Metabolic Risks in Older Adults Receiving Second-Generation Antipsychotic Medication

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Metabolic syndrome is prevalent in older adults and increases the risk of cardiovascular disease. Second-generation antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) increase the risk of metabolic syndrome and present many challenges for psychiatrists. In this article, we review the relationships between second-generation antipsychotics and metabolic syndrome with a focus on older adults. Because few studies focus exclusively on older adults, we augment this review with relevant findings from younger adults. The differential risk factors of each medication are reviewed, as are recent findings in monitoring and treating metabolic syndrome. Olanzapine and clozapine are more strongly associated with metabolic risks, whereas aripiprazole and ziprasidone are less associated. Although lifestyle modifications can help to reduce some aspects of metabolic syndrome, lifestyle modifications in conjunction with metformin therapy appear to be most effective.

Introduction

Metabolic syndrome is increasingly common in the United States—afflicting about 20% of the population [1]—and is now considered a global epidemic. There are gradations in the severity of metabolic side effects, but metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) modified criteria as meeting at least three of the five criteria listed in Table 1, which represent a combination of risk factors for cardiovascular disease and type 2 diabetes [2].

Prevalence of metabolic syndrome in older adults

Metabolic syndrome is age dependent and more prevalent in older adults across cultures [3]. In a cross-sectional Norwegian study, prevalence was greater in people 80 to 89 years old (47.2% in men, 64.4% in women) compared with those 20 to 29 years old (11.0% in men, 9.2% in women) [3]. Evidence that metabolic syndrome is more common in older women than men [4] may reflect higher rates of obesity and hypertension in older women [5•]. The incidence of metabolic syndrome in women tends to increase after menopause, suggesting that hormone imbalance can also contribute to its onset.

Affective and psychotic disorders in older adults

Metabolic syndrome associated with antipsychotic treatment is at the forefront of treatment considerations, not only because of the health risks posed to patients but also because of metabolic syndrome's effects on medication compliance and health care costs. Newer second-generation antipsychotics (SGAs) (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) carry an almost fourfold greater risk of association with metabolic syndrome than first-generation antipsychotics [6]; we have confined our discussion here to the SGAs.

SGAs are indicated for treating schizophrenia and bipolar disorder, which are relatively common among older adults. Bipolar disorder, for example, has a prevalence of almost 5% in older adults [7]. In psychiatric hospital settings, late-onset bipolar disorders were found to have a prevalence of 5% to 25% and were more common than late-onset schizophrenia or schizoaffective disorders [8]. In a longitudinal, community-based survey of Australians at least 70 years old, 7.5% had at least one psychotic symptom [9]. Based on several studies, the lifetime prevalence of schizophrenia is estimated to be about 4% in the general population [10].

Screening

Screening for metabolic syndrome is an important element of the psychiatric evaluation of patients who are prescribed antipsychotics, especially SGAs. Ideally, the

Table 1. ATP III criteria for metabolic syndrome and ADA guidelines for monitoring patients on SGAs*

	Assessment time					
Risk factor	**Baseline**	**4 wk**	**8 wk**	**12 wk**	**Annually**	**Criterion**
Waist circumference†	X	X	X	X	X	Men: > 40 inches
						Women: > 35 inches
Fasting triglycerides	X			X		≥ 150 mg/dL
HDLs	X					Men: < 40 mg/dL
						Women: < 50 mg/dL
Blood pressure	X			X		≥ 130/85 mm Hg (or on antihypertensive agent)
Fasting glucose	X			X		≥ 110 mg/dL (or on insulin or hypoglycemic agent)

*Three or more criteria must be met.
†ADA screening guidelines suggest monitoring weight [27], but other research [2,11] has found waist circumference to be more sensitive.
ADA—American Diabetes Association; ATP III—National Cholesterol Education Program Adult Treatment Panel III; HDL—high-density lipoprotein; SGA—second-generation antipsychotic.

risk factors in Table 1 should be assessed before initiating SGA therapy so that a baseline can be established. When interpreting such measures, secondary causes of abnormalities should be considered, especially in older adults. For example, elevated low-density lipoprotein cholesterol can be caused by diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, or medication.

