REVIEW

ONLINE FIRST

Systematic Review of Early Cardiometabolic Outcomes of the First Treated Episode of Psychosis

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Context: The increased mortality associated with schizophrenia is largely due to cardiovascular disease. Treatment with antipsychotics is associated with weight gain and changes in other cardiovascular risk factors. Early identification of modifiable cardiovascular risk factors is a clinical imperative but prospective longitudinal studies of the early cardiometabolic adverse effects of antipsychotic drug treatment other than weight gain have not been previously reviewed.

Objectives: To assess the methods and reporting of cardiometabolic outcome studies of the first treated episode of psychosis, review key findings, and suggest directions for future research.

Data Sources: PsycINFO, MEDLINE, and Scopus from January 1990 to June 2010.

Study Selection: Subjects were experiencing their first treated episode of psychosis. Subjects were antipsychotic naive or had been exposed to antipsychotics for a short known period at the beginning of the study. Cardiometabolic indices were assessed. Studies used a longitudinal design.

Data Extraction: Sixty-four articles were identified describing 53 independent studies; 25 studies met inclusion criteria and were retained for detailed review.

Data Synthesis: Consolidated Standards of Reporting Trials and Strengthening the Reporting of Observational Studies in Epidemiology checklists were used to assess the methods and reporting of studies. A qualitative review of findings was conducted.

Conclusions: Two key hypotheses were identified based on this review: (1) in general, there is no difference in cardiovascular risk assessed by weight or metabolic indices between individuals with an untreated first episode of psychosis and healthy controls and (2) cardiovascular risk increases after first exposure to any antipsychotic drug. A rank order of drugs can be derived but there is no evidence of significant class differences. Recommended directions for future research include assessing the effect on cardiometabolic outcomes of medication adherence and dosage effects, determining the therapeutic window for antipsychotic use in adults and youth, and testing for moderation of outcomes by demographic factors, including sex and age, and clinical and genetic factors.

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TWENTY-FIVE YEARS AFTER DIagnosis, individuals with schizophrenia have a mortality risk that is 3 times that of the general population.[1] Although risk of suicide is increased 18-fold over 25 years,[1] the very low base rate for suicide in the wider community means that the major cause of mortality and morbidity among individuals with schizophrenia is actually natural causes, predominantly cardiovascular disease.[1,2] Antipsychotic drugs, such as clozapine, can save lives by reducing the impulsiveness and aggression that can lead to suicide[3,4] but they can also alter risk for cardiovascular disease by causing weight gain[5,6] and possibly hypertension and lipid and glucose abnormalities.[7] The risk for cardiovascular disease appears to be increasing among individuals with schizophrenia,[1] creating an ever-widening gap between the life expectancy of the seriously mentally ill and the broader community.[8] Determining if antipsychotic drugs reduce or increase overall mortality associated with schizophrenia or other psychoses is therefore a pressing issue[9,10] and the identification of, and intervention directed at, modifiable risk factors for cardiovascular disease among the seriously mentally ill, a clinical imperative.

Research is needed to understand the nature and magnitude of the cardiovas-

Table. Cardiometabolic Indices Assessed by the Studies Reviewed Herein and Their Association With Cardiovascular Outcomes

