antipsychotic medications may cause clinically significant and even dangerous amounts of weight gain in many individuals. Not only are there differences between individuals in weight gain, but the extent of the weight gain also varies by drug. Increasing but controversial evidence also suggests that some antipsychotic medications may have direct effects on intermediary metabolism, beyond their effects on weight. Unfortunately, cigarette smoking is also endemic in mentally ill individuals, further adding to the medical problems confronting these patients. Each is of particular importance, because patients usually need lifelong treatment, and the effects of overweight, metabolic abnormalities, and cigarette smoking are likely to be cumulative. The causes of metabolic abnormalities in patients taking antipsychotic drugs are multiple, complex, and not completely understood. However, some medicines may clearly impose an additional medical burden on this already high-risk population. Psychiatric illnesses themselves carry significant mortality and morbidity. Thus, when treating the mentally ill, we must clearly insist that medicines are effective in treating the primary psychiatric problems. However, it is also essential to consider the potent impact of medicines that may compromise metabolism when planning treatment.


*Based on a presentation given by Dr. Petty at a roundtable discussion held in December 2003, Baltimore, Maryland, with supplemental material added during the editorial process.
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The newer atypical antipsychotic drugs are widely used, particularly in the United States and Western Europe. Some of these drugs appear to be particularly liable to cause weight gain and may be associated with other metabolic problems. In this article, we use the terms “newer antipsychotic” and “second-genera-
tion antipsychotic” drugs. The term “atypical antipsychotic,” although widely used, gives the mistaken impression that all the newer antipsychotic drugs form a class, which clearly they do not, either on biochemical or pharmacologic grounds. The newer antipsychotics show considerable heterogeneity in terms of specific domains of efficacy as well as side-effect profiles. While our efforts in medicine are being directed toward diet or exercise, which may help to curb the epidemic of overweight and diabetes, we would be remiss if we did not address anything that may exacerbate obesity, particularly in people already at increased risk for metabolic and cardiovascular problems. Furthermore, there are particular issues in managing these problems in people who are struggling with major mental illnesses.

Our discussion will revolve around 7 key questions:

1. Compared with the general population, what are the metabolic differences in the mentally ill and how do they factor into treatment?
2. What are the effects of psychotropic medications on metabolism?
3. Must we accept that metabolic problems are an inevitable consequence of using effective medications?
4. To what extent are weight gain and metabolic disturbances predictable and/or treatable in the mentally ill?
5. Can we give the same advice on weight loss strategies to those suffering from mental illness that we offer to people in the general population?
6. What are the effects of other cardiovascular risk factors?
7. Do we need to be particularly concerned about metabolic emergencies in the mentally ill?

Responding to some of these questions, in September 2003, the US Food and Drug Administration (FDA) sent a letter to manufacturers of all the newer antipsychotic drugs asking them to include in their labeling a recommendation for monitoring blood glucose and for symptoms of diabetes in patients receiving these drugs, particularly if the patient has risk factors, including obesity and a family history of diabetes. At the time of writing, these requests have been accepted by some but not all manufacturers.

The meeting on which this paper is based took place in December 2003. At that time, we were eagerly awaiting the conclusions of a consensus panel drawn from the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. These guidelines were published in February 2004, and because they are extremely pertinent to our deliberations and recommendations, this article includes information about these new guidelines.

**Obesity, Insulin Resistance, Insulin Resistance Syndrome, and Type 2 Diabetes**

Excessive weight is best assessed in terms of body mass index (BMI), which is weight in kg divided by height in m². BMI correlates most closely with health problems and takes into account a person's height. In the United States, overweight is currently defined as a BMI of 25.0 to 29.9 kg/m²; obesity is a BMI of 30.0 kg/m² or above. Typically, we see a progression from obesity to insulin resistance, to the insulin resistance syndrome, and finally to diabetes. Insulin resistance is defined as an impaired biologic response to insulin.1,2 Insulin resistance is a primary defect in the majority of patients with type 2 diabetes. In nondiabetic individuals, insulin resistance in combination with hyperinsulinemia has a strong predictive value for the future development of type 2 diabetes.³

