Addressing cardiometabolic risk during treatment with antipsychotic medications

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Purpose of review

To raise awareness of and inform evidence-based practice regarding medical and behavioral interventions for antipsychotic medication-induced metabolic abnormalities.

Recent findings

The current literature indicates that individuals with severe and persistent mental illness have significantly worse health outcomes and premature mortality than the general population, owing to a combination of under-recognition and treatment of medical risk factors, reduced access to care, sedentary lifestyle and poor diet, and the potential contribution of adverse metabolic side effects of antipsychotic medications such as weight gain, hyperglycemia and dyslipidemia. A combination of administrative, behavioral and medical approaches to addressing these medical risks may be more effective than any one of these approaches alone.

Summary

Treatment with antipsychotic medications can induce significant weight gain and abnormalities in lipid and glucose metabolism that increase risk for cardiovascular disease and diabetes in a population already at risk from multiple other sources. Managing the side effects of antipsychotics and lowering risk in general is an important aspect of the management of chronic mental illness. There are a variety of effective medical and behavioral interventions that can be employed to achieve primary and secondary prevention aims.

Keywords

antipsychotic medications, metabolic syndrome, obesity, schizophrenia

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Introduction

Antipsychotic medications can improve psychiatric symptoms and clinical outcomes for people with serious mental illness, but can also produce side effects that range in severity from mildly unpleasant to significant safety concerns. In particular, some antipsychotic medications are associated with metabolic adverse effects that can significantly influence risk for morbidity and mortality with long-term use. In people with severe and persistent mental illness (SPMI) who have major barriers to accessing medical care, metabolic risk factors such as obesity, hyperglycemia and hypertension are under-recognized and under-treated. Compared with the general population, treated patients with SPMI have been observed to be twice as likely to meet Adult Treatment Panel III (ATP-III) criteria for the metabolic syndrome, a collection of risk factors for diabetes mellitus and cardiovascular disease (CVD), including coronary heart disease (CHD), stroke and peripheral vascular disease (Table 1) [1,2]. In fact, people with SPMI in public sector treatment settings in the United States have life expectancies 25–30 years shorter than the general population and most often die of CVD [3].

The metabolic adverse event profiles of currently available antipsychotic medications have been well described [4]. In this review, we will focus on evidence regarding the variety of risk-reduction interventions available to clinicians and evaluate the evidence supporting their clinical utility, with a particular emphasis on weight-loss strategies.

Monitoring

The best-established risk factors for CVD and premature mortality include elevated serum cholesterol [especially total, low-density lipoprotein (LDL), and nonhigh-density lipoprotein cholesterol], elevated blood pressure, cigarette smoking, hyperglycemia, and obesity. These risk factors are potentially modifiable and are therefore important targets for screening, monitoring and prevention

Table 1 Clinical diagnosis of the metabolic syndrome [2]

Risk factor	Defining level
Abdominal obesity	Men – waist circumference >40 inches Women – waist circumference >35 inches
Fasting glucose	≥110 mg/dl
Triglycerides	≥150 mg/dl
High-density lipoproteins (HDLs)	Men – <40 mg/dl Women – <50 mg/dl
Blood pressure	≥130/85 mmHg

efforts that aim to lower risk for CVD and premature mortality in this population [5].

A number of similar practice guidelines for the management of CVD risk factors have been developed in the United States and abroad. The practice guidelines for the management of dyslipidemia and hypertension published by the United States Public Health Service's National High Blood Pressure Education Program and National Cholesterol Education Program (e.g. the Adult Treatment Panel guidelines, ATP-III) offer well developed screening and monitoring methods that are useful in the general adult population with or without a psychiatric diagnosis [2]. Two guidelines specifically for individuals treated with antipsychotic medications include the Mount Sinai Guidelines [6] and a Consensus Statement developed at a meeting led by the American Diabetes Association (ADA) and cosponsored by the American Psychiatric Association (APA), the American Association of Clinical Endocrinologists (AACE), and the North American Association for the Study of Obesity (NAASO) [7] (Table 2). These guidelines more or less conform with ATP-III and offer specific goals for monitoring of weight, BMI, waist circumference, plasma glucose and lipids, particularly following the initiation or dose modification of an antipsychotic medication. The guidelines offer less specific direction with regard to the selection of risk-reduction interventions triggered by the recommended screening. A detailed white paper reviewing the effects of antipsychotic medications on cardiometabolic risk as well as risk reduction approaches derived from ATP-III, ADA and AACE guidelines is forthcoming from the APA.

