Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications

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\begin{abstract}
Individuals with major mental illness are a high-risk group for cardio-metabolic derangements due to genetic predisposition, developmental and environmental stressors, and lifestyle. This risk is compounded when they receive antipsychotic medications. Guidelines for screening, monitoring, and managing these patients for metabolic problems have been in place for several years. Despite this, recent reports document that this population continues to receive poor care in this regard. In this article, we review the metabolic profile of atypical antipsychotic medications and offer guidelines to reduce the metabolic complications of these agents.
\end{abstract}

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1. Introduction

The prevalence of the metabolic syndrome and individual cardiovascular risk factors including obesity, dyslipidemia, diabetes mellitus, cigarette smoking, and hypercholesterolemia are greater in individuals with major mental illness compared with the general population [1-6]. While unhealthy lifestyle [1,7,8] and apparent genetic predisposition [9-11] contribute to this, there is growing evidence that treatment with antipsychotic medications may be a factor in the increased prevalence of the cardio-metabolic problems among patients with major mental illness [12-15].

Guidelines to screen and monitor patients receiving atypical antipsychotic drugs have emerged over the last few years [16,17]. Despite these guidelines, screening for, monitoring of, and managing metabolic disturbances among patients with major mental illness remains poor [18-21], underscoring the need to further improve awareness among clinicians on this important subject. In this article, we review the metabolic side effects of atypical antipsychotic medications, discuss the mechanisms that may underlie the medication-associated metabolic effects, and recommend monitoring and management strategies.

2. Metabolic syndrome and cardio-metabolic risk factors

Metabolic syndrome refers to a group of metabolic disturbances that interact synergistically to increase the risk of atherosclerotic cardiovascular disease. The syndrome also predisposes to diabetes mellitus, onset of which increases cardiovascular risk even further, such that diabetes is considered a cardiovascular risk equivalent [22,23]. Core features of metabolic syndrome are overweight including increased abdominal (visceral) fat, atherogenic dyslipidemia, insulin resistance, and hypertension. Pro-thrombotic and pro-inflammatory states are found in this setting. Organizations vary in their definition of the metabolic syndrome (Table 1).

Questions remain as to whether the metabolic syndrome can predict cardiovascular disease and diabetes mellitus more accurately than its components [24,25]. For purposes of this review, we will embrace the clinical utility of this syndrome. For a detailed discussion of the metabolic syndrome and its components, please see the reports by the National Heart, Lung, and Blood Institute and the American Heart Association [23,26].

Cardiovascular risk factors expand beyond the various definitions of the metabolic syndrome. The National Cholesterol Education Program’s Adult Treatment Panel (ATP III) categorizes cardiovascular risk factors into underlying, major, and emerging risk factors [23]. The underlying risk factors are obesity (especially abdominal), physical inactivity, and atherogenic diet. The major risk factors are cigarette-smoking, hypertension, elevated LDL, low HDL, family history of premature coronary heart disease, and aging. The emerging risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, pro-inflammatory state, and pro-thrombotic state.

3. Atypical antipsychotic medications and metabolic disturbances

Atypical antipsychotics currently available in the United States (in order of market approval) are: clozapine (1990), risperidone (1994), olanzapine (1996), quetiapine (1997), ziprasidone (2000), aripiprazole (2001), and paliperidone [the main active metabolite of risperidone] (2006). All these agents are available in Europe as well. Atypical antipsychotics available in Europe but not in the United States are amisulpride, melperone, sertindole, sulpiride, and zotepine. The relative potential for these agents to cause metabolic disturbances is reviewed below and is summarized in Table 2. Information available for melperone, sertindole, sulpiride, and zotepine is very limited. Preliminary findings suggest that paliperidone has low metabolic liability [27].

3.1. Weight gain

The risk and magnitude of short-term and long-term weight gain are highest for clozapine and lowest for ziprasidone [12,28,29]. For other antipsychotics the risk can be “quantified” for short-term use with olanzapine having high risk,
Table 1 - The metabolic syndrome as defined by the World Health Organization [100,101], Adult Treatment Panel III [22,26], International Diabetes Federation [102].