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**Figure 1. Insulin Resistance Predisposes Individuals to Other Types of Diseases**

- Abnormal Obesity and Inactivity
- Glucose Intolerance
- Genetics
- Medications
- Cigarette Smoking
- Fetal Malnutrition
- Dyslipidemias
- Endothelial Dysfunction
- Polycystic Ovary Syndrome
- Type 2 Diabetes
- Other Related Effects of Obesity
- Certain Malignancies

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1. Insulin resistance is defined as an impaired biologic response to insulin.
2. Insulin resistance is a primary defect in the majority of patients with type 2 diabetes.
3. Insulin resistance in combination with hyperinsulinemia has a strong predictive value for the future development of type 2 diabetes.
Insulin is a potent growth factor for adipose tissue, leading to both hypertrophy and hyperplasia of fat cells. Fat is a tissue; with insulin resistance, circulating insulin levels rise and may stimulate the growth of fat deposits. Because fat (particularly intra-abdominal or visceral fat) is closely associated with insulin resistance, it follows that a vicious circle may occur, with increased abdominal fat being both a cause and a consequence of insulin resistance.

Type 2 diabetes is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Typically in type 2 diabetes, the primary problem is with insulin resistance in both the liver and in peripheral tissues. A subsequent loss of normal insulin release by the pancreas may culminate in pancreatic failure. The reasons for the concern about diabetes itself is the chronic hyperglycemia, which may cause an array of symptoms and is associated with long-term damage, dysfunction, and failure of various organs. Injury to large and small blood vessels results in damage to the kidneys and eyes. A matter of increasing concern is the association between large-vessel disease and “prediabetic” conditions, such as insulin resistance and impaired fasting glucose.

Type 2 diabetes is responsible for more than 90% of diabetes cases. People with type 2 diabetes are usually insulin resistant, with insulin production that is inadequate to maintain normal glucose levels. Typically, insulin production becomes progressively worse over time. There are many causes of insulin resistance; some of the key causes are summarized in Figure 1, together with some of the more common potential consequences of insulin resistance.

The onset of type 2 diabetes is usually gradual and may occur at any age but usually occurs in people older than 20 years. The pattern of the disease has changed enormously in recent years. It used to be described as a disease of obese people older than 40 years (hence the old term, adult-onset diabetes). However, cases are now occurring in younger people as we are seeing the consequences of the global obesity pandemic. Paradoxically, cases also occur in people who are not overweight or obese. It was previously thought that diabetic ketoacidosis, a particularly ominous problem in diabetes, rarely occurred in people with type 2 diabetes. However, research has shown that it occurs quite often in type 2 diabetes.
OBESITY AND MENTAL ILLNESS

Overweight and obesity are increasing rapidly in the general population, and more than 60% of the adult US population is in one of these categories.\textsuperscript{10} Overweight increases the risk of several other diseases, including type 2 diabetes, lipid abnormalities, heart attack, stroke, hypertension, osteoarthritis, and certain cancers. The effects of overweight/obesity and these other diseases are additive with regard to risk of heart disease (Figure 2).\textsuperscript{11,12} As shown in Figure 2, there is an almost linear relationship between overweight/obesity and mortality risk. Importantly, mentally ill patients are more than twice as likely to smoke cigarettes as the general population and account for up to 45% of the cigarettes sold in the United States.\textsuperscript{13-15}

There is a serious lack of physical well-being in individuals with major mental illness. Among these patients, the average age of death is 10 to 20 years earlier than in the general population.\textsuperscript{16-19} In part, this is due to suicide, but other factors are involved, including cardiovascular disease, type 2 diabetes, obesity, respiratory illness, and substance abuse.\textsuperscript{20,21} Weight problems have long been observed in people with mental illness, even before the availability of antipsychotic medications.\textsuperscript{22-25}

