Diabetes, Psychiatric Disorders, and the Metabolic Effects of Antipsychotic Medications

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Diabetes is considered to be one of the most psychologically demanding of the chronic medical illnesses and is often associated with several psychiatric disorders. Antipsychotic medications, first introduced in the 1950s, are a vital component of the medical management of several of these psychiatric disorders. These medications are often prescribed by nonpsychiatric physicians. During the period 1997–2000, according to a large U.S. survey, nearly 1% of all health care visits resulted in an antipsychotic prescription, and almost one-third of these prescriptions were written by nonpsychiatrists. The use of newer “atypical” antipsychotics, in particular risperidone and olanzapine, increased during this period, whereas the use of conventional antipsychotics decreased.

This article will review the atypical, or second-generation, antipsychotics and their current uses. The relationship between diabetes and two of the most frequent indications for the use of these medications (schizophrenia and behavioral and psychological symptoms of dementia) will be examined. Additionally, this article will explore the complex association between antipsychotic medications and obesity, hyperglycemia, and dyslipidemias.

Indications for Antipsychotic Medications

The frequent co-occurrence of diabetes and psychiatric disorders has been recognized for several centuries and is thought to be related to several factors. Because patients are responsible for 95% of disease management, a diagnosis of diabetes can lead to increased levels of anxiety, depressive symptoms, and lowered self-esteem. This is especially true in individuals who have underlying psychiatric disorders. Literature has suggested that certain psychiatric illnesses may be independent risk factors for diabetes. Additionally, poorer glycemic control and resultant increases in diabetes-related complications have been associated with the presence of a psychiatric disorder. Much interest has been generated recently because of increasing reports of a possible causal relationship between some of the newer antipsychotic medications and metabolic abnormalities.

Antipsychotic medications are widely used to treat a variety of psychiatric disorders. They are the foundation of treatment for psychotic disorders and are primarily indicated to treat acute exacerbations of schizophrenia and to prevent relapses. Several of these agents have also received Food and Drug Administration (FDA) approval to treat manic and mixed phases of bipolar disorder, either as monotherapy or as adjuncts to mood stabilizers. Common off-label uses of these medications include the treatment of the behavioral and psychological symptoms of dementia (BPSDs), psychotic and treatment-resistant depressions, autism, behavioral problems associated with developmental disorders, and post-traumatic stress disorder.

The first-generation (also called “conventional” or “typical”) antipsychotics (Table 1) are effective in treating the so-called positive symptoms of schizophrenia, most notably hallucinations, delusions, aggression, and hostility. Their primary disadvantage has been the lack of response of negative symptoms (such as apathy, social isolation and withdrawal, and lack of motivation) and the high rate of extrapyramidal side effects, including dystonic reactions, akathisia, drug-induced Parkinsonism, and tardive dyskinesia.

Both the efficacy and adverse effects of these drugs are associated with antagonism at the D2 receptors. Efficacy is associated with at least 60% occupancy of these receptors. However, when receptor occupancy exceeds 80%, there is an increased risk of acute extrapyramidal symptoms, as well as hyperprolactinemia.

The development of the second-generation agents (or “atypicals”) came from the need for effective antipsychotics that caused fewer and less severe side effects. The effectiveness of these drugs appears to be comparable to that of older agents in treating positive symptoms of schizophrenia, whereas the relative effect size on negative symptoms

IN BRIEF

Psychiatric disorders can be a risk factor for, as well as a complication of, diabetes. Antipsychotic medications, widely used to treat a variety of psychiatric conditions, are also associated with diabetes. This article explores the complex relationship among psychiatric disorders, antipsychotic medications, and risk factors for metabolic syndrome and diabetes.

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has been modest and not as great as originally hoped. The exception is clozapine, which has been found to be superior to conventional agents in treating refractory schizophrenia and has been associated with reduced risk of suicide attempts. The risks of extrapyramidal side effects are generally lower with the atypical medications, but as a group, these drugs are more expensive, and several have been associated with significant metabolic effects.