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal girth</td>
<td>2 or more of the following</td>
<td>3 or more of the following</td>
<td>Must have central obesity</td>
</tr>
<tr>
<td></td>
<td>Waist-to-hip ratio &gt;0.9 in men, &gt;0.85 in women AND/OR BMI &gt;30 kg/m²</td>
<td>Waist circumference ≥102 cm (40 in.) for men and ≥88 cm (35 in.) for women</td>
<td>Central obesity (waist circumference ≥94 cm for European men and ≥80 cm for European women; other ethnic groups have specific values)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Urinary albumin excretion rate ≥20 µg/min OR albumin-to-creatinine ratio ≥30 mg/g</td>
<td>Triglycerides ≥1.7 mmol/L (150 mg/dL)</td>
<td>Triglycerides ≥1.7 mmol/L (150 mg/dL)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Serum triglycerides ≥1.7 mmol/L (150 mg/dL)</td>
<td>Triglycerides ≥1.7 mmol/L (150 mg/dL)</td>
<td>Triglycerides ≥1.7 mmol/L (150 mg/dL)</td>
</tr>
<tr>
<td>Low high density lipoproteins</td>
<td>HDL &lt;0.9 mmol/L (35 mg/dL) in men and &lt;1.0 mmol/L (39 mg/dL) in women</td>
<td>HDL &lt;1.03 mmol/L (40 mg/dL) in men and &lt;1.3 mmol/L (50 mg/dL) in women</td>
<td>Low HDL &lt;1.03 mmol/L (40 mg/dL) in men and &lt;1.29 mmol/L (50 mg/dL) in women</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure ≥140/90 mmHg</td>
<td>Blood pressure ≥130/85 mmHg</td>
<td>Blood pressure ≥130/85 mmHg</td>
</tr>
<tr>
<td>Plus any 1 of the following</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus or pre-diabetes</td>
<td>Type 2 diabetes mellitus: Fasting plasma glucose ≥7 mmol/L (126 mg/dL) OR 2-h post-glucose load ≥11.1 mmol/L (200 mg/dL)</td>
<td>Fasting plasma glucose ≥6.1 mmol/L (110 mg/dL)</td>
<td>Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) OR previously diagnosed type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance: Fasting plasma glucose &lt;7 mmol/L (126 mg/dL) AND 2-h post-glucose load &lt;7.8 mmol/L (140 mg/dL)</td>
<td>Impaired fasting glucose: Fasting plasma glucose ≥6.1 mmol/L (110 mg/dL) and &lt;7 mmol/L (126 mg/dL) AND 2-h post-glucose load &lt;7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin resistance: Glucose uptake below lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Or on specific treatment for these conditions.
b 2001 definition identified fasting plasma glucose of ≥110 mg/dL as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L) [26].
quetiapine and possibly zotepine having moderate risk, and risperidone, sertindole, amisulpride, aripiprazole, and ziprasidone having mild risk. With long-term use, differences in weight-gain liability of these agents are not as great [29].

Clozapine administration may lead to weight gain of 4–12 kg in 13–85% of patients [30]. In a recent review, Newcomer and Haupt [12] based on pooled multiple doses data from the clinical trial programs reported that mean weight gain over one year is about 1 kg with aripiprazole and ziprasidone, about 1.5 kg with amisulpride, 2–3 kg with quetiapine and risperidone and and over 6 kg with olanzapine (>10 kg in patients who received a daily dose between 12.5 mg and 17.5 mg). The authors of this review noted that their findings paralleled the results of recent prospective randomized comparisons of individual agents. In another recent review of pivotal trials, Conley and Kelly [31] reported that 29% of patients receiving olanzapine, 25% taking quetiapine, 18% receiving risperidone, 10% taking ziprasidone, and 7% of patients taking aripiprazole can expect greater than 7% increase in their baseline body weight in the short-term. Some assert that with the exception of clozapine, atypical antipsychotic drug-induced weight tends to stabilize in several months to a year [32].

3.2. Dyslipidemia

Dyslipidemia associated with atypical antipsychotic drug administration was comprehensively reviewed by Meyer and Koro [33] a few years ago and several studies on this subject have appeared since then [34–41]. This literature suggests that administration of atypical antipsychotic drugs may result in dyslipidemia including reduced HDL and elevated cholesterol, triglycerides, and LDL. The risk of dyslipidemia appears to be high with clozapine, olanzapine, and quetiapine and mild with risperidone and amisulpride. Ziprasidone and aripiprazole are least likely (or unlikely) to cause dyslipidemia and may improve the lipid profile of patients switched from another antipsychotic drug to one of these agents [38,42]. Weight gain associated with atypical antipsychotic drug administration may explain dyslipidemia, but this lipid disturbance may occur independent of weight gain [41,43].