We pause here to consider the barriers to the systematic collection and use of the data recommended by the major guidelines. In a recent retrospective analysis of 1998–2003 Medicaid claims data from four states [8••], fewer than 20% of people starting treatment with a second-generation antipsychotic medication received baseline glucose testing and fewer than 10% received baseline lipid testing, with individuals under 20 or over 60 years of age least likely to be screened. The same study found a modest increase in surveillance of fasting glucose (7–11%) and lipids (2–3%) after initiation of the new drug, and a trend toward higher monitoring levels from 1998 to 2003. A 2003 national survey [9] of clinicians treating people with schizophrenia found variable awareness of the metabolic side effects of antipsychotic drugs, with 59% of clinicians recognizing weight gain, 51% recognizing

Table 2 Guidelines for monitoring metabolic side effects of antipsychotic medications

		Mount Sinai [6]	Consensus Conference [7]
Obesity	Procedure	BMI measurement	Weight measurement
	Frequency	At baseline and every visit for 6 months after initiation/change of antipsychotic medication and every 3 months thereafter	At baseline and every month for 3 months after initiation/change of antipsychotic medication and every 3 months thereafter
	Cutoff	BMI gain of one point	Weight gain >5% of baseline
	Intervention	Close monitoring, behavioral or medical therapy for weight loss, change of antipsychotic medication	Cross-titration to another antipsychotic medication
Diabetes	Procedure	Fasting plasma glucose level or hemoglobin A1c level	Fasting plasma glucose
	Frequency	At baseline and 4 months after initiation/change of antipsychotic medication; thereafter annually	At baseline and 3 months after initiation/change of antipsychotic medication; thereafter annually for high-risk patients and every 5 years for low-risk patients
	Cutoff	Fasting plasma glucose >125, hemoglobin A1c >6.1%	Fasting plasma glucose >125
	Intervention	Referral to internist	Referral to internist
Hyperlipidemia	Procedure	Lipid screening of total cholesterol, low-density and high-density lipoprotein cholesterol and triglycerides	Fasting lipid panel
	Frequency	If LDL >130, every 6 months; if LDL <130 every 2 years	At baseline and 3 months after initiation/change of antipsychotic medication; thereafter annually for high-risk patients and every 5 years for low-risk patients
	Cutoff	LDL >130	Undefined
	Intervention	Referral to internist or initiation of low-fat diet with serial lipid monitoring and initiation of lipid-lowering drug if LDL remains elevated	Referral to internist

LDL, low-density lipoprotein.

diabetes and only 22% recognizing dyslipidemia as known complications of antipsychotic use. The survey then assessed compliance with screening guidelines for these metabolic sequelae and found that fewer than 30% of clinicians routinely monitored weight, fasting glucose or fasting lipids.

These data reveal that the gap in clinicians' awareness of potential adverse events that could be encountered during antipsychotic treatment incompletely accounts for the low rates of monitoring. Therefore, other factors, including but not limited to clinician behavior, poor access to general medical services, inadequate medical record-keeping infrastructure, lack of in-system compliance incentives and lack of centralized oversight, may represent barriers to higher quality care. Reliable clinical screening and monitoring is a critical first step for recognizing and considering possible intervention approaches in any high-risk population, especially in the setting of limited clinical resources in which targeting of resources to appropriate patients can be particularly important.