Patients taking some newer antipsychotic medications are known to gain significant amounts of weight. Figure 3 shows the estimated mean weight gain in short-term studies with the some of the antipsychotic medications available in 1999.\textsuperscript{26} Little work has looked at weight gain over the long term, though the existing data have suggested that weight gain with clozapine, olanzapine, quetiapine, and risperidone continues over time.\textsuperscript{27} A retrospective analysis of the olanzapine registration studies, however, suggested that weight gain may eventually plateau with this agent, and that weight gain over the first few weeks of treatment is predictive of eventual overall weight gain.\textsuperscript{28,29} There are some indications that the precise pattern of weight gain varies with different psychotropic agents, implying that different mechanisms underlie weight gain with different agents.\textsuperscript{30} From this evidence, there clearly are differences in the weight gain potential of different agents, which is consistent with clinical observations. It is of considerable interest and clinical importance that some agents appear to cause little weight change. The data in Figure 4 were culled from the US labels for the 5 antipsychotic agents in question, indicating that ziprasidone and aripiprazole have the lowest propensity to cause weight gain. Furthermore, in Figure 5 we see low rates of weight gain with aripiprazole compared with placebo and haloperidol, with the intriguing observation that people with the highest BMI at study entry lost weight during the trial.\textsuperscript{31} The advent of medications that are clinically effective and not associated with significant metabolic problems represents a genuine advance in psychiatry.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Clinically Significant (\geq 7\%) Weight Gain During Antipsychotic Treatment}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Weight Gain with Antipsychotics Is Greater in Those with Lower Baseline Weight}
\end{figure}

Data from US labels.

\textsuperscript{*}P < .05.

BMI = body mass index (1 kg = 2.2 lb).

The cause of weight gain with some antipsychotic medications is a subject of intense research efforts. It was quickly discovered that the causes vary in different species and in sexes, making it difficult to draw firm conclusions. Weight gain appears to be associated with multiple factors (Figure 6). There is evidence that some antipsychotic drugs may reduce basal metabolic rate and that they exert specific actions on the feeding and satiety centers in the lateral and ventromedial hypothalamus. There also appears to be a relationship between weight gain and the degree of antagonism of histamine and serotonin receptors. Some medications may change the body's sensitivity to the hormone leptin (which has a role in controlling feelings of satiety), whereas others are associated with the release of tumor necrosis factor-alpha and other cytokines, which may cause insulin resistance and stimulate appetite. There also appears to be a relationship between weight gain and the degree of antagonism of histamine and serotonin receptors.

There are some robust predictors of weight gain with antipsychotic drug use. First is an increased appetite during treatment, particularly for carbohydrates. The main reason that patients gain weight is not so much from what they eat but from what they drink—carbohydrate-rich drinks, such as soda and juice, are often culprits. Patients may also experience nocturnal binge eating. Patients with psychotic symptoms may have other obstacles to weight loss. Positive symptoms may cause problems (eg, a person had the delusion that his bones would crumble if he lost weight). Negative symptoms may also take their toll, as may lethargy from medication use. Patients also may have considerable cognitive handicaps, which may make patient education more difficult. Mentally ill patients also tend to have limited incomes, thus making it more difficult for them to use popular weight management programs or to eat healthy meals. Some live in group homes, which tend to purchase the least expensive food to stay within budget.

### Type 2 Diabetes and Mental Illness

Among people with mental illness, the rates of type 2 diabetes are nearly double those reported for the general population, ranging from 9% to 14% of patients with schizophrenia and bipolar disorder. Family history appears to be a strong influence, with 18% to 30% of patients with schizophrenia having a family history of type 2 diabetes, which is comparable to rates in first-degree relatives of people from the general population with type 2 diabetes. Several factors are implicated in the higher prevalence among the severely mentally ill, including lifestyle (poor diet, lack of exercise); high rates of smoking, which may itself increase the risk of developing diabetes; stress; and side effects from common medications, such as thiazide diuretics, beta blockers, corticosteroids, and theophylline. Stress in particular increases the activity of lipoprotein lipase, which increases stores of abdominal fat.