### Table 2 – Approximate relative likelihood of metabolic disturbances with atypical antipsychotic medications (see text for discussion).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight gain</th>
<th>Glucose metabolism abnormalities</th>
<th>Dyslipidemia</th>
<th>Metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>–</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Clozapine</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Melperone</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Medium</td>
<td>Medium to low</td>
<td>Low</td>
<td>–</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Medium</td>
<td>Medium to low</td>
<td>High</td>
<td>–</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Medium</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

3.3. Insulin and glucose metabolism abnormalities and diabetes mellitus

Atypical antipsychotic medications may have unfavorable effects on insulin and glucose regulation [12,40,44–47]. Specifically, the risk of insulin resistance and hyperglycemia is high with clozapine and olanzapine, moderate to low with quetiapine and risperidone, and low with aripiprazole, amisulpride, and ziprasidone.

Treatment with antipsychotic medications may be associated with sudden onset of hyperglycemia with or without complications [12]. Bayesian data-mining analysis of the FDA adverse event reporting system (1968–2004) [48] showed that on average, the ranking of association strength in this regard is strong for clozapine and olanzapine, medium for quetiapine, and low for ziprasidone, aripiprazole and risperidone.

Literature describing the association between antipsychotic medications and new onset diabetes mellitus or worsening of existing diabetes mellitus [12,15,49–52] is difficult to interpret and evidence for a causative association between use of antipsychotic medications and diabetes mellitus is inconclusive [53]. We have drawn a few generalizations from the literature. (1) Atypical antipsychotics associated with greater weight gain are generally associated with a higher risk for type 2 diabetes mellitus. Some studies, however, report a comparable diabetogenic effect for clozapine, olanzapine, risperidone, and quetiapine [54], especially in young adults [55]. (2) Age appears to be a factor contributing to antipsychotic-induced diabetes mellitus, with younger adults being at greater risk than older adults [49,56–58]. (3) Although most new-onset type 2 diabetes mellitus cases are associated with substantial weight gain or obesity, about 25% are not [12], implying that adiposity alone does not explain the association. (4) In some cases, medication-induced diabetes mellitus might remit after switching from a “high potential” medication to one with a “low potential”.

3.4. Metabolic syndrome

Several recent studies looked at the risk of the metabolic syndrome among patients taking atypical antipsychotic drugs. Again, this risk is high with clozapine and olanzapine and
4. Atypical antipsychotics and the metabolic syndrome: pathogenesis

Metabolic risk factors associated with major mental illness among patients taking atypical antipsychotic medications appear in Fig. 1. Certain antipsychotic medications increase appetite and lead to adiposity. Affinity of the antipsychotic drugs for histamine-1 (H1) receptors closely correlates with their weight-gaining potential [63] and appears to involve H1 receptor-linked activation of hypothalamic AMP-kinase [64]. Also, 5-HT2C receptor antagonism may contribute to weight gain [65]. The effect atypical antipsychotics have on hormones involved in appetite regulation is not clear [66]. However, the H1 and 5HT2C blocking effects of antipsychotic medications may interfere with leptin-mediated appetite suppression [65,67].

Adiposity alone does not explain the diabetogenic potential of atypical antipsychotic medications [12]. Animal and human studies describe the acute adverse effect of clozapine and olanzapine on insulin and glucose metabolism [68]. Significant insulin resistance has also been documented in non-obese individuals receiving clozapine or olanzapine versus those receiving risperidone [45]. Diminished or inefficient insulin release from pancreatic beta-cells as well as peripheral insulin resistance may underlie the diabetogenic effect of certain antipsychotic medications. Blocking muscarinic type 3 (M3) and 5-HT1A receptors may be a factor to diminished pancreatic beta-cell responsiveness and blocking 5HT2C receptor may suppress glucose uptake in skeletal muscle [63].

Some antipsychotic medications may impair and/or alter the action of insulin on adipocytes leading to progressive lipid accumulation [69]. The impaired effect of insulin on adipocytes may partly explain weight-gain independent dyslipidemia [41,43]. Increased food intake and peripheral insulin resistance perpetuate adiposity and release of several adipokines—some of which contribute to cardio-metabolic risk [70].

5. Assessing, monitoring, and managing patients receiving atypical antipsychotic medications

We will use consensus guidelines (Table 3) developed jointly by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity [71] to monitor patients taking atypical antipsychotic drugs. We are mindful of other guidelines [16,17].