Although assessing the risks in Table 1 is feasible, comprehensive and repeated measures may present challenges in extremely busy practices or in situations with limited resources. The presence of abdominal obesity and/or elevated fasting blood glucose has been found to identify 100% of the psychiatric patients with metabolic syndrome [11]. The positive predictive value (true positives divided by the sum of true positives and false positives) of just these two measures is 46%, which Straker et al. [11] pointed out compares favorably with other screening tests commonly used for other conditions (eg, fecal occult blood and mammography).

Analyses of a health management organization database revealed that patients being treated for bipolar disorder are significantly more likely to meet criteria for metabolic syndrome than nonbipolar patients [12]. In particular, patients with bipolar disorder exhibited a high prevalence of obesity, high triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels [12]. The prevalence of metabolic syndrome in patients with schizophrenia in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was approximately 40% in men and 50% in women [13].

Metabolic Risks of SGAs

Older adults, by virtue of age and the presence of other illnesses, are at a greater risk of being afflicted by metabolic disorders. Thus, one might presume that the use of antipsychotic agents, which have been shown to produce metabolic complications across age groups, would be at least as likely to do so in older adults. Unfortunately, research on the metabolic effects of antipsychotics in older adults is lacking, and no data specific to this issue exist. Consequently, the issues that we review reflect findings across age groups. In reviewing the risks of SGAs, we describe each metabolic perturbation and then discuss the contributions of different antipsychotics. It is important to remember that the antipsychotic medications themselves are not the only cause of increased metabolic risk, but they do lead to increased risk in concert with hereditary tendencies and other illnesses.

Mechanism

The exact mechanism through which antipsychotics, especially SGAs, lead to metabolic abnormalities is not thoroughly understood. If one considers the general receptor profile of such agents, it is possible that antagonism of H1 histamine receptors and $5HT_{1A}$/$5HT_{2C}$ serotonergic receptors initially contributes to increased appetite. The role of $5HT_{2C}$ antagonism may be questionable, however, because clozapine and ziprasidone are strong $5HT_{2C}$ antagonists, but ziprasidone is associated with little if any weight gain (in contrast to the significant weight gain associated with clozapine) [14]. A comprehensive discussion of the mechanism of SGA-mediated weight gain and metabolic syndrome is beyond the scope of this article, but the mechanism is complex [15].

Weight gain

Obesity is an important public health problem in the United States, as nearly one third of adults are obese (body mass index [BMI] ≥ 30) [16]. Unfortunately, weight gain is a side effect associated with a variety of psychotropic medications, from mood stabilizers to antidepressants to antipsychotics. Although some commonalities may exist across the mechanisms of drugs, genetic predisposition

and lifestyle are major contributing factors, and antipsychotic therapy also can play a significant role.

A randomized trial of 173 patients of all ages with schizophrenia or schizoaffective disorder revealed that compared with olanzapine, aripiprazole was associated with weight loss and lesser changes in total cholesterol after 16 weeks [17]. This finding is in agreement with other smaller scale studies, including a post hoc analysis of a double-blind trial of aripiprazole versus placebo in the treatment of rapid-cycling bipolar disorder. That study revealed no statistically significant changes in weight, lipid, or glucose levels in 28 patients [18]. A preliminary report of 31 patients diagnosed with schizophrenia who were started on aripiprazole therapy reported decreased weight, waist circumference, fasting glucose levels, and lipid levels [19].

Interestingly, some findings suggest that younger patients gain more weight than older patients as a result of SGA therapy. For example, patients older than 37 years of age gained less weight than those less than 37 years old [20]. This finding suggests that there may be a lesser metabolic impact on older patients; however, data regarding the dissociation of weight gain and dyslipidemia (described in the next section) may negate this apparent benefit.

