Strategies for prevention and management of second generation antipsychotic-induced metabolic side effects

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ABSTRACT

Preventing, minimizing and managing risks associated with second generation antipsychotic (SGA) use in patients with schizophrenia and other psychotic disorders is a priority for clinicians working with this population. Among these risks is metabolic syndrome. As this population exhibits increased rates of obesity, diabetes and atherogenic dyslipidemia compared to the general population, metabolic syndrome deserves serious consideration in patient care planning for managing risks. This article comprehensively reviews different strategies and recommendations for prevention and/or management of metabolic abnormalities associated with the use of SGAs. Baseline screening and follow-up metabolic monitoring as well as education and counseling on risk for SGA-induced weight gain and other metabolic abnormalities, physical activity and healthy diet for weight maintenance/loss should be promoted shortly after initiation of SGAs. In select patients, the clinician can consider simplifying the antipsychotic treatment regimen by switching to an agent with a lower propensity of metabolic side effects or possibly adding metformin for weight loss and glucose metabolism regulation in those experiencing a first episode of schizophrenia. Future research should focus on combinations of interventions and treatment modalities and exploration of novel interventions.

KEYWORDS

second generation antipsychotic (SGA), side effect, metabolic syndrome, monitoring

BACKGROUND

Metabolic disturbances and metabolic syndrome (MetS) are highly prevalent in patients with severe mental disorders1-4 and play an important role in the development of atherosclerosis.5 MetS includes a cluster of risk factors, such as abdominal obesity, high blood pressure, atherogenic dyslipidemia, insulin resistance and hyperglycemia that interact synergistically to increase the risk for coronary heart disease (CHD) and diabetes mellitus.6 Schizophrenia itself may be a risk factor for MetS and metabolic disturbances, but there is also increasing evidence that use of antipsychotics, particularly second-generation antipsychotics (SGAs), have metabolic consequences that contribute to the risk.3-7

In current clinical practice, “atypical” or second-generation antipsychotics (SGAs) have become mainstay in the management of schizophrenia, and other psychiatric conditions in children, adolescents and adults.8 Currently, there are ten SGAs available in the US: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). They vary in their efficacy, formulation, receptor-binding properties, and type and extent of side effect profiles.3 Aside from clozapine that can be associated with agranulocytosis,9,10 and thus is reserved for treatment-resistant schizophrenia, severely-ill refractory patients or patients with schizophrenia who are at high risk for suicide, SGAs have become first-line agents for their indicated uses and have largely replaced first-generation antipsychotics (FGAs). In general, SGAs carry lower risk for tardive dyskinesia and extrapyramidal symptoms (EPS) compared to FGAs when administered at clinically therapeutic doses. However, varying degrees of weight gain, atherogenic dyslipidemia, hyperglycemia, and even MetS are clinically-important metabolic side effects of SGAs.11-20 The use of SGAs is also associated with new onset of type 2 diabetes mellitus (T2DM), worsening of pre-existing type 1 (T1DM) or T2DM, and rare cases of diabetic ketoacidosis and hyperosmolar-hyperglycemic state.21-23 Second generation antipsychotic induced dysmetabolic effects are usually evident within the first 12 weeks after initiation of medication.24 The extent of weight gain and metabolic disturbances and consequent risk for MetS depends on the specific SGA prescribed along with patient-specific factors.11-20 The metabolic effect appears to be an intrinsic effect of individual SGAs, and there appears to be a dose-dependent relationship between clozapine or olanzapine use and metabolic complications.25,26 Preliminary evidence suggests a dose-response relationship between...
Clozapine and olanzapine serum concentrations and weight gain, however, the association between antipsychotic dose and metabolic outcomes is not clear. Yood et al. followed adult patients (mean age: 44) exposed to aripiprazole, clozapine, olanzapine, ziprasidone, risperidone, and ziprasidone for at least 45 days between January 2002 and March 2005. Newly- treated diabetes patients were identified using pharmacy data indicators of initiation of anti-diabetic therapies. They reported the risk of T2DM for patients on olanzapine, quetiapine and risperidone appeared to be dose-dependent. Olanzapine demonstrated increased risk at the second tertile dose (5-<10 mg/day) (HR: 1.7, 95%CI: 1.0-3.1) and third tertile dose (≥10 mg/day) (HR: 2.5, 95%CI: 1.4-4.5). Quetiapine (>150 mg/day) and risperidone (≥2 mg/day) exhibited elevated risk only at third dose tertile. No T2DM risk was associated with lower doses of quetiapine (≤150 mg/day) or risperidone (≤2 mg/day). Unlike the three aforementioned medications (olanzapine, quetiapine, risperidone), ziprasidone and aripiprazole did not exhibit a dose-dependent association with T2DM or an elevated rate of new-onset T2DM.