The association between obesity, insulin resistance, and diabetes was first deduced in the 1930s, and the specific association with abdominal obesity was noted in the 1940s. However, it is only within the past 2 decades that an intermediate syndrome has been recognized linking coronary artery disease and type 2 diabetes, “two of the most deadly and lethal diseases in the United States.” The metabolic syndrome (also known as the insulin resistance syndrome, Syndrome X, and dysmetabolic syndrome) is characterized by low levels of high-density lipoprotein cholesterol (“good” cholesterol), obesity, hypertension, elevated fasting glucose levels, and high triglyceride levels. The precise criteria and boundaries of the syndrome remain the subject of intense interest and debate. It can be detected in
clinical practice through history, physical examination, and laboratory evaluation (Table 1).54

As we have seen, people with schizophrenia are at increased risk for developing type 2 diabetes. An important question is whether these patients also have evidence of insulin resistance and metabolic syndrome. A recent study of outpatients with schizophrenia showed high but variable rates of insulin resistance and insulin resistance syndrome and identified several previously undiagnosed cases of type 2 diabetes in subjects taking clozapine, olanzapine, risperidone, quetiapine, chlorpromazine, piperazine, and ziprasidone (Table 2).55

Hyperglycemia and diabetes were first linked to chlorpromazine within 1 year of its introduction in France. Over the years, many reports have linked hyperglycemia to phenothiazines. However, there were far fewer cases with butyrophenones.66-67 Cases have also been reported with clozapine, olanzapine, quetiapine, risperidone, and loxapine.66-76 For many years, a nagging worry has been that problems with diabetes—in particular diabetic ketoacidosis—might be more common with the dibenzodiazepines, not only because of case reports, but also because some epidemiologic studies appear to point in that direction, as do some basic science investigations.77-81 Other studies have found no difference between agents.82 It has been something of a puzzle why diabetes is more common in the mentally ill. A study from Ireland of first-episode patients with schizophrenia found that these patients had 3.4 times the amount of intra-abdominal fat and higher levels of cortisol compared with healthy controls.83

**HYPERLIPIDEMIA IN MENTAL ILLNESS**

Although there are not much data detailing lipid levels in patients with severe mental illness, it is clear that antipsychotic therapy increases the risk of dyslipidemia. As with weight gain, insulin resistance, and diabetes, development of abnormal lipid levels varies with the choice of antipsychotic medication. Haloperidol and risperidone are associated with significantly higher total cholesterol levels compared with aripiprazole (Figure 7).84

**CONSENSUS DEVELOPMENT CONFERENCE ON ANTIPSYCHOTIC DRUGS AND OBESITY AND DIABETES**

In February 2004, a Joint Consensus Conference position paper was published on antipsychotic drugs and obesity and diabetes.85 It was developed by the American

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**Table 1. Metabolic Syndrome Criteria**

As defined by the NCEP ATP III Expert Panel, the presence of any 3 of the following parameters is diagnostic of the metabolic syndrome.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Men: &gt;40 in (102 cm)</td>
</tr>
<tr>
<td></td>
<td>Women: &gt;35 in (88 cm)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Men: &lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women: &lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>