Many patients with dementia will experience a variety of BPSDs requiring medication treatment. BPSDs are associated with nursing home placement, accelerated cognitive decline, and increased caregiver burden.

A recent literature review examined double-blind, placebo-controlled, randomized clinical trials or meta-analyses of antipsychotic drug therapy for patients with dementia and neuropsychiatric symptoms. For typical antipsychotics, no difference among the specific agents studied was found, and efficacy was small, with frequent occurrence of adverse side effects. Results for the atypical antipsychotics showed modest, statistically significant efficacy for risperidone and olanzapine, with minimal adverse effects at the lower doses used to treat elderly patients with dementia.

However, use of atypical antipsychotics in this population is complicated by recent reports of a possible increased risk for cerebrovascular events and higher mortality rates. To date, no randomized clinical trials have directly compared the efficacy of typical and atypical antipsychotics in this population. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) protocol for Alzheimer’s disease, a trial developed in collaboration with the National Institute of Mental Health, will compare atypical antipsychotics. This 36-week study will compare treatment with risperidone, olanzapine, quetiapine, citalopram, and placebo for outpatients with Alzheimer’s disease who experience delusions or hallucinations and/or clinically significant aggression or agitation.

### Diabetes and Schizophrenia

It is unclear whether schizophrenia is an independent risk factor for diabetes because no study has controlled for all the major risk factors for diabetes, although the literature suggests that this could be the case. During the early 20th century, several researchers found that glucose intolerance and hyperglycemia occurred with increased frequency among patients with dementia praecox.

More recent studies have reported similar findings. Ryan et al. compared 26 antipsychotic drug-naive patients with schizophrenia with age- and sex-matched control subjects and found a higher prevalence of impaired fasting glucose (15 vs. 0%, \( P < 0.02 \)) and higher insulin resistance (\( P < 0.01 \)). Drug-naive schizophrenia patients have also been found to have more than three times as much intra-abdominal fat (which is correlated with insulin resistance) as age- and BMI-matched control subjects.

It is clear, however, that the prevalence of diabetes and its risk factors is much greater among patients with serious mental illness. For example, patients with schizophrenia are more likely than age-matched control subjects to lead a sedentary lifestyle, consume fewer fruits and vegetables, and have other cardiovascular risk factors, in particular, tobacco use. Additional studies have found the prevalence of both diabetes and obesity to be two to four times higher in people with schizophrenia than in the general population, with overall prevalence estimates for diabetes among patients with schizophrenia ranging from 16 to 25%.

Antipsychotic medications, especially the newer atypicals, have unfortunately contributed to the prevalence of obesity in the medicated schizophrenic population, with current estimates ranging from 40 to 60% versus 30% of the general adult population. In addition, use of the newer atypical antipsychotics appears to increase the risk of acquiring or exacerbating type 2 diabetes, even, rarely, causing diabetic ketoacidosis and death.

Research on diabetes and schizophrenia has largely focused on prevalence estimates rather than on long-term diabetes outcomes. It is likely, however, that diabetes outcomes are poor in this population for several reasons. First, the relative risk of mortality associated with schizophrenia is 1.6–2.6 times higher than that of the general population, with the leading

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**Table 1. Daily Dosing Recommendations for Conventional and Atypical Antipsychotic Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Treatment</th>
<th>Maintenance Therapy</th>
<th>Geriatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>300–1,000</td>
<td>300–600</td>
<td>25–75</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>30–100</td>
<td>30–60</td>
<td>2–8</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>6–20</td>
<td>6–12</td>
<td>2–4</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>15–50</td>
<td>15–30</td>
<td>2–6</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6–20</td>
<td>6–12</td>
<td>2–4</td>
</tr>
<tr>
<td><strong>Atypical Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>200–800</td>
<td>200–800</td>
<td>25–50</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4–10</td>
<td>4–10</td>
<td>1–2</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10–20</td>
<td>10–20</td>
<td>5–10</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>200–800</td>
<td>200–800</td>
<td>50–200</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80–160</td>
<td>80–160</td>
<td>—</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10–30</td>
<td>10–30</td>
<td>5–10</td>
</tr>
</tbody>
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cause of death being cardiovascular disease.\textsuperscript{25} The average age of death is 61 years for people with schizophrenia versus 76 years for the general population.\textsuperscript{23} Second, patients with schizophrenia have high prevalence rates (as high as 75\%) of smoking.\textsuperscript{15} Third, non-adherence to treatment is common and estimated to be \textasciitilde{} 50\%.\textsuperscript{26} Finally, this group often suffers from impaired insight, poor access to medical care, lower levels of psychosocial support, and increased levels of stress, all of which can worsen medical outcomes.