Antipsychotic-induced weight gain is a very common and serious problem in patients with psychotic disorders. It is associated with increased central obesity, and weight gain and consequent excess of visceral fat can lead to exacerbation of co-morbid conditions, development of insulin resistance, hypertension, and lipid abnormalities as well as patient noncompliance. This emphasizes the need for prevention and management of weight gain associated with antipsychotic treatment. In addition, weight/obesity-independent drug mechanism(s) for hyperglycemia, T2DM and dyslipidemia were suggested.

Clozapine and olanzapine represent the highest offenders causing metabolic disturbances, while aripiprazole and ziprasidone seem to have the most favorable metabolic profiles. Based on available evidence, it appears the newer SGAs: asenapine, iloperidone, lurasidone and paliperidone, possess lower propensity for significant changes in weight, glycemic and lipid profiles. However more long-term data needs to be compiled in order to comprehensively evaluate their metabolic safety. The relative potential for commonly-used SGAs to induce individual metabolic disturbances is summarized in Table 1.

Prevention and Management of SGA-Induced Metabolic Disturbances

The treatment and treatment goals should be individualized and considered in the context of the patient’s psychiatric condition, contraindications and precautions, metabolic profile, and other patient-specific factors. There is no current consensus on the prevention and management of weight gain and other SGA-induced metabolic disturbances. Several strategies and recommendations for limiting the possibility or extent of antipsychotic-induced metabolic disturbances have been proposed (Table 2) and can be broadly divided into monitoring, choice of antipsychotic, non-pharmacologic and pharmacologic interventions.

Monitoring and Initial SGA Selection Strategies

In 2004, the American Psychiatric Association (APA), the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity (NAAASO) jointly developed consensus guidelines that recommend scheduled screening for and monitoring of the metabolic problems on commencement of a SGA and periodically thereafter as shown in Table 3. It should be noted that elevated post-load glucose precedes elevated fasting glucose in the development of T2DM. Therefore, FPG testing alone might be less reliable, missing cases of impaired glucose tolerance. A 75-g oral glucose tolerance test (OGTT) is a more sensitive indicator for glucose tolerance in early diagnosis of diabetes. However, this test is not routinely performed in patients on SGAs and is not recommended by 2004 consensus guidelines. This could be due to the fact that OGTT requires more cooperation and compliance from patients and thus clinicians might struggle to successfully complete the testing. Additionally, when fasting samples are difficult or impossible to obtain from a patient, glycosylated hemoglobin (A1C) can be considered as a screening test for elevated plasma glucose and diabetes since it does not requiring fasting. Current recommendations from the ADA include the following criteria for prediabetes: A1C 5.7%–6.4% or FPG 100–125 mg/dL or 2-hr plasma glucose (OGTT) 140–199 mg/dL. Criteria for T2DM diagnosis are A1C ≥ 6.5% or FPG ≥126 mg/dL or 2-hr plasma glucose (OGTT) ≥200 mg/dL.

Appropriate selection of an antipsychotic is one of the important steps in prevention of metabolic complications for psychiatric patients. Baseline screening information (Table 3) should be considered when making the antipsychotic choice. When initiating an antipsychotic,
the patient, caregivers and family should be informed regarding drug-induced metabolic risks and symptoms of emergent diabetes and diabetic ketoacidosis so they would know what to expect and for what they should watch. It is essential that appropriate ongoing metabolic monitoring should be included in the patient’s care plan (Table 3).