**Table 2. Insulin Resistance and Syndrome X: US Outpatients**

<table>
<thead>
<tr>
<th>Antipsychotic Drug</th>
<th>Insulin Resistance*</th>
<th>Syndrome X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (n = 14)</td>
<td>84.6 (11/13)</td>
<td>64.3 (9/14)</td>
</tr>
<tr>
<td>Olanzapine (n = 41)</td>
<td>57.5 (23/40)</td>
<td>39.0 (16/41)</td>
</tr>
<tr>
<td>Risperidone (n = 13)</td>
<td>100 (12/12)</td>
<td>61.5 (8/13)</td>
</tr>
<tr>
<td>Quetiapine (n = 11)</td>
<td>77.8 (7/9)</td>
<td>72.7 (8/11)</td>
</tr>
<tr>
<td>Ziprasidone (n = 3)</td>
<td>66.7 (2/3)</td>
<td>66.7 (2/3)</td>
</tr>
<tr>
<td>CAP-O (n = 6)</td>
<td>50.0 (2/4)</td>
<td>50.0 (3/6)</td>
</tr>
<tr>
<td>CAP-D (n = 5)</td>
<td>80.0 (4/5)</td>
<td>80.0 (4/5)</td>
</tr>
<tr>
<td>Unmedicated (n = 5)</td>
<td>60.0 (3/5)</td>
<td>0 (0/5)</td>
</tr>
</tbody>
</table>

*Patients discovered to have diabetes were removed from insulin resistance count but included in Syndrome X count.

CAP-O = oral conventional antipsychotic; CAP-D = depot conventional antipsychotic.

Data from Littrell et al19
Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. They set out to answer 5 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 second-generation antipsychotic drugs are used?
3. What is the relationship between the use of these drugs and incidence of obesity or diabetes?
4. Given the above risks, how should patients be monitored for the development of significant weight gain, dyslipidemia, 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 the development of obesity, dyslipidemia, and diabetes?

After an analysis of currently available data and after presentations from representatives of several pharmaceutical companies with an interest in the matter, the panel came to the conclusion that some second-generation antipsychotic drugs show higher rates of diabetes than others (Table 3). The panel also specified very precise guidelines for monitoring patients (Table 4) and recommended that clinicians be familiar with the clinical features of diabetic ketoacidosis:

**Symptoms**
- Thirst
- Polyuria
- Weight loss
- Nausea, vomiting, diarrhea, abdominal pain
- Precipitating event (eg, infection)

**Signs**
- Drowsiness and confusion
- Dehydration
- Hyperventilation
- Acetones on the breath
- Hypothermia
- Hypotension, tachycardia
- Shock
- Loss of consciousness

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**Table 3. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

D = discrepant data.

**Table 4. Monitoring Protocol for Patients Taking Second-Generation Antipsychotic Drugs**

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>4 wk</th>
<th>8 wk</th>
<th>12 wk</th>
<th>Quarterly</th>
<th>Annually</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
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</table>

BMI = body mass index.

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**Figure 7. Change in Cholesterol Levels in Patients Treated with Antipsychotic Agents**

Short Term (4- to 6-week), Fixed-Dose, Placebo-Controlled Studies

![Figure 7. Change in Cholesterol Levels in Patients Treated with Antipsychotic Agents](image-url)
While the panel’s conclusions may not please everyone, the suggestions concerning monitoring and the awareness of ketoacidosis are most welcome.

**CONCLUSION**

Patients with schizophrenia are already at increased risk for obesity, diabetes, cardiovascular disease, and other medical illnesses. The effects of these problems, coupled with the fact that many of these patients also smoke cigarettes, compounds the medical burden. The adverse metabolic effects of some newer antipsychotic agents may impose an additional medical burden on this high-risk population. Important differences exist between the weight and metabolic adverse-effect profiles of antipsychotic drugs. Aripiprazole and ziprasidone appear neutral with regard to weight change, glucose levels, and serum lipid levels. Monitoring this high-risk population for metabolic risks is important to their well-being.

**DISCUSSION**

**Choosing an Antipsychotic**

*Ms Valentine:* I’m not working in the psychiatry area exclusively right now, and I haven’t worked with the atypical antipsychotic medications much. However, I am now seeing psychiatric patients who have diabetes. Are the atypical antipsychotic drugs all equally effective?

