# Clinical and Practical Psychopharmacology

# Cardiometabolic Risks in Schizophrenia and Directions for Intervention, 1: Magnitude and Moderators of the Problem

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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## ABSTRACT

Patients with schizophrenia have increased prevalence rates for many cardiac risk factors. As an example, the metabolic syndrome is common in schizophrenia, with elevated rates for the syndrome and its components evident in first-episode schizophrenia patients, itself. These rates are further elevated in multiepisode patients. Weight gain is a clinical marker of cardiometabolic risk. Antipsychotic drug treatment may drive at least part of the increased cardiometabolic risk; the effects are externally evident in the form of weight gain, with different drugs having different effects on weight and metabolic parameters. Finally, sedentariness and smoking are 2 common behaviors that increase cardiometabolic risks in schizophrenia. It is important for psychiatrists who treat schizophrenia to evaluate the cardiometabolic risks in their patients so that appropriate lifestyle and pharmacologic interventions can be planned.

## Clinical Question

Overweight, obesity, and the metabolic syndrome (MetS) are common in schizophrenia, particularly in association with antipsychotic drug treatment.[1,2] Patients with schizophrenia are therefore at increased risk of adverse cardiovascular and cerebrovascular events and mortality associated therewith.[3–6] What interventions should be considered for patients at increased risk? This initial article presents a statement of the magnitude and moderators of the problem; potential interventions will be examined in a subsequent article.

## Introduction

There are many different definitions of MetS[2,7]; these essentially require endorsement of 3 of the following 5 criteria: increased waist circumference, increased triglycerides level, low HDL cholesterol level, high blood pressure (BP), and high fasting blood sugar level. Cutoff values are specified for each criterion, at least one of which (waist circumference) requires adjustment for ethnicity. A normal-value criterion is considered endorsed if the patient is receiving an appropriate treatment for it, such as an antihypertensive medication for hypertension.

Persons with MetS may be symptom free; however, MetS increases the risk of several adverse health outcomes, notably type 2 diabetes mellitus, cardiovascular and cerebrovascular events, and complications thereof.[8,9] Overweight/obesity, the commonest component of MetS, is itself associated with adverse health consequences; these include MetS and its consequences, osteoarthritis, obstructive sleep apnea, nonalcoholic fatty liver disease, and even cancer.[10]

## Brief Historical Notes

Weight gain with antipsychotic drugs was, in an earlier era, considered to represent improvement in physical health resulting from an improvement in mental health. However, it has long been recognized that weight gain with antipsychotic drugs is also a health concern.[11–13] Stray reports on diabetes in patients receiving neuroleptic drugs were published as early as in the 1950s and 1960s; by the late 1990s, it became clear that atypical antipsychotic drugs such as clozapine, olanzapine, and quetiapine were associated with dysregulation of glucose and lipid metabolism, and new-onset diabetes mellitus.[14–17] Presently, all antipsychotic drugs are labeled with a warning that their use may be associated with metabolic risks.

## Metabolic Disturbances in Early Schizophrenia

Patients with psychosis are known to be at increased risk of MetS, or at least of its components, even before exposure to antipsychotic drugs. For example, data from the European First-Episode Schizophrenia Trial[18] showed that the prevalence of MetS was 5.7% in antipsychotic-naive first-episode schizophrenia (FES) patients (n = 157) and 6.1% in FES patients with brief antipsychotic exposure (n = 326); these figures were similar to the prevalence in age-matched persons in the general population. However, 58.5% of the patients had one or more elevated metabolic risks at baseline: 28.5% had low HDL levels, 24.2% had elevated blood

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- The metabolic syndrome and its components are common in schizophrenia, with prevalences increased from early during the course of the illness itself (even before antipsychotic drug exposure).
- Antipsychotic drug exposure is associated with the risk of weight gain and metabolic dysregulation; the risks vary with different antipsychotic drugs.
- Patients with schizophrenia smoke, are sedentary, and may have still other cardiometabolic risk factors.
- Psychiatrists who treat schizophrenia need to evaluate the cardiometabolic risks in their patients so that appropriate lifestyle and pharmacologic interventions can be planned.

pressure, 17.7% had elevated triglycerides levels, 8.2% had abdominal obesity, and 7.3% had elevated blood sugar levels. A case-control study[19] also reported increased prevalence of metabolic disturbances and MetS in 122 drug-naive or drug-free patients with schizophrenia.