Table 1. Relative incidence of metabolic abnormalities with selected SGAs

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Weight Gain</th>
<th>Dyslipidemia</th>
<th>Hyperglycemia</th>
<th>MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>high</td>
<td>high</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>moderate</td>
<td>high</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>mild-moderate</td>
<td>mild</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

Table 2. Prevention/management strategies for SGA-induced metabolic disturbances

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>DISADVANTAGES</th>
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</thead>
<tbody>
<tr>
<td>PREVENTION OF ANTIPSYCHOTIC-INDUCED METABOLIC DISTURBANCES</td>
<td></td>
</tr>
<tr>
<td>Baseline screening/monitoring and appropriate selection of SGA</td>
<td>Decrease in SGA options</td>
</tr>
<tr>
<td>Nutritional and physical activity counseling or referral to a dietitian, psychologist or weight loss program</td>
<td>Lack of acceptance and adherence</td>
</tr>
<tr>
<td>MANAGEMENT OF ANTIPSYCHOTIC-INDUCED METABOLIC DISTURBANCES</td>
<td></td>
</tr>
<tr>
<td>Structured ongoing metabolic monitoring</td>
<td>Increased responsibility for psychiatrists and other clinicians</td>
</tr>
<tr>
<td>Patient, caregivers and family education regarding metabolic risks of SGAs and symptoms of emergent diabetes and diabetic ketoacidosis</td>
<td>Increased responsibility for psychiatrists and other clinicians</td>
</tr>
<tr>
<td>Switch from antipsychotic polypharmacy to monotherapy if clinically feasible</td>
<td>Increased risk for illness worsening or relapse</td>
</tr>
<tr>
<td>Antipsychotic switch to an alternative SGA with low/lower propensity for metabolic disturbances</td>
<td>Increased risk for illness worsening or relapse</td>
</tr>
<tr>
<td>Adjunctive pharmacological interventions</td>
<td>Potential lack of efficacy</td>
</tr>
<tr>
<td>Treatment of defined metabolic problems (T2DM, dyslipidemia, hypertension, diabetic ketoacidosis, and MetS) according to the current clinical guidelines/recommendations</td>
<td>Increased risk for drug interactions</td>
</tr>
</tbody>
</table>