Patients with Alzheimer's disease may exhibit less weight gain than younger patients when treated with SGAs. For example, in a study of patients with Alzheimer's disease, 159 treated with olanzapine did not exhibit significant weight gained compared with 47 matched patients who received placebo [21]. Of course, one must keep in mind the US Food and Drug Administration warning regarding increased death when SGAs are prescribed to patients with dementia-related psychosis.

Weight gain can be beneficial for some older adults: the prevalence of malnutrition in community-dwelling older adults is approximately 11% [22]. However, SGAs should not be used to treat weight loss in older adults, as malnutrition is readily treated through supplements. Although SGA-associated weight gain may be less of a concern in undernourished older patients, serum triglycerides should still be monitored.

Dyslipidemia

Dyslipidemias are highly prevalent in non–psychiatrically ill older adults: 39% of 65- to 74-year-old adults have cholesterol levels greater than 240 mg/dL [23]. High levels of low-density lipoprotein cholesterol are a risk factor for coronary heart disease, making it a primary target of therapy in ATP III guidelines [11]. Although we are not aware of studies of dyslipidemias resulting from SGA therapy that pertain specifically to older adults, some research suggests that older adults exhibit SGA-related increases in cholesterol that are similar to those in younger adults [24].

Weight gain is usually seen as a precursor to dyslipidemia in the realm of SGA therapy. However, growing recent evidence indicates that the two are not coupled as tightly as commonly thought. A naturalistic study that included 160 patients on monotherapy with olanzapine or clozapine found that compared with 82 unmedicated patients, the olanzapine or clozapine patients demonstrated hypertriglyceridemia even though BMI was similar to that of the unmedicated group [25]. In a double-blind, randomized trial comparing the metabolic changes associated with olanzapine and risperidone in patients with schizophrenia or schizoaffective disorder, not only were BMI increases greater in the olanzapine group, but men exhibited an increase in total cholesterol disproportionate to their weight gain [26]. Even more striking was that weight gain and lipid increases were apparent after 8 weeks of therapy. This finding highlights the importance of monitoring weight and lipids early in the course of treatment. Such dissociations suggest that lipids should be monitored even in the absence of documented weight gain.

Hyperglycemia

The prevalence of diabetes is approximately 1.5 to 2 times greater among patients diagnosed with schizophrenia or affective disorders than in the general population [27], although the extent to which other risk factors contribute to this increase is unclear. Of course, patients with schizophrenia or affective disorders are most likely to be treated with SGAs. Importantly, some researchers have argued that therapy with SGAs may "unmask" hyperglycemia [28]. In a public health study of bipolar disorder in patients with diabetes, olanzapine, quetiapine, and risperidone were all found to be associated with development or exacerbation of diabetes [29]. A 3-month naturalistic study in which 183 patients were started on SGAs revealed that clozapine, olanzapine, and quetiapine all had negative effects on glucose metabolism compared with aripiprazole [30].

As with dyslipidemia and weight gain, hyperglycemia and weight gain may be uncoupled. In a study of patients with schizophrenia, the effects of SGAs on glucose regulation varied independently of weight gain [31].

Finally, recognizing diabetic ketoacidosis is important when treating older patients with SGAs. The clinical presentation of diabetic ketoacidosis can include the rapid onset of polyuria or polydipsia, weight loss, nausea or vomiting, dehydration, rapid respiration, confusion, and coma.