A systematic review and meta-analysis of 19 studies of unmedicated FES patients (pooled N = 1,325) found that the overall prevalence of MetS was 9.8%. Individual risk factors were 40.2% for smoking, 26.6% for overweight, 24.3% for high BP, 20.4% for low HDL, 16.9% for high triglycerides, 6.4% for high blood sugar, and 2.1% for diabetes.[1]

In 394 patients with FES in the Recovery After an Initial Schizophrenia Episode (RAISE) study, after a mean of 47.3 days of lifetime antipsychotic exposure it was observed that 13.2% of patients had MetS; 15.4% were prediabetic, 2.9% had diabetes, 48.3% were obese/overweight, 56.5% had dyslipidemia, 39.9% had prehypertension, and 10.0% had hypertension. Greater illness duration predicted increased body mass index (BMI), waist circumference, fat mass, and fat percentage, but not metabolic parameters; greater duration of antipsychotic use predicted lower HDL, increased non-HDL cholesterol, and increased triglycerides.[20]

Interestingly, a review of data from 5 studies conducted in persons at ultrahigh risk of psychosis found that the BMI was similar to that of healthy controls and was in the normal range for the population.[21]

### Metabolic Disturbances in Multiepisode Schizophrenia

The risk of MetS and the components thereof are sharply elevated in patients who have experienced repeated episodes of schizophrenia. In a systematic review and meta-analysis of cardiometabolic abnormalities in patients with multiple episodes of schizophrenia, Vancampfort et al[22] reported that, relative to population controls, multiepisode patients had an increased risk of MetS (4 studies; N = 868; odds ratio [OR] = 2.35; 95% confidence interval [CI], 1.68–3.29), diabetes (15 studies; N = 106,720; OR = 1.99; 95% CI, 1.55–2.54), abdominal obesity (5 studies; N = 6,632; OR = 4.43; 95% CI, 2.52–7.82), hypertension (4 studies; N = 2,410; OR = 1.36; 95% CI, 1.21–1.53), low HDL (2 studies; N = 647; OR = 2.35; 95% CI, 1.78–3.10), and high triglycerides (2 studies; N = 647; OR = 2.73; 95% CI, 1.95–3.83).

In this meta-analysis, risks were significantly higher for multiepisode patients relative to drug-naive patients for abdominal obesity (50.0% vs 16.6%), elevated triglycerides (39.0% vs 23.3%), low HDL (41.7% vs 24.2%), and MetS (34.2% vs 10.0%), but not hypertension (37.3% vs 31.6%). There were no significant differences between drug-naive and FES patients.[22]

A very recent meta-analysis of 57 studies reported an 11.5% (95% CI, 9.8%–13.5%) prevalence of type 2 diabetes mellitus in schizophrenia. The prevalence was significantly higher in multiepisode patients relative to FES patients (13.1% vs 4.0%).[23]

### Weight Gain as a Clinical Marker of Cardiometabolic Risks

Weight gain is a signal that is commonly used as a marker of the cardiometabolic risks associated with schizophrenia and its treatment. This is because weight gain is a change that is obvious to patients, their families, and their doctors, and it is easily measured in the clinic. Weight gain is also an early marker; changes are evident within weeks of treatment onset,[24] and these early changes predict more significant long-term weight gain.[25] Additionally, a validated criterion exists for clinically significant change in body weight (7% or greater). It goes without saying that weight gain is reflected in an increased waist circumference, which is an important criterion defining MetS.