Medical interventions for hyperlipidemia

ATP-III and the ADA offer specific guidelines for managing hyperlipidemia [2]. Briefly, clinicians are advised to obtain fasting levels of LDLs, total cholesterol (TC), triglycerides and high-density lipoproteins (HDLs) and to correlate them with clinical signs of atherosclerotic disease and with the presence of major risk factors for CHD events or the risk equivalent condition of diabetes mellitus. On the basis of these data, clinicians may stratify patients into risk profiles that correspond with variable target levels of LDL, and then initiate behavioural therapy and possibly pharmacotherapy in an effort to achieve the appropriate target LDL level as well as routine targets for HDL, triglyceride and TC. Behavioral therapies consist of therapeutic lifestyle changes (TLCs) including a diet low in fat and high in fiber, increased physical activity and weight management. Drug therapies include statins, bile acid sequestrants, niacin and fibric acids, and should be initiated after 3 months of TLC, if targets are not achievable by TLC alone, or concurrent with TLC if risk is sufficiently elevated as defined by ATP-III (Reference ATP-III). Also, concurrent with the initiation of TLC, clinicians are advised to screen for metabolic syndrome and, if identified, to treat its underlying components with intensified weight management and increased physical activity while initiating drug therapy as needed for hypertension and hyperlipidemia. In general, ATP-III specifies that secondary causes of dyslipidemia should be addressed wherever possible as a first step in management (e.g. drugs that could be contributing to dyslipidemia).

Despite specific United States Public Health Service (USPHS) guidelines for the treatment of dyslipidemia, hyperglycemia and hypertension, it is notable that, in the sample of patients entering the Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE), 88% of those with dyslipidemia, 62% of those with hypertension and 30% of those with diabetes were receiving no pharmacotherapy for these cardiometabolic risk conditions [10].

In general, a close collaboration between psychiatrists and internists may help to optimize patient care.

Interventions for weight loss

There are a number of strategies for the prevention and treatment of the metabolic risk during antipsychotic treatment, including the selection of antipsychotic and other medications associated with less risk for weight gain, regular implementation of TLC, or the augmentation of psychotropic medications with weight-control medications.

A number of lines of evidence, including head-to-head randomized clinical trials, have demonstrated that certain antipsychotic medications are associated with a greater risk of weight gain, as well as other adverse metabolic effects, relative to other agents. The large CATIE study indicated that olanzapine treatment was associated with the greatest adverse effect on metabolic endpoints like body weight and plasma triglyceride, and increasing, for example, the prevalence of a metabolic syndrome diagnosis at 3 and 9 months in contrast to other tested agents such as perphenazine and ziprasidone, which produced limited adverse metabolic effects in this sample or even improvements in some metabolic parameters [11•]. This observation is consistent with a growing number of experimental and larger scale pharmacoepidemiologic studies [11•,12•,13].

Of note, one recent study [14•] found that, although there were significant differences in antipsychotic-induced weight gain in people with first-episode psychosis treated with haloperidol, risperidone or olanzapine 3 months after initiation of treatment, these statistical differences were not observed 1 year into treatment, suggesting the substantial potential for weight gain during treatment with many agents during initial treatment exposures. It should be noted that patients on nonolanzapine medications in that study experienced larger weight increases than had been observed in other similar studies. These patients also received more of some adjunctive medications than those on olanzapine, and almost 50% of patients in all treatment groups in that study were using cannabis and many were also using alcohol, suggesting that other environmental factors might contribute to increase weight gain even when patients are taking 'lower risk' agents. Another recent study [15•] of first-episode patients, and concurrently recruited controls, further

confirmed that substantial weight gain is associated with antipsychotic prescribing in younger populations, and this study also observed that almost all (91%) patients receiving olanzapine had clinically significant weight gain.