Differences Among SGAs

SGAs have variable associations with metabolic syndrome and the diagnostic elements that comprise it. Some approximations of the metabolic changes associated with SGAs are provided in Figure 1. Clozapine was not included in all the studies but had a greater weight gain (8.8 pounds) than olanzapine after 10 weeks of therapy [14]. Aripiprazole was not included in either study used to create Figure 1. In this section, we briefly compare medications based on the

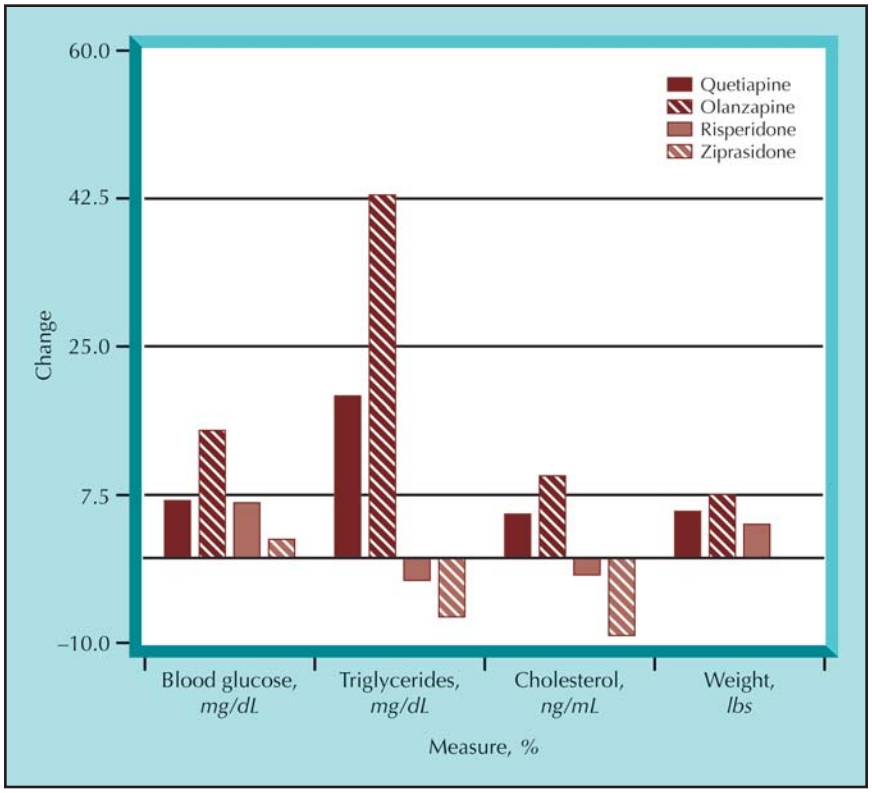

Figure 1. Relative metabolic impact of second-generation antipsychotics. All data were derived from Lieberman et al. [51], except for weight data, which represent the average changes in weight after 10 weeks of therapy as reported by Allison et al. [14].

previous discussion. The conclusions must remain speculative because the necessary long-term direct comparisons of medications have not been performed.

Aripiprazole

In general, aripiprazole appears to have a mild impact on metabolic measures. Many studies suggest that aripiprazole has little association with weight gain and may be associated with weight loss. A study in which patients with various diagnoses were switched from another antipsychotic to aripiprazole revealed a decrease in total cholesterol and weight but no differences with respect to triglycerides or fasting blood glucose [32]; a secondary analysis of patients who were previously taking olanzapine revealed stronger effects. With respect to metabolic syndrome, aripiprazole seems to contribute little to the risk factors and may be associated with a reduction in risk when switching from a different SGA. We are not aware of studies of aripiprazole specifically in older populations, but clinical experience suggests that it is reasonably well tolerated without excessive sedation.

Clozapine

Clozapine is notoriously associated with metabolic syndrome—weight gain in particular. Some studies have found that among patients with schizophrenia, the prevalence of metabolic syndrome in those taking clozapine was 54%, compared with 21% of patients in a comparison group [33]. Keeping in mind the many similar cases of weight gain associated with clozapine, there is little to be offered in its defense with respect to metabolic syndrome. Nevertheless, clozapine is highly effective in treating severe mental illness. When metabolic syndrome arises as a result, it may be worthwhile to consider possible interventions that we describe subsequently. In older adults, however, the side effects of clozapine (eg, marked sedation, constipation) can outweigh its considerable benefit.