**Diabetes and Dementia**

The prevalence of type 2 diabetes increases with age, as does the prevalence of dementia. Several prospective studies have found that the risk for developing dementia increases with the presence of obesity in middle age and diabetes in later life.\textsuperscript{17-29} In animal studies, depletion of neuronal insulin receptors has been found to mimic some features of the neurodegeneration seen in Alzheimer’s disease.\textsuperscript{30} This supports the idea that part of the pathophysiology of Alzheimer’s disease may be related to neuronal insulin resistance. Additionally, hyperglycemia is accompanied by an accelerated rate of advanced glycation end product (AGE) formation. AGEs have been demonstrated to accumulate in the neuritic plaques and neurofibrillary tangles of Alzheimer’s disease.\textsuperscript{31} AGEs also appear to accelerate \(\beta\)-amyloid aggregation through cross-linking of extracellular proteins and may contribute to tau protein and tangle formation and oxidative stress.\textsuperscript{32}

Further, type 2 diabetes has been found to be an independent risk factor for Alzheimer’s disease and vascular dementia.\textsuperscript{33-35} The effect of diabetes is especially pronounced in carriers of the APOE-4 gene. The relationship appears to be synergistic, leading to a more than fivefold increase in the risk for Alzheimer’s disease for subjects with diabetes and APOE-4 compared with those without these two factors.\textsuperscript{33} The presence of multiple cardiovascular risk factors at midlife substantially increases the risk of late-life dementia in a dose-dependent manner,\textsuperscript{34} and type 2 diabetes is associated with a twofold increased risk of vascular dementia.\textsuperscript{35}

Memory deficits are not part of normal aging. When an older patient begins to forget or miss appointments, stops checking fingersticks, or inconsistently takes or refills prescriptions, clinicians must have a high index of suspicion that a cognitive disorder may be present. Older adults who report memory problems merit a cognitive assessment.

A cognitive screening instrument allows providers to objectively document these deficits and, with repeat administrations, monitor the course of impairments. The most widely used instrument is the Mini-Mental State Exam, which, when used in combination with the Clock Drawing Test, provides sufficient sensitivity and specificity to be used on an annual basis.\textsuperscript{36}

A laboratory dementia work-up (complete blood count, metabolic profile, rapid plasma reagin, thyroid function tests, and \(B_{12}\) and folate serum levels) should also be completed to rule out treatable causes of cognitive impairment. Any identified reversible causes of cognitive impairment, such as medications, nutritional deficiencies, or metabolic disturbances, should be treated. Neuropsychological testing is also helpful if the etiology of cognitive impairment is uncertain.

**Antipsychotic Medications and Obesity**

Shortly after the introduction of chlorpromazine, clinicians noticed that antipsychotics use led to weight gain. It was further noted that lower-potency agents (chlorpromazine and thioridazine) induced greater weight gain than the higher-potency drugs (fluphenazine and haloperidol). Conventional antipsychotics-associated weight gain appears to be comparable for oral and depot formulations of the same drug.