### Medication (and Choice Thereof) as a Moderator of the Cardiometabolic Risk

Relative to placebo, in short-term randomized controlled trials (RCTs), patients with FES gain a mean of 3.22 kg and a mean of 1.4 BMI points; in long-term studies, the weight gain is a mean of 5.30 kg and the increase in BMI is by a mean of 1.86 points.[26] Overall, however, data from meta-analysis suggest that there is no clear signal that a longer duration of antipsychotic treatment is associated with greater weight gain; possible exceptions are when drugs strongly associated with weight gain (eg, olanzapine, clozapine) are used and when clinically significant weight gain is the outcome criterion.[27] Clinically significant weight gain and dysregulation of metabolic parameters are observed after antipsychotic exposure in pediatric samples, as well.[28]

In a systematic review and network meta-analysis of 212 RCTs (pooled N = 42,049), Leucht et al[29] found that only haloperidol, ziprasidone, and lurasidone were not associated with an increased risk of weight gain relative to placebo; the greatest weight gain was observed with clozapine, zotepine, and olanzapine (Table 1).

In another systematic review and meta-analysis (56 RCTs, pooled N = 21,691) that compared asenapine (9 RCTs), iloperidone (11 RCTs), lurasidone (8 RCTs), and paliperidone (28 RCTs) with placebo in patients with schizophrenia or bipolar disorder, De Hert et al[30] found that, in short-term studies, only lurasidone was not associated with clinically significant weight gain (Table 2) and that absolute weight gain, relative to placebo, was least with lurasidone (Table 3). Mean

**Table 1. Weight Gain (from least to greatest) With Antipsychotic Drugs in Patients With Schizophrenia: Comparison With Placebo[a,b]**

*Haloperidol, SMD = 0.09; 95% CI, −0.00–0.17*
*Ziprasidone, SMD = 0.10; 95% CI, −0.02–0.22*
*Lurasidone, SMD = 0.10; 95% CI, −0.02–0.21*
Aripiprazole, SMD = 0.17; 95% CI, 0.05–0.28
Amisulpride, SMD = 0.20; 95% CI, 0.05–0.35
Asenapine, SMD = 0.23; 95% CI, 0.07–0.39
Paliperidone, SMD = 0.38; 95% CI, 0.27–0.48
Risperidone, SMD = 0.42; 95% CI, 0.33–0.50
Quetiapine, SMD = 0.43; 95% CI, 0.34–0.53
Sertindole, SMD = 0.53; 95% CI, 0.38–0.68
Chlorpromazine, SMD = 0.55; 95% CI, 0.34–0.76
Iloperidone, SMD = 0.62; 95% CI, 0.49–0.74
Clozapine, SMD = 0.65; 95% CI, 0.31–0.99
Zotepine, SMD = 0.71; 95% CI, 0.47–0.96
Olanzapine, SMD = 0.74; 95% CI, 0.67–0.81

[a]Data from the meta-analysis of Leucht et al.[29]
[b]Italics indicate drugs with nonsignificant weight change.
Abbreviations: CI = confidence interval, SMD = standardized mean difference.

**Table 2. Risk (Relative to Placebo) of Clinically Significant (7% or Greater) Weight Gain With Newer Atypical Antipsychotic Drugs in Short-Term (12-Week Duration or Less) RCTs[a,b]**

Asenapine: 5 RCTs (pooled N = 1,360); RR = 4.09 (95% CI, 2.25–7.43); NNH = 17
Iloperidone: 4 RCTs (pooled N = 1,930); RR = 3.13 (95% CI, 2.08–4.70); NNH = 11
Paliperidone: 12 RCTs (pooled N = 4,087); RR = 2.17 (95% CI, 1.64–2.86); NNH = 20
*Lurasidone: 6 RCTs (pooled N = 1,793); RR = 1.42 (95% CI, 0.87–2.29); NNH NS*

[a]Data from the meta-analysis of De Hert et al.[30]
[b]Italics indicate drug with nonsignificant risk.
Abbreviations: CI = confidence interval, NNH = number needed to harm, NS = nonsignificant, RCT = randomized controlled trial, RR = relative risk.

**Table 3. Mean Weight Gain (Relative to Placebo) With Newer Atypical Antipsychotic Drugs in Short-Term (12 Weeks Duration or Less) RCTs[a]**

Asenapine: 1.16 (95% CI, 0.83–1.49) kg; 3 RCTs (pooled N = 751)
Iloperidone: 2.50 (95% CI, 1.92–3.08) kg; 1 RCT (N = 300)
Paliperidone: 1.54 (95% CI, 0.91–1.57) kg; 15 RCTs (pooled N = 3,552)
Lurasidone: 0.49 (95% CI, 0.17–0.81) kg; 5 RCTs (pooled N = 999)

[a]Data from the meta-analysis of De Hert et al.[30]
Abbreviations: CI = confidence interval, RCT = randomized controlled trial.