Growing evidence indicates switching from an antipsychotic associated with greater risk for weight gain to one that is associated with less weight gain risk can lead to weight loss. An open-label extension study [16••] of 185 people switched to ziprasidone from olanzapine or risperidone found mean reductions in body weight of 9.8 and 6.9 kg, respectively, whereas mean body weight was largely unchanged in patients switched to ziprasidone from high-potency first-generation antipsychotics such as haloperidol. Similarly, a European study [17•] of 550 patients randomized to aripiprazole versus clinician-chosen 'treatment as usual', either olanzapine, quetiapine or risperidone, found that the group on aripiprazole lost 1.7% of their baseline weight, whereas the comparator group gained 2.1% of their baseline weight, on average. The first large-scale, double-blind randomized study [18••] clearly establishing 'proof-of-concept' for the weight loss opportunity associated with switching involved overweight patients currently treated with olanzapine who were randomized to stay on that medication or to switch to aripiprazole for 16 weeks. Patients continuing treatment with olanzapine had further increases in body weight and fasting plasma triglyceride and other lipid fractions, whereas patients switching to aripiprazole experienced weight loss and lipid improvements. Although there were somewhat more dropouts in the aripiprazole arm (perhaps not unexpected in a study in which only one arm is changing medication), mean clinical global improvement (CGI) ratings remained in the range of 'no change' to 'minimal improvement' for both treatment conditions.

A number of strategies for augmentation of the antipsychotic regimen with other medications to treat the weight gain have also been studied, though with generally small effect sizes or poor tolerability. A retrospective chart review [19•] of 100 patients prescribed the anticonvulsant topiramate for weight control in the setting of antipsychotic, lithium or valproate therapy were found to have a statistically and clinically significant reduction in BMI from 29.7 to 28.0. Similarly, a trial [20•] comparing sibutramine and topiramate found that both are comparably associated with weight loss of 3–4 kg in 24 weeks. Both studies noted high discontinuation rates due to side effects.

Metformin, the oral hypoglycemic, has a somewhat more favorable side effect profile and has been tested as a treatment for antipsychotic-induced weight gain. A recent small ($n = 40$) randomized controlled study [21••] of metformin for the attenuation of olanzapine-induced weight gain found that fewer patients gained more than 7% of their baseline body mass after 12 weeks of treatment when taking metformin. A similar randomized controlled trial [22•] showed that metformin was associated with a 1.4 kg weight loss over 12 weeks, whereas placebo was weight neutral. A combined approach using sibutramine with metformin in olanzapine-treated patients failed to improve weight loss over metformin alone [23•]. It remains unclear whether weight loss on metformin is related to potential insulin sensitizing effects, or simply to gastrointestinal adverse effects of treatment that can reduce appetite.

Overall, adjunctive pharmacologic strategies remain experimental and have insufficient evidence to support their use in general practice at this time. A recent Cochrane meta-analysis [24] concluded that given the limited data evaluating the effectiveness and safety of adjunctive pharmacologic interventions, and particularly the lack of well powered randomized controlled trials in this area, clinical practice should remain focused on primary prevention through the selection of safer antipsychotic medications and anticipatory guidance regarding diet and physical activity when initiating antipsychotic treatment.

Behavioral interventions

Behavioral interventions including nutrition and exercise education in a group environment have had a moderate degree of success in the treatment of antipsychotic-induced weight gain, similar to their effectiveness in the general population. In a nonpsychiatric sample of motivated prediabetic patients, the diabetes prevention programme (DPP) showed that overweight people with impaired glucose tolerance could reduce their risk of developing diabetes by 58% by using behavioral approaches including diet and exercise, aimed at weight reduction [25]. Two additional large trials had similar results [26,27].

Interventions specifically targeting eating habits in people with chronic mental illness have shown some promising results, likely by reducing binge-eating symptoms common in this patient population [28•]. One study that tested a nutrition curriculum consisted of six 1 h sessions over 3 months for people taking olanzapine curbed weight gain from 6 kg without intervention to 2 kg with intervention and large weight gain of more than 7% of baseline body mass was reduced from 64% without intervention to 13% in the treatment group. Longer term studies have shown persisting benefit. Over a 3-year period, a behavioral intervention consisting of weekly weight monitoring along with nutrition discussion and education sessions was found to be associated with a 5 kg

Table 3 Characteristics of effective behavioral interventions

Nutrition	Low-calorie, low-fat diet
	Food groups
	Portion control
Exercise	Physical activity of moderate intensity
	In-class demonstrations
	Exercise homework
Structure	Group or individual sessions
	Regular meetings
	Frequent weigh-ins
	Cultural sensitivity

weight loss and two-point reduction in BMI [29]. Interestingly, the degree of weight loss has been correlated only with the number of sessions attended [30•].