Table 3. Adult monitoring protocol of patients on SGAs

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 wks</th>
<th>8 wks</th>
<th>12 wks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></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>X</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-pharmacologic interventions such as cognitive behavioral therapy (CBT) and nutritional counseling, alone or in combination with an exercise program, showed promise as they were helpful in some patients with antipsychotic-induced weight gain. They also lack side effects and drug interactions that can be associated with adjuvant pharmacologic treatments. It was suggested that prevention studies with individual psychoeducational programs including diet and/or physical activity seemed to have the highest impact on antipsychotic-induced weight gain. Therefore, early education and counseling on physical activity and healthy diet for weight maintenance/loss should be promoted shortly after initiation of SGA therapy and referral to a dietitian, psychologist or weight loss program should be considered when appropriate. This is even more important for those who are initiated on a SGA with high propensity for weight gain and those who are at higher risk for antipsychotic-induced weight gain including young individuals, especially children and adolescents, antipsychotic-naive patients, underweight patients at the beginning of treatment, and those who experience early significant weight gain. The most recent meta-analysis expanded upon two prior publications that reported similar results indicating significant benefits of non-pharmacologic interventions for weight and BMI reduction. Recently, Caemmerer et al. expanded on these studies by including additional RCTs with non-pharmacologic interventions, and analyzing their effect on other cardiometabolic indices. This meta-analysis of 17 RCTs with 810 participants (mean age: 38.8 years; 85.6% schizophrenia-spectrum disorders) reported that non-pharmacologic interventions led to a significant reduction in weight (-3.12 kg; CI: -4.03, -2.21, p<0.0001) and BMI (-0.94 kg/m²; CI: -1.45, -0.43, p=0.0003) compared with control groups. In addition to weight-loss benefits, patients also experienced significant decreases in waist circumference, % body fat, glucose, insulin, total cholesterol, LDL-cholesterol, and triglycerides. No benefit was observed in the values of HDL-cholesterol and systolic blood pressure. The loss of 3.12 kg in the non-pharmacologic intervention group as reported above is comparable to weight reduction observed with metformin (2.94 kg) and topiramate (2.52 kg) use as reported by Maayan et al., keeping in mind the limitations that exist in making a direct comparison between different studies. Currently, there is a large heterogeneity among different studies investigating an effect of various non-pharmacologic interventions on antipsychotic-induced metabolic disturbances, and more long-term data needs to be compiled in order to comprehensively evaluate their short-term and long-term benefit. There seems to be merit in promoting initiation of and adherence to healthy lifestyle interventions among patients being treated with SGAs.
experiencing a weight gain >5% of initial weight, worsening hyperglycemia, and/or dyslipidemia, changing to a SGA with lower risk for metabolic side effects.6 The switch to another antipsychotic with better metabolic side effects is also endorsed in the 2010 Outcomes Research Team (PORT)34 and the 2012 World Federation of Societies of Biological Psychiatry (WFSBP) guidelines.33 This strategy was demonstrated to improve weight and lipid profile benefits with minimal risks of worsening symptoms or relapse.62-65 A multcenter, double-blind, twelve-week RCT by Stroup et al. with 173 participants demonstrated that changing from olanzapine to aripiprazole resulted in a statistically significant weight loss after antipsychotic switch.66 At week 16, weight decreased significantly (p<0.001) in the aripiprazole-treated group (Δ: -1.8 kg, n=85) compared to the olanzapine-treated group (Δ: +1.41 kg, n=88). Improvements in total cholesterol, TG and HDL cholesterol levels were also reported. Recently, Chen et al. studied the effectiveness of switching antipsychotic drug treatment to aripiprazole or ziprasidone to improve metabolic profile and atherogenic dyslipidemia in a 12-month, prospective, open-label study.52 They concluded patients changing to either ziprasidone or aripiprazole when they were experiencing SGA-induced metabolic side effects had the potential to improve weight, BMI, TG and TG/HDL indices.

It needs to be stressed that before considering a change to another SGA, one needs to weigh the benefit of switching to ziprasidone, aripiprazole or another lower-metabolic risk SGA against the potential risk for loss of efficacy, destabilizing a stable patient, relapse, interaction, contraindication, non-metabolic side effects such as QTc prolongation and EPS.63,64 It is recommended that a new SGA is cross-titrated rather than old agents being abruptly discontinued.65 Pre-switch SGA should be gradually tapered with a similarly gradual initiation and dose titration of ziprasidone or aripiprazole, and discontinued when the new SGA is in a clinically effective dose. To ensure a patient’s clinical stability and medication tolerability, careful monitoring and follow-up should be required during antipsychotic switching.62-64