**Table 4. Sedentariness in Persons With Psychosis[a]**

1. Persons with psychosis (n = 2,033) spent 11.0 (95% CI, 8.72–13.30) h per day being sedentary.
2. Sedentary behavior was greater when objectively recorded (7 studies, pooled N = 254) than when self-reported (6 studies, pooled N = 1,779); the difference was substantial: 12.6 h vs 6.9 h per day, respectively.
3. Sedentary behavior was greater in persons with psychosis (n = 216) than in controls (n = 150). The SMD was 1.13 (95% CI, 0.50–1.77), and the absolute difference was 2.8 h per day.
4. Higher age was associated with greater sedentariness.

[a]Results from the meta-analysis of Stubbs et al.[34]
Abbreviations: CI = confidence interval, SMD = standardized mean difference.

weight gain with drugs such as chlorpromazine, olanzapine, and clozapine, in particular, can be quite substantial—in the region of 5 kg and above, particularly in the longer term.[27]

Antipsychotic-related weight gain is multifactorial in etiology and depends not only on the drug but also on, for example, genetic factors that may moderate their pharmacodynamic effects.[31,32]

## Sedentary Behavior as a Moderator of the Cardiometabolic Risk

Lack of physical activity, lack of physical fitness, and sedentariness increase cardiovascular risks.[33] In a systematic review and meta-analysis/meta-regression analysis, Stubbs et al[34] identified 13 studies (pooled N for psychosis, 2,033) that measured sedentary behavior in persons with psychotic conditions, including schizophrenia spectrum and (1 sample of) bipolar disorder. Important results of the study are presented in Table 4; in summary, persons with psychosis were found to show considerable sedentary behavior; this was significantly greater in patients than in controls and was more apparent in objective assessments than from self-reports.

Patients with psychosis may display reduced activity levels, for example, for reasons related to diminished interests and motivation, or medication-related sedation, or weight gain due to any cause. In this meta-analysis,[34] the mean BMI of the pooled sample was 29; that is, the average patient was overweight. Thus, the sample was biased toward sedentariness because being overweight is known to be associated with lower levels of physical activity. However, between overweight and sedentariness, it may not be easy to identify which one is the cause and which is the effect, and the two states are probably interdependent. Importantly, in this study,[34] the meta-regression analysis found that the BMI was unrelated to sedentary time, implying that weight, per se, may not have driven the finding of sedentariness.

## Other Moderators of Cardiometabolic Risk

All variables that moderate the cardiometabolic risk in healthy individuals have the potential to moderate the cardiometabolic risk in persons with schizophrenia; a family history of ischemic heart disease is a simple example of such a moderating variable. A further discussion on the subject is out of the scope of the present article. However, one important moderator, smoking, requires especial mention.

In a meta-analysis of 17 studies,[21] smoking was identified in 33% (95% CI, 24%–42%) of persons at ultrahigh risk of psychosis; this figure was significantly higher than that in control subjects (OR = 2.26; 95% CI, 1.48–3.48). Another meta-analysis,[35] which examined 31 studies in first-episode psychosis, estimated the prevalence of tobacco use at 58.9% (95% CI, 54.3%–63.4%); tobacco use was more common in patients than in healthy controls (OR = 6.04; 95% CI, 3.03–12.02). Similar, high, values for odds of smoking were obtained in a meta-analysis of 42 studies from across the world in patients with schizophrenia; the odds in male patients were double those in female patients.[36]

## Summary

Patients with schizophrenia are at increased risk of MetS and of other cardiac risk factors, including sedentariness and

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smoking. Most antipsychotic drugs also increase the risk of weight gain and MetS. It is important for psychiatrists to be aware of cardiometabolic risks in their patients so that appropriate lifestyle and pharmacologic interventions can be planned.

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