Olanzapine

With the exception of clozapine, olanzapine appears to have the largest deleterious effect on metabolic risk factors. It is associated with greater increases in weight, blood glucose, cholesterol, and triglycerides than the other SGAs in the comparison. Recent analyses of the CATIE schizophrenia trial data provide further evidence that olanzapine is more strongly associated with increased triglyceride levels relative to perphenazine [34]. Clinically, the average increases are not likely to be very important. For example, a 15-point increase in blood glucose by itself is not clinically meaningful, but in a patient who already suffers from glucose dysregulation, it may be undesirable. Some patients will exhibit increases greater than the average, so monitoring blood glucose is still warranted.

Olanzapine also produces greater weight gain than other SGAs, except clozapine. Psychiatrists may have anecdotal stories of individual patients who exhibit extreme weight gains on olanzapine, but it is important to bear in mind that switching to a different agent after a patient did not engage in appropriate lifestyle modifications could have arrested weight gains.

Risperidone

Risperidone has a weaker association with metabolic risks than clozapine and olanzapine [28], but it is still associated with metabolic syndrome. A recent study of patients with bipolar disorder did not reveal differential prevalence of metabolic syndrome in those taking quetiapine, risperidone, or olanzapine [35]. However, this study contradicted an earlier one, which found that olanzapine was associated with increased fasting glucose and lipid levels compared with risperidone in younger patients [36].

One crossover study found that when overweight and obese patients 18 to 65 years old were switched from olanzapine to risperidone, significant decreases in weight, waist circumference, and blood pressure were observed [37]. Overall, however, the risk of hyperglycemia and diabetes appears to be slightly lower for risperidone than for olanzapine.

Quetiapine

Metabolic risks associated with quetiapine appear to be lower than those associated with clozapine, olanzapine, and risperidone. In a study of 920 patients with bipolar disorder, quetiapine had the lowest association with diabetes (risk ratio, 1.8), although it was still significantly greater than that of the control group [38]. The same finding held in a subsequent study of bipolar disorder patients who were Medicaid participants in the Midwest [29]. Even so, evidence suggests an association between quetiapine and metabolic syndrome [39].

Compared with clozapine and olanzapine, quetiapine is associated with less weight gain. In an open-label study, patients diagnosed with schizophrenia who were switched from olanzapine to quetiapine exhibited an average weight loss of 2.3 kg, although there was no evidence of alterations in metabolic parameters [40]. Analyses of the CATIE schizophrenia trial data, however, suggested an association between increased triglyceride levels and quetiapine [34].

Ziprasidone

The metabolic risks of ziprasidone are notably lower than other SGAs, and like aripiprazole, ziprasidone has been associated with mild weight loss [41]. A double-blind, 6-week study in which patients with schizophrenia or schizoaffective disorder were randomly assigned to ziprasidone or olanzapine revealed that ziprasidone had no effect on body weight, cholesterol, or triglycerides [42]. Meyer et al. [34] also found that ziprasidone appears to be neutral with respect to triglyceride levels.

Perhaps the most compelling evidence of ziprasidone's lower metabolic risks derives from switching studies. In an open-label study of 312 patients diagnosed with schizophrenia, patients were switched from other antipsychotics (mainly olanzapine, risperidone, and haloperidol to ziprasidone [43]. Significant improvements were seen in cholesterol, HDLs, and triglycerides after switching to ziprasidone.

Management of Metabolic Abnormalities

Although there are differences in terms of metabolic risks associated with different SGAs, it is important to monitor patients regardless of which SGA they are taking. Sometimes, switching SGAs is not feasible due to lack of clinical response or undesirable side effect profiles. Thus, some patients may incur metabolic syndrome, which must be managed. In this section, we review suggested monitoring guidelines and recent information about treating and managing metabolic syndrome.

Monitoring

Table 1 provides a recommended monitoring schedule for patients who are prescribed SGAs. The American Diabetic Association guidelines suggest monitoring weight frequently [27]. However, based on other research, we tend to recommend monitoring waist circumference given its greater sensitivity to metabolic syndrome [2,11]. In high-risk patients, it may be wise to monitor weight and waist circumference.