Risk Factor	Measure	Associated Outcome
Body weight and central obesity	Total body weight; 7%/4-kg increase in body weight; BMI; intra-abdominal, subcutaneous, and total body fat; waist circumference; waist to hip ratio; adiponectin level; ghrelin level; IL-6/IL-12 level; leptin level; resistin level; visfatin level	Central obesity promotes insulin resistance, dyslipidemia, endothelial dysfunction and hypertension; outcomes include type 2 diabetes, the metabolic syndrome, and cardiovascular disease. Genes encoding bioactive substances such as cytokines (eg, IL-6, visfatin) and protein hormones (eg, adiponectin and leptin) are all abundantly expressed in visceral fat. IL-6 may exert a direct inflammatory effect on the heart and peripheral circulation. Adiponectin and leptin are inversely associated with visceral fat accumulation. Adiponectin has antidiabetic, antihypertensive, antiatherogenic, and anti-inflammatory functions. Leptin regulates satiety and thereby appetite and weight. Ghrelin is thought to be an appetite stimulant. Some argue central obesity is a better discriminator of cardiovascular risk than BMI or total body weight; others argue there is no consensus regarding what is clinically more meaningful.
Blood glucose level	C peptide level; fasting, random, postprandial plasma glucose level; fasting insulin level; insulin resistance; diabetes	C peptide is made when proinsulin is split into insulin and C peptide and is used to gauge how much insulin is being produced by the body. Elevated blood glucose level (hyperglycemia) and insulin level (hyperinsulinemia) are associated with the development of insulin resistance, type 2 diabetes, hypertension, the metabolic syndrome, and cardiovascular disease.
Hypertension	Blood pressure	Elevated blood pressure is a risk factor for atherosclerosis and cardiovascular disease.
Inflammation	VCAM-1 level; E-selectin level; IL-12 level; heart rate; creatine kinase level	Cell adhesion molecules, including VCAM-1 and the selectins (P, E, and L), are inflammatory markers found in atherosclerotic plaques and implicated in the initiation and development of atherosclerosis and therefore the metabolic syndrome and cardiovascular disease. Adhesion molecules might add information for clinical risk prediction and as therapeutic targets. Increased heart rate may accompany increased inflammation and increases mechanical strain on the heart. An elevated creatine kinase level can indicate inflammation of the heart muscle (myocarditis).
Dyslipidemia	Fasting total cholesterol level; fasting LDL cholesterol level; fasting HDL cholesterol level; fasting triglyceride level; dietary fat consumption	Plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are all risk factors for cardiovascular disease and targets for therapeutic intervention.
Stress	Cortisol level	Stress elevates cortisol levels, which affects glucose metabolism, insulin release, blood pressure, and inflammatory response.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; VCAM-1, vascular adhesion molecule 1.

cular risk factors associated with schizophrenia and other psychoses in the early phase of illness to track the effects of different drug treatments for psychosis on key risk factors for cardiovascular disease. Distinguishing pretreatment status from treatment effects is important for understanding the source of cardiovascular disease associated with psychosis and to inform decisions regarding medication review and other interventions. This distinction can only be made at the very beginning of treatment in patients with a first episode of psychosis who have not previously been exposed to antipsychotic drugs or who have been exposed for a short known period.[11] First-episode psychosis is an intermediate diagnosis used in the early phase of psychotic illness until the clinical picture stabilizes.[12] Most first episodes of psychosis will eventually be diagnosed as schizophrenia in younger cohorts, or as schizophrenia, bipolar disorder, or major depression with psychotic features in samples unselected for age at onset.[13]

The aims of this report are to:

1. Identify prospective longitudinal treatment studies of the first episode of psychosis that include assessment of cardiometabolic outcomes. These include body weight and central obesity and associated biomarkers, hyperglycemia and hyperinsulinemia, dyslipidemia, hypertension, and inflammatory markers (**Table**).
2. Summarize the methods and quality of reporting of identified studies.
3. Conduct a review of the early cardiometabolic outcomes of treated psychosis and report key findings.
4. Suggest directions for future research.

METHODS

DATA SOURCES

Two search strings were used to identify studies: ["first episode psychosis" AND metabolism] and [psychosis AND naive AND "glucose OR insulin OR cholesterol OR triglycerides OR blood pressure OR weight"]. The search was limited to English-language publications and was conducted using MEDLINE (via PubMed), PsycINFO, and Scopus for the period from January 1, 1990, through June 15, 2010. The reference lists of identified articles were also hand searched.

STUDY SELECTION

Studies were included if (1) subjects had a first episode of psychosis; (2) subjects were antipsychotic drug naive or only re-

cently exposed to antipsychotics for a short known period at the initiation of the study; and (3) a prospective longitudinal study design was implemented. File audits, cohort studies, and drug trials (blind or open) were all eligible. Medical record file audits were considered only if they used data from clinics that conducted routine monitoring of all patients.

DATA EXTRACTION

Items from the Consolidated Standards of Reporting Trials (CONSORT)[14,15] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[16,17] checklists were used to assess the methods and quality of reporting (eTable 1, http://www.archgenpsychiatry.com). We added 4 additional fields—industry sponsorship, assessment of medication compliance, follow-up psychiatric diagnosis, and if tests for differences in cardiometabolic outcomes across different antipsychotics were conducted.