5.1. Baseline assessment and follow-up

Besides guidelines provided in Table 3, consider ethnicity, dietary habits, physical activity, support system, cigarette smoking, and alcohol and drug abuse. Consider previous response to and side effects of medications that the patient is using or has used. Keep in mind that psychotropic medications other than antipsychotic drugs such as some antidepressants and mood stabilizers may link to weight gain [72–74].

Even for patients free of metabolic disturbances, monitor potential risk factors as shown in Table 3. Weight gain may not be dose-dependent and individuals with low body mass index (BMI) at baseline may be particularly vulnerable to weight gain [31]. Glucose and lipid metabolism abnormalities may...
Table 3 – American Diabetes Association (ADA) and American Psychiatric Association (APA) consensus guidelines for baseline assessment and monitoring of patients receiving atypical antipsychotic medications [71]a.

<table>
<thead>
<tr>
<th>Personal/family historyb</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (body mass index)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

a More frequent assessments may be warranted based on clinical status.
b Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease.

occur without weight gain [12,41,43]. For patients who gain significant weight (greater than 7% of baseline body weight) and were free of metabolic abnormalities at the beginning of treatment, we recommend checking fasting lipid profile and fasting glucose after 6 months as well. Patients who have cardio-metabolic risk factors should have their fasting lipid profile checked every 2 years instead of every 5 years and most patients with diabetes mellitus should have their fasting lipid profile measured at least once a year. Central obesity is a better predictor of metabolic derangements than BMI. Because antipsychotic-induced weight gain can be significant early in treatment, we recommend measuring waist circumference 3 and 6 months after starting treatment and then annually. Antipsychotic medications may contribute to hypertension by causing weight gain and/or insulin resistance. Blood pressure should be monitored yearly or more often if indicated. Look for symptoms and signs of diabetes mellitus and diabetic ketoacidosis during the first several months, especially in patients taking clozapine, olanzapine or quetiapine. Checking glycosylated hemoglobin (HbA1c) levels may identify those patients who are developing glucose metabolism problems [75]. Check “at risk” patients 3 and 6 months after starting treatment. The frequency of monitoring will be different for those patients who develop metabolic derangement and will be dictated by the treatment guidelines for that specific derangement.

5.2 Liaison between the primary care physician and the psychiatrist

Current studies indicate that patients with major mental illness do not receive adequate evaluation and effective treatment of their cardio-metabolic problems [18–21,76–79]. Effective communication between the primary care physician and the psychiatrist is particularly important for the chronic mentally ill because of their impaired capacity to care for themselves. Such communication will improve monitoring, help early detection of metabolic derangements, and limit duplication of clinical or laboratory workup. Monitoring for metabolic side effects is primarily the responsibility of the physician prescribing antipsychotic medication and in most cases that would be a psychiatrist. If the primary care physician observes that the patient is being prescribed such drugs without being monitored effectively, he/she should discuss this with the psychiatrist. The psychiatrist may not have the expertise to manage any abnormalities that are detected and in such situations the primary care physician will most likely take over both monitoring and management. Liaison should extend to any healthcare professionals involved in the care of patients with chronic mental illness and cardio-metabolic problems.

5.3 Selection of atypical antipsychotic medication

Atypical antipsychotic drugs have comparable efficacy and largely differ based on their side-effect profile [80,81]. Therefore choosing a drug would be based on risk factors and metabolic state of the patient, metabolic side-effect profile of the drug (Table 2), responses and side effects to previous treatments, and patient preference. Combining medications associated with weight gain will increase the likelihood of weight gain [73]. If a patient requires several psychotropic medications (for example, a mood stabilizer or an antidepressant plus an antipsychotic), try to avoid combining drugs associated with weight gain.

5.4 Patient education and interventions for modifiable risk factors

Education of the patient and, when possible, significant others and other care-providers (e.g., case manager, respite worker) optimizes treatment and drug compliance, and reduces unfavorable metabolic side effects. Patient education is an ongoing process and should be provided in a manner and at a pace manageable for the patient. It should cover topics including those related to the patient’s illness, what to expect from the medication(s) in terms of response and side effects, symptoms and signs of diabetes and diabetic ketoacidosis, modifiable cardio-metabolic risk factors, and importance of treatment compliance.