Among the atypical medications, varying degrees of weight gain have been reported. Hummer et al.\textsuperscript{37} reported that after 1 year of treatment, 36\% of patients treated with clozapine had gained \textasciitilde{} 10\% of their initial body weight. Seven patients continued to gain weight, reaching a maximum gain of 30\% of their initial body weight. Clozapine-induced weight gain does not appear to plateau early in treatment, and it has been shown to continue for 30 weeks. Olanzapine, with a similar chemical structure, has also been associated with significant weight gain. In prospective, double-blind studies, olanzapine has led to nearly twice the weight gain of risperidone.\textsuperscript{38} This weight gain is not apparently related to dose and can persist for up to 1 year.\textsuperscript{39}

Weight gain for risperidone and quetiapine appears to be intermediate among the antipsychotic medications. Weight gain is reported to be lower than that seen with olanzapine and clozapine but greater than that seen with conventional drugs. Weight gain associated with risperidone and quetiapine does appear to correlate with dose. Ziprasidone is associated with little weight gain, even after 1 year of treatment. Average weight gain associated with aripiprazole after 1 year of treatment was \textasciitilde{} 2 kg. Among the atypical antipsychotics, the relative tendency to cause weight gain is as follows: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = aripiprazole.\textsuperscript{40}

The mechanism of antipsychotics-induced weight gain is undetermined, but several neurotransmitter systems have been implicated. Initially, there was speculation that histamine receptor blockage was responsible for the conventional antipsychotic-induced weight gain. Affinity for histamine receptors does correlate with medication-induced weight gain\textsuperscript{41} and is supported by empirical data. Olanzapine, with the highest affinity for histaminic receptors, is also associated with high rates of weight gain. Conversely, ziprasidone and aripiprazole, associated with lower risks of weight gain, have lower affinities for histamine receptors.
Blockade of the serotonin receptor 5-HT2C has been associated with increased appetite and obesity in mice. Most atypicals are antagonists at this receptor, and this may partially explain patient reports of increased appetite. These effects, however, can be mitigated by other receptor activities, such as ziprasidone’s norepinephrine reuptake inhibition. This is likely to explain some of the variability in weight findings among the various atypical antipsychotics, most of which have antagonistic properties at the 5-HT2C receptor.

Antipsychotic Medications and Hyperglycemia
Case reports and retrospective database analyses suggest that conventional and atypical antipsychotics are associated with significant increases in fasting glucose concentrations. This hyperglycemia can result in new-onset type 2 diabetes, metabolic acidosis or ketosis, and even hyperglycemia-related deaths. Most cases of new-onset type 2 diabetes occur within the first 6 months of treatment and are often, although not always, associated with significant weight gain or obesity. A family history for diabetes is also associated with an increased risk.

There seems to be variability among the specific second-generation antipsychotics with respect to the incidence rates of diabetes. Koro et al.,42 in a large population-based, case-control study, found the risk of diabetes associated with antipsychotics to be quite variable. Olanzapine had 4.2 times the risk associated with conventional agents and 5.8 times the risk associated with no treatment. Risperidone had 1.6 times the risk of conventional drugs and 2.2 times the risk of no treatment.42 Several large population retrospective studies have found that olanzapine and clozapine are associated with a significantly higher rate of diabetes than the conventional antipsychotics risperidone and quetiapine. The risk of diabetes, however, is higher with antipsychotic treatment use than in a general patient population sample.22,43,44

Several mechanisms of glucose dysregulation have been proposed to explain this association. The medications most associated with diabetes are also those that induce the greatest amount of weight gain. There are patients who develop diabetes, however, in the absence of weight gain, so other causes must be sought. These drugs may disrupt hypothalamic regulation of glucose serum levels through hypothalamic dopamine antagonism. Additionally, elevated insulin levels have been found in 46% of clozapine-treated patients, compared with 21% of those receiving conventional medicines49 and 71% of a small sample of olanzapine-treated patients, suggesting that insulin resistance is a possible mechanism.

Recently, Johnson et al.46 found that in vitro low concentrations of olanzapine and clozapine (both potent muscarinic antagonists) inhibited cholinergic-induced insulin secretion by blocking muscarinic M3 receptor activity. Risperidone and ziprasidone had no such effects. These findings suggest an added role for potent anticholinergic activity as a contributing factor for development of diabetes. This is consistent with early findings of a higher association between low-potency conventional antipsychotics and increased weight gain. The low-potency drugs, in general, are much more anticholinergic than high-potency medications.