Of note, we are not aware of any studies specifically evaluating the efficacy of intervention primarily aimed at increasing the level of physical activity in patients with SPMI. These studies would be quite important, as it is known that people taking antipsychotic medications have reduced metabolic expenditure [31]. Further, the value of increasing energy expenditure in the enhancement of weight loss in people taking antipsychotic medications has been described [32]. Further studies comparing the relative contribution of nutrition counseling and physical training are warranted to assist in the development of new programmes.

There may be synergy in combining nutrition education with physical activity counseling through behavioral interventions. In one study [33], a combined behavioral therapy in first-episode, treatment-naïve patients limited average weight gain to 4 kg compared with 7 kg in the control group and reduced the proportion of participants gaining more than 7% of their baseline weight from nearly 80% in the control group to 39% in the intervention group. An adaptation of the DPP in chronically treated patients resulted in a 2.5 kg weight loss over the course of 16 weeks [34]. In a 14-week multicenter trial [35••] of a group-based behavioral treatment, 41% of patients who attended behavioral treatment lost 5% or more of their baseline weight compared with 14% of control patients.

Presently, it is unclear which key ingredients in behavioral therapy are the most effective in producing weight loss or attenuating weight gain in people taking antipsychotic medications. We propose a number of attributes that appear to be consistently employed in the most effective programmes (Table 3).

Conclusion

As we have reviewed above, there exists a significant body of data demonstrating that antipsychotic-induced metabolic dysfunction is a major clinical problem associated with significant potential morbidity and mortality and, consequently, should be addressed using evidence-based guidelines and treatments. Many clinical trials examining specific treatment approaches have been conducted or are currently underway and will assist the clinician in selecting optimal therapies for the treatment of metabolic side effects of antipsychotic medications.

It is clear that psychiatrists and internists caring for people taking antipsychotic medications must be aware of the potential for metabolic dysfunction resulting from these treatments and consider them when initiating antipsychotic treatment and in regular follow-up assessments. Those people who gain weight, become hypertensive or develop abnormalities in their lipids and glucose metabolism should receive appropriate care for these conditions to reduce their risk of developing CHD, stroke, peripheral vascular disease and neuropathy.

With regard to selecting specific interventions for the treatment of antipsychotic-induced metabolic abnormalities, clinicians face a choice between simplifying the psychotropic and medical polypharmacy by switching to antipsychotic drugs with fewer metabolic side effects and initiating TLC therapy and adjunctive treatment with behavioral and medical interventions targeting the concerning side effects. As we have reviewed, it is clear that established approaches, including monitoring and initiating interventions (including TLC, statins, or both) directed by national guidelines, are being underutilized in the SPMI population. These mainstream interventions, combined with switching to antipsychotic medications associated with fewer metabolic side effects, offer clinicians a potent, simple and rational approach to treating the metabolic side effects of antipsychotic medications. These principles conform to the tenets of ATP-III in that they attempt to address secondary causes of risk prior to superimposing new interventions.

Other pharmacologic interventions currently under investigation may have a role in the treatment of the metabolic syndrome in the SPMI population, but currently the extent of that role remains undefined and secondary to the prevention approaches described above. These new interventions require further evaluation with regard to their potential for long-term reduction in coronary artery disease, stroke and all-cause mortality. These data will enable the cost-efficacy analysis that could translate clinical evidence into public health policy. As a part of this examination, further delineation of the 'key ingredients' of behavioral and medical approaches could assist in optimizing the use of the clinician's resources in treating the metabolic side effects of antipsychotic medications.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 657).

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