*Dr Petty:* With the newer agents, that appears to be true. It is very important to draw a distinction between the older agents (eg, haloperidol) and the newer ones. When treating schizophrenia, however, it is more complicated than just saying, “Drug A is as good as drug B.” Schizophrenia is a complex multifaceted disease, so we have to tease apart the positive symptoms, the negative symptoms, mood, and cognition, as well as quality of life and subjective wellness. We look at all of those different domains and whether the drug will prevent relapse. So, it is a slightly more complex question in schizophrenia than, “Does A or B work?” We have few studies comparing different novel antipsychotic drugs, but what evidence we have suggests that all of these agents are probably equally good but that there are subtle nuances suggesting that one may be better than another in a particular domain. We may use drugs in combination when there are different domains that have been particularly damaged by the illness. So, if one drug causes less weight gain and if indeed it is just as effective, the clear question for the clinician is, “Why not use that one?”

*Ms Littrell:* We are talking about metabolic abnormalities as one adverse event. The newer drugs are so effective and they are nonsedating—which often is not perceived as a good thing among nurses in the inpatient setting. Nurses like patients to be quiet, calm, and asleep for the most part. So, it has been a big challenge to teach them that not having the patient sleep 14 to 16 hours per day is a benefit. Family members do not realize this, either. We have had family members come in and tell us the medicines aren’t working because their children are up until 11:00 PM. Most teenagers stay up until 11:00 PM, but the families are used to their children taking pills at 6:00 PM and being asleep by 7:00 PM or 8:00 PM and sleeping until the next morning. So, we have to be sensitive to nurses’ subjective experience.

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**Key Points**

- Severely mentally ill patients suffer from an enormous burden of physical disease. These individuals tend to die prematurely.
- The lifestyles of mentally ill patients are often unhealthy; most smoke cigarettes, and many do not receive essential health screening and primary medical care.
- Compared with the general population, insulin resistance and the metabolic syndrome are more common in people with schizophrenia, as are obesity, type 2 diabetes, and hyperlipidemia.
- Some antipsychotic agents have been shown to cause clinically significant weight gain, though this does not appear to be a problem with those most recently introduced in the United States.
- Some antipsychotic agents may also increase the risk of developing type 2 diabetes and hyperlipidemia.
- Diabetic ketoacidosis is an uncommon but serious problem that has been reported with some medications. It is important for clinicians to be aware of its clinical manifestations.
- Because our patients are already at increased risk for cardiovascular and other diseases, it is essential to treat the primary psychiatric problem as well as possible metabolic abnormalities and to avoid increasing this risk further. Assessing for risk factors is important in these patients.
**Dr Parks:** That is an excellent point. What is desirable behavior on an inpatient unit is not desirable behavior in the community. There is quite a bit of switching medications. A patient gets hospitalized and is put on high doses of low-potency antipsychotic medications that are mildly sedating. He gets discharged, and at his first outpatient visit, the family member says, “He is only awake about 6 hours per day and then he just sits.” So, the patient gets switched to lower doses of high-potency antipsychotic medications, right after he has been discharged. There is a lot of flip-flopping of drug choice, because the different groups have different goals—both of them short term, unfortunately.

**Dr Petty:** I entirely endorse what you’re saying. Everybody needs to be reminded that we are dealing with a group of lifelong illnesses. That is important with regard to side effects, because whatever you choose is going to have long-term impact on patients. So, we need to be thinking beyond what we do today and tomorrow, and we need to be generating long-term strategic plans for patients.

**Dr Parks:** As a group, it is not possible to say that one atypical agent is better than the other, perhaps with the exception of clozapine (which is better than the others). However, for most patients there are clearly 1 or 2 drugs that are better than most of the others. So, for individual patients, there are people who will do much better—for mysterious reasons—on one antipsychotic drug versus another (e.g., on Geodon® [ziprasidone] as opposed to Risperdal® [risperidone]). The next patient may do very well on Seroquel® [quetiapine], and there is no way to predict this. I end up trying numerous drugs, and after several years, I’ll ask the patient to pick the one that worked best. Not every physician wants to go through all of that, but we don’t have any markers as to who is going to do best on which drug.