Antipsychotic Medications and Dyslipidemias
Increased serum levels of total cholesterol, LDL cholesterol, and triglycerides are all associated with obesity and weight gain. Because several of the newer antipsychotics are associated with significant weight gain, one would expect that hyperlipidemia should also be associated with the use of these medications. Results of database analyses, chart reviews, and clinical trials indicate that clozapine and olanzapine use is associated with increased serum triglyceride levels. This hypertriglyceridemia correlates directly with weight gain. Findings are equivocal regarding changes in cholesterol levels.

Divergent results are seen with risperidone and quetiapine. Koro et al.42 found no increase in hyperlipidemia associated with risperidone. However, smaller studies have reported increased serum triglyceride levels. Methodological problems exist in the results for quetiapine, ziprasidone, and aripiprazole, including small numbers of patients studied. The doses of quetiapine used were small, so that a dose-related effect would be missed. Additionally, studies did not control for earlier treatments with lipid-lowering drugs. This may explain some of the inconsistent findings for both risperidone and quetiapine. If patients who had previously taken a drug that increases lipid levels were then switched to a different agent, their lipid levels may have decreased because the primary responsible agent was discontinued.

Very preliminary data suggest that ziprasidone and aripiprazole may not have adverse effects on lipid levels. For patients who have elevated cholesterol or triglyceride levels associated with previous antipsychotic treatment, switching to either of these medications may lead to a return to baseline levels.

Diabetes and Antipsychotic Medications
Older adults
None of the available antipsychotic drugs is specifically indicated for use in the geriatric population. In 2003, the FDA issued warnings that the use of atypical antipsychotics in older adults with dementia was associated with an increased risk of cerebrovascular events. Table 2 details the incidence rates of these events in pooled samples compared to placebo. Although these incidents occurred with low frequency, patients and caregivers need to be informed of the association. Behavioral and other nonpharmacological interventions should be the first-line treatment of choice for BPSDs. In fact, in the various
randomized clinical trials of atypical antipsychotics, the placebo response rates have ranged from 36 to 60%. This suggests that many BPSDs do respond to nonpharmacological treatments.

In 2005, an additional FDA advisory reported an increased risk of all-cause mortality in older adults with dementia treated with atypical antipsychotics. The FDA analyzed 17 placebo-controlled randomized clinical trials of four atypical agents (risperidone, olanzapine, aripiprazole, and quetiapine). The mortality rate for elderly patients with dementia was ~1.6–1.7 times that of placebo. It is unknown how much of the risk is associated with the medication and how much is simply inherent in the population being studied. Study subjects were frail, mostly institutionalized elderly with multiple risk factors for vascular disease. These findings are therefore particularly concerning for older diabetic patients, who are likely to have other risk factors for cerebrovascular events, including history of stroke. Thus, the benefits of instituting treatment with these medications must be weighed against potential risks.

An added consideration is that, at times, there may be risks associated with no treatment. Older adults with BPSDs can be and often are aggressive. They are occasionally capable of injuring other residents or staff members of their nursing home, their caregivers and relatives, and themselves. Side effect profiles must be considered in light of other medical diseases that may be present, as well as simultaneously administered medications. Minimally, risk factors for vascular disease should be evaluated. Medical management, including control of glucose, hypertension, and dyslipidemias, should be optimized to reduce this risk.

Children and adolescents
Atypical antipsychotics, including those that are less likely to induce weight gain, have a greater effect on weight gain in children and adolescents. Among children and adolescents treated for a variety of conditions (schizophrenia, autism, and pervasive developmental disorder), significant weight gain has been associated with the use of clozapine, olanzapine, risperidone, and quetiapine. Weight gain associated with aripiprazole has been studied in a small sample (n = 14) of children and adolescents with bipolar disorder. Change in weight ranged from +5 kg to −21 kg, with 86% losing weight (average weight loss was 3 ± 6 kg). At present, there are insufficient data on ziprasidone in this age group.