Prevention and treatment

The high prevalence of metabolic syndrome in patients who are prescribed SGAs demands that clinicians take preventive measures at the onset of SGA therapy. Patients should be educated and encouraged to make appropriate lifestyle changes (ie, exercise, healthy diet, and smoking cessation). At times, of course, efforts to alter lifestyle—especially in older adults—may be met with inordinate resistance and can turn into a lost battle. Clinical status does not always prevent switching medications, so the signs of metabolic syndrome must be treated. Interventions to prevent and treat have met with varying degrees of effectiveness, as we describe in the next sections.

Physical activity

Regular physical activity has been consistently associated with reduced incidence of metabolic syndrome. For older adults, Park et al. [44] have demonstrated that yearlong daily exercise reaching the intensity of three or more metabolic equivalents for at least 20 minutes daily was associated with decreased incidence of metabolic syndrome risk factors. Interestingly, although exercise improves fitness, reductions in BMI specifically were more strongly associated with favorable changes in risk factors for metabolic syndrome [45].

Diet

Dietary changes in patients taking SGAs should include reductions in cholesterol and saturated fat consumption. Restricted-calorie diets low in carbohydrates and higher in unsaturated fat facilitate weight loss and reduce markers for cardiovascular disease risk in obese adults [46]. Reduced sodium intake in older hypertensive adults reduces cardiovascular morbidity and premature death.

Dietary fiber is associated with improved metabolism and weight loss and is useful in treating hyperglycemia, dyslipidemia, and hypertension [47].

As in the general population, a major impediment to implementing lifestyle and diet changes to address weight gain is patient compliance. Among chronically mentally ill older patients, socioeconomic factors can present distinct challenges in terms of complying with lifestyle changes. Implementing supportive social groups for outpatients taking SGAs can help to support patients who struggle to adhere to dietary changes.

Oral hypoglycemics

Some studies have described the use of oral hypoglycemic agents to treat metabolic syndrome induced by SGAs. In a series of 24 patients with schizophrenia, 8 weeks of treatment with metformin led to decreased weight, fasting blood glucose levels, and triglyceride levels [48]. A double-blind, placebo-controlled study of patients with first-episode schizophrenia revealed that metformin attenuated weight gain associated with olanzapine [49•]. However, a randomized trial showed metformin plus lifestyle interventions to be superior to metformin alone and to lifestyle change plus placebo in reducing metabolic risk factors in patients taking SGAs [49•]. Although lifestyle modifications do not have the side effects of metformin use, patients who do not realize sufficient benefit from lifestyle modifications may benefit from adding metformin.

Statins

There are limited reports regarding the use of statins to treat dyslipidemia related to the use of SGAs. Preliminary open-label data suggest that statins can decrease LDLs and triglycerides but do not increase HDLs [50]. At this point, considering the well-controlled data for metformin and its ability to address multiple metabolic risk factors, metformin would seem to be preferable to statins in treating signs of metabolic syndrome.

Conclusions

Metabolic syndrome is a growing societal problem that is becoming more common in the treatment of psychiatric illness because of increased SGA use. Although more research on SGAs and metabolic syndrome in older patients is needed, it seems likely that the problem will be even greater than it is in younger patients. SGAs vary considerably in their association with metabolic syndrome, and all appear to be associated with some degree of metabolic risk, although aripiprazole and ziprasidone appear to have the weakest associations. In individual patients, SGAs may prove differentially effective, and clinicians may need to continue a medication despite its contribution to metabolic syndrome. Lifestyle changes are the least invasive way to address signs of metabolic syndrome, but recent work demonstrates that lifestyle changes plus therapy with metformin may be the best way to address this troubling syndrome in the presence of SGAs.

Disclosures

Dr. Brooks serves on the speakers' bureau for Eli Lilly and Company, Bristol-Myers Squibb, Pfizer, and AstraZeneca Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

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