**Dr Saklad:** There is some work being done on pharmacogenomics. Arranz and colleagues published an article in *Lancet* showing that they were able to predict clozapine responders based on genetic polymorphisms. I believe that we will be able to eventually identify a probable responder to different drugs. The hardest part is defining what a good responder is. There are so many ways of measuring response; a good response in one condition may be a marginal response in another—just as the adverse effect of sedation in an inpatient acute unit is a desirable outcome, but long term, it’s a harmful outcome.

**Dr Parks:** Whose definition of winner shall prevail—our view or the patient’s view? They may have a different desired outcome from ours.

**Dr Petty:** There is a whole field of research looking at the importance of considering different perspectives. It may seem obvious that the aims of healthcare professionals are sometimes different from those of the patient and the family, yet this has only recently become a focus for research. The patient’s aspirations are often entirely different from ours. As an example, we have done a great deal of work on sexual dysfunction. This can be the absolute deal-breaker for many patients, yet research has shown that most doctors in the United States (including psychiatrists), never even ask their patients about sexual dysfunction. Yet, to most people, it is actually one of the most important aspects of life.

**Dr Parks:** Engaging family members is extremely important. If a family member thinks that the medication is terrible and doesn’t know what to do and how to use it, they will sabotage the outcomes. They may not mean to, but they will definitely bring the patient back by the hand and say, “He is not staying on this.”

**Ms Huckshorn:** Also, in psychiatry, in both the public and private sector, we have competing priorities, which are decreasing violence on the units and reducing coercion, seclusion, and restraint. So, if we are proposing the use of less-sedating medication, that is going to be quite different from what has been encouraged over the past couple of years.

### Diabetes and Antipsychotic Use

**Dr Margolis:** Why do patients with type 2 diabetes have ketoacidosis? It doesn’t make sense to me.

**Dr Petty:** Although it used to be thought that ketoacidosis was something that only occurred in patients with type 1, or insulin-dependent diabetes, that view has changed a lot in recent years. About one third of ketoacidosis cases in the United States presenting to the emergency department are in patients with type 2 diabetes.89 Reviewing the case reports, particularly those cases identified by the FDA, in those patients on antipsychotics who have developed ketoacidosis, these cases may occur extremely rapidly and usually within the first 12 weeks of exposure to the antipsychotic agent, often even before the weight started increasing. It is a difficult thing to study, since it is clearly not that common, but when it occurs, it can...
have terrible consequences. It is worth remembering that the decision by the Japanese regulatory authorities to ask for a label change with olanzapine and then quetiapine was due to cases of ketoacidosis, which included a small number of fatalities. The cause of the ketoacidosis associated with some antipsychotic drugs is not at all clear, but it is possible that people are somehow becoming intensely resistant to the actions of insulin. We have also speculated there may be some entirely different mechanism; pancreatitis has been described with some antipsychotic agents and is more common in people who abuse alcohol and some other drugs.

Ms Littrell: The FDA mandate for additional warning on atypical antipsychotics is very important. Are we legally bound to assess for side effects of the antipsychotic drug or any medication, and educate about that?

Dr Parks: The newer antipsychotic medications are used [off-label] for many disorders other than schizophrenia—eg, most old people in a nursing home if their behavior is disagreeable, most children whose behavior is disagreeable, most bipolar disorder patients, and most mentally retarded people. We're giving these drugs for everything and to everyone. Are there any differential effects in these other diagnostic groups?

Dr Petty: Interestingly, elderly groups tend not to gain very much weight, but of course there are exceptions. Even with high weight gains, they tend to not be much of a problem. We have few studies of metabolism in children given these drugs, but so far they seem to indicate that although weight gain can be a tremendous problem with some agents, dysregulation of metabolism is not. But we must emphasize that those studies are still in their infancy, not least because at this time no antipsychotic agent is indicated for use in children and adolescents.

Ms Littrell: Earlier this year in our study of inpatients with bipolar disorder type 1, 26% were found to have type 2 diabetes.

REFERENCES