The influence of psychological factors must also be considered when working with diabetic children and adolescents. For example, Erikson describes adolescence as a time when the person must emotionally separate from parental figures in order to affirm a separate identity, while at the same time striving for acceptance and belonging from peers. Diabetes control often deteriorates during this stage. Diabetic teenagers, for example, may fail to adhere to recommended dietary restrictions because they want to fit in with peers. Parental attempts to help with diabetes regimens may be viewed as intrusive and overprotective. Often, referral to a diabetic teen support group can be beneficial. Children who begin to exhibit behavioral or significant academic difficulties, however, may benefit from a mental health evaluation. Ideally, this evaluation should be performed by a child psychiatrist or psychologist who has experience in working with chronically ill children and who is accustomed to frequently communicating with other medical professionals.

Identification of Risk Factors for Diabetes
Many patients taking atypical antipsychotics are not adequately screened for diabetes risk factors. A 2004 consensus conference of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity recommended several baseline evaluations at the initiation of medication use. Clinicians should obtain a personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease. Inquiries should also be made regarding history of gestational diabetes in female patients. A baseline height, weight, and umbilical circumference should be measured and BMI calculated. Baseline blood pressure, fasting plasma glucose, and lipid levels should be checked. These recommendations provide for a very high quality of care because many patients with schizophrenia may have diabetes, elevated lipids, and hypertension and be unaware of it.

Ideally, patients’ weight should be monitored at each visit. Blood pressure, glucose, and lipid levels should be rechecked at 12 weeks and annually thereafter. In addition, nutrition and wellness classes for patients and their families can be helpful, and, increasingly, exercise groups are being incorporated into mental health programs to promote healthy lifestyle choices.

Treatment Considerations
Antipsychotic medications are the basis of treatment for schizophrenia. Schizophrenia is a devastating illness, with an early age of onset. For patients...
who respond, these medications often prevent a lifetime of severe disability and protect both patients and others from aggressive and dangerous behavior.

The benefits of a particular medication for a specific person may outweigh the potential risks, even when those risks include diabetes and dyslipidemias. This is why it is so important to screen for diabetes risk factors. If these risk factors are found during baseline screening—particularly overweight (BMI 25–29 kg/m²), obesity (BMI > 30 kg/m²), presence of metabolic syndrome or diabetes, dyslipidemia, or hypertension—the antipsychotics that are more highly associated with weight gain and diabetes should be avoided. If patients develop clinical symptoms of hyperglycemia (polydipsia and polyuria), a serum glucose level should be obtained, and appropriate initiation of treatment should ensue. This could include consultation with an endocrinologist and dietician, possible initiation of hypoglycemic agents, and consideration of continuation versus change in antipsychotic medication.

Most importantly, patients' psychiatric illnesses should not discourage clinicians from addressing metabolic issues. Patients with schizophrenia can successfully lose weight and improve diabetes outcomes. This was demonstrated by a recent 52-week prospective trial of exercise and nutritional interventions and behavioral therapy. Additionally, controlling psychiatric illnesses with appropriate antipsychotic medications can often lead to improved insight regarding medical diagnoses, enhanced adherence to medical recommendations, and improved medical outcomes.

Summary
Antipsychotic medications are frequently prescribed by nonpsychiatric clinicians, and the use of atypical antipsychotics is increasing. Although these medications have some efficacy and tolerability advantages over the conventional drugs, they have recently been differentially associated with an increased risk of weight gain, diabetes, and hypertriglyceridemia. In the frail geriatric population with diabetes and BPSDs, these medicines have been additionally associated with a possible increased risk of cerebrovascular events and higher mortality rates. In children and adolescents, a working knowledge of child development and recognition of the influence of psychological factors on treatment adherence is critical.

Screening for cardiovascular and metabolic risk factors is particularly important when atypical antipsychotics are to be prescribed. This baseline screening should include questions about personal and family history of diabetes risk factors and measurement of blood pressure, fasting glucose, and serum lipids. Diabetes risk reduction, including nutritional and physical activity counseling, control of blood pressure, lowering of cholesterol and triglyceride levels, weight loss, and increased physical activity, can have a positive impact on both diabetes and the psychiatric illnesses and can be successfully utilized in patients with schizophrenia.

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