A meta-analysis of 32 RCTs (n=1,482) with 15 pharmacologic agents (amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, phenylpropolamine, reboxetine, rosiglitazone, sibutramine, topiramate, and metformin+sibutramine) found only five medications that significantly reduced risk for antipsychotic-induced weight gain compared to a placebo.53 However, out of those medications, only metformin and topiramate are currently available in the United States. Metformin is an oral antidiabetic agent that decreases hepatic gluconeogenesis and increases peripheral insulin sensitivity. The use of metformin in diabetic patients was associated with improved glycemic control and moderate weight loss.55 The antidiabetic effect of metformin is particularly interesting because of its dual effects of decreasing body weight and improving insulin sensitivity. It has been suggested that metformin’s effect on body weight is due to reduction in appetite,56 that can be secondary due to taste disturbance, nausea or increase in anorexic glucagon-like peptide 1.67 Multiple RCTs with metformin in doses ranging from 750 to 2500 mg/day for periods from 12-16 weeks demonstrated short-term, modest loss of olanzapine-induced weight gain in patients with schizophrenia.68-71 It should be noted that contradictory studies exist that reported no difference between metformin and placebo groups regarding olanzapine-induced weight gain during similar trials.70,72 Generally metformin was well-tolerated and only limited mild gastrointestinal symptoms were reported. Recently, Maayan et al. reported from their RCT meta-analysis findings of significant weight reduction in metformin groups compared to placebo (mean:-2.93kg, p<0.003) in patients treated with olanzapine, risperidone, quetiapine, and a few SGA combinations.53 Based on existing data, metformin might be a particularly promising option for antipsychotic-induced weight gain and glucose metabolism dysregulation in the subpopulation experiencing first episode of schizophrenia.53,68,69 In addition, it was reported that metformin treatment (750 mg/day) in this subpopulation may bolster weight reduction and decrease FPG, and insulin resistance index (IRI) attained through healthy lifestyle changes.69 Hasnain et al. proposed using a “point system” approach to facilitate decision-making about when to consider a metformin trial.73 This system is based on various characteristics such as family history of diabetes or CVD, BMI, waist circumference, current hyperglycemia and/or impaired glucose tolerance. Each item is assigned a score with individual items ranging from 1-5 points. Patients scoring ≥4 points on the point system are identified as potential candidates for a metformin trial.73 In addition, they suggested discontinuing metformin if benefits are not noted after 6-8 months of treatment.

Another agent showing some promise in management of weight gain related to SGAs is the anticonvulsant, topiramate; however, current data are limited. Three RCTs found topiramate treatment with doses between
100-200 mg/day for 12-weeks to be effective for weight and BMI reduction in patients also treated with clozapine or olanzapine.\textsuperscript{74-77} There was a dose-dependent relationship between topiramate in both benefit and side effects. More patients experienced a weight loss of at least five percent in the topiramate 200 mg/day-group than in other groups. In addition, there were significantly more incidents of paresthesia with topiramate 200 mg/day (~60%) compared to topiramate 100 mg/day (25%) and placebo (10%).\textsuperscript{74} Maayan et al. found that adjunct treatment with topiramate resulted in a mean weight change of -3.95 kg (95%CI:1.77-6.12) in SGA-treated psychotic patients.\textsuperscript{53} In general, topiramate was associated with more reports of side effects including paresthesia, dizziness, psychomotor slowing, drooling and headache.\textsuperscript{76,78} In addition, patients taking topiramate experienced worsening of psychiatric symptoms compared to placebo.\textsuperscript{74} The mechanism by which topiramate induces weight loss is not currently known; however, it is believed that topiramate exerts this effect via central nervous system modulation.

**CONCLUSIONS**

Weight gain, dyslipidemia, and hyperglycemia in patients with psychiatric disorders secondary to SGA use are concerning because they can affect patients’ medication adherence and increase risk for atherosclerosis and coronary heart disease. In order to prevent and or manage SGA-induced metabolic side effects, recommendations include structured metabolic screening/monitoring, lifestyle and dietary modifications, antipsychotic switch from polypharmacy to monotherapy, and change to alternative SGAs with low/lower propensity for metabolic disturbances. In addition, various adjuvant pharmacologic agents have been used to counteract antipsychotic-induced side effects, particularly weight gain. Metformin and topiramate are the agents with the most promising albeit contradictory, though neither medications was able to entirely counter weight gain related to SGA use. Compared to topiramate, metformin has a better safety profile, larger body of clinical evidence and longer period of clinical use for weight loss and glucose metabolism dysregulation. There are a limited number of studies with issues including sample size, heterogeneous patient populations, and relatively short trial periods of metformin and topiramate; thus, more research needs to be done to generate evidence for any short- and long-term benefits associated with the use these medications in therapy. Current evidence is insufficient to support widespread use of metformin and topiramate in clinical practice. When non-pharmacologic interventions or an antipsychotic switch fails or when neither is feasible, metformin may be a viable option for some patients.

**REFERENCES**