Modifiable cardio-metabolic risk factors such as, overweight/obesity, cigarette smoking, lack of physical activity and unhealthy diet are common in patients with major mental illness [1,7,8,82,83] and should be addressed even in patients free of metabolic derangements. If resources allow, educate other relevant health professionals (dietitian, psychologist, activity-recreational therapist, and addiction counselor, etc.).

6 Pharmacological interventions for antipsychotic-induced metabolic derangements

The primary care physician is central to managing and monitoring the physical health of patients requiring treatment with antipsychotic drugs [71,84]. The patient benefits when there is
a collaborative approach between the psychiatrist and physician. Such collaboration may require psychiatrists to improve their knowledge of physical treatments.

There is a growing body of literature documenting the benefits of switching from an antipsychotic drug with high risk of metabolic side effects (including weight gain) to one with low risk (Table 2). This option has been suggested by Barnett et al. [17] based on the joint guidelines of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity [71]. We strongly recommend this course as the initial intervention when possible in all patients who show worsening metabolic profile including significant weight gain. Specific guidelines for switching antipsychotic medications have been developed [89].

Various agents including ephedrine, sibutramine, orlistat, topiramate, nateglinide, naltrexone, amantadine, reboxetine, fluoxetine, and topiramate have been studied as potential anti-obesity treatments in antipsychotic-treated patients developing metabolic derangements. Two recent publications [90,91], found insufficient evidence to support the general use of any of these agents to limit or reverse the metabolic complications associated with antipsychotic-drug therapy. However, trial of one or more of these medications may be advisable if more conservative interventions like switching to a metabolically safer antipsychotic is not possible and lifestyle interventions have failed [92]. Insulin-sensitizing agent, Metformin, has been shown to prevent or attenuate weight gain and insulin resistance associated with antipsychotic use in several recent studies of short-term duration (8–16 weeks) [93–97]. Most of these studies used adult patients receiving olanzapine. However, one study on children and adolescents also had subjects taking quetiapine and risperidone [95]. Another study included patients receiving clozapine, risperidone, and sulphuride [96]. Dose range of metformin in these studies was 750–2550 mg per day and the drug was tolerated reasonably well.

The beneficial effect of metformin administration on weight and glucose metabolism may be more pronounced in patients who undergo lifestyle intervention consisting of psychoeducation, dietary modification based on the American Heart Association step 2 diet (less than 30% of total energy fraction from fat), and an individualized exercise program [96]. In this study of 12-weeks duration metformin use alone was more effective than lifestyle intervention plus placebo in increasing insulin sensitivity and reversing weight gain but metformin along with lifestyle intervention offered the greatest benefit. A large multicenter study using individuals from the general US population showed that either metformin use or intensive lifestyle intervention may delay or prevent the onset of diabetes mellitus in patients with impaired glucose tolerance [98]. In this study, the metformin group lost weight during the first year of treatment. However, this loss was not as pronounced or sustained as that observed for the intensive lifestyle group. Taken together, these findings suggest the potential use of metformin in patients with major mental illness receiving antipsychotic medications. However, we need long-term studies to clearly establish the utility of metformin plus lifestyle modification. Thiazolidinediones (rosiglitazone and pioglitazone) may improve cardiovascular risk factors through multiple mechanisms [99] but so far they have not been systematically studied for treatment of antipsychotic-induced weight gain and metabolic derangements.

If the metabolic derangement evolves into a disorder, then treatment guidelines specific to that disorder dictate management. Pharmacological interventions should not exclude non-pharmacologic strategies.

7. Conclusions

Despite the availability of well-published clinical guidelines, patients with chronic mental illness receiving atypical antipsychotic medications remain vulnerable to the cardiometabolic complications of these drugs. In general, patients taking clozapine and olanzapine are most vulnerable and those taking aripiprazole and ziprasidone are least vulnerable to these complications. Preliminary data on paliperidone also suggests it to have low metabolic risk. Patients taking amisulpride, risperidone, and quetiapine fall in between. We have emphasized the need for screening, monitoring, and management of these patients. Management includes close liaison between the primary care provider and the psychiatrist.

We recommend large-scale studies using present guidelines that include the primary care provider and the psychiatrist working together. New strategies and technologies might emerge from such studies, facilitate cooperation and enhance patient care.

Conflict of interest

Dr Pandurangi is on the speaker’s bureau of Astra-Zeneca, Bristol Myers Squibb, Janssen and Pfizer Pharmaceuticals. Other authors do not have any conflict of interest to declare.

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