RESULTS

PROSPECTIVE LONGITUDINAL TREATMENT STUDIES OF THE FIRST EPISODE OF PSYCHOSIS

Sixty-four articles were identified describing 53 independent studies; 25 studies met inclusion criteria and were retained for detailed review (eTable 1). Studies were excluded because they did not consist solely of patients with first-episode psychosis (n=21), patients were not antipsychotic drug naive at entry to the study and recent brief exposure was not explicitly specified (n=5), or exposure was not brief (ie, at least 6 months) (n=2).

METHODS AND QUALITY OF REPORTING

Industry Sponsorship

Ten studies received support from the pharmaceutical industry (eTable 1).

Study Design and Hypotheses

Studies reviewed comprised 10 randomized trials, 5 nonrandomized trials, and 10 observational cohort studies (eTable 1). One randomized trial, 1 nonrandomized trial, and 4 cohort studies included healthy controls to conduct a cross-sectional case-control comparison of baseline cardiometabolic indices.[18-24] Cardiometabolic outcomes (predominantly weight) were a primary outcome measure in 16 studies[18-21,23-34]; the primary outcome was treatment efficacy or all-cause medication discontinuation, with cardiometabolic measures a secondary outcome, in the remaining studies (eTable 2).

Sample Ascertainment and Subject Participation

Two studies described in detail the population from which subjects were ascertained and both appear to have ascertained samples representative of the broader population of patients.[35,36] All studies provided information on eligibility criteria. Four randomized trials, 1 nonrandomized trial, and 4 cohort studies excluded subjects who used recreational drugs,[28] had recent alcohol or drug abuse,[37] or a substance use disorder.[18-20,25,33,36,38] The drugs were not specified. Six studies excluded individuals with any cardiometabolic abnormality at baseline.[18,19,25,28,30,31] Only 2 studies reported the number of potential subjects who met eligibility criteria. Four studies reported the percentage of eligible individuals approached who subsequently consented to participate in the study (eTable 1) (for Addington et al,[27] no participation rate is recorded because it was a retrospective medical file audit study). All others reported that their sample consisted of all consecutive admissions at 1 or more treatment centers.

Drug-Naive Status and Medication

Patients were either antipsychotic naive or had been exposed to antipsychotics for between 9 days and 16 weeks. All studies described the medication administered, but only 4 formally assessed medication compliance, using pill counts,[35,39] prescription counts,[20] or patient report.[40]

Selection of Control Subjects

Eight studies included controls (eTable 1). Controls were recruited from hospital staff,[19,24] universities, and the general community[21,24] and an anonymous workplace health screening program.[18] The other studies provided no information on how controls were recruited. No study provided any information on how many controls were initially approached or any differences between control participants and nonparticipants in the study. All but 1 study[21] attempted to match controls to cases on at least some pertinent characteristics such as age, sex, and ethnicity.

Sample Size and Follow-up

Sample size varied (n=9-555) but most studies were small. Only 4 studies ascertained more than 200 patients. One study provided an explicit description of how subjects were followed up for postbaseline assessments.[28] For 3 studies, it could be inferred that follow-up of subjects was routinely conducted because subjects appeared to have been inpatients for the duration of the study.[30,31,39] Others did not provide any information on how subjects were tracked through the course of the study, how and where follow-up assessments were conducted, and methods used to try to find subjects lost to follow-up. Nine studies provided information about the reasons that follow-up assessments could not be conducted[21,23,30,31,35,36,40-42] (simply stating that patients were discharged from the hospital or dropped out of the study was not considered sufficient). The average follow-up time across studies was 31.7 weeks (median, 52 weeks) but ranged from 4 weeks[34] to 2.5 years[23] (3 years including the additional follow-up study by Addington et al[43]).

Analytical Methods Including Missing Data Handling

Subgroup analyses or tests of interaction were generally not well described or justified. The methods used for han-

dling missing data were described in only 6 studies. For 3 others, it could be inferred that a complete case analysis was conducted.[27,29,40]

Subject Characteristics

Four studies did not provide information on diagnoses,[21,26,27,33] and 1 provided incomplete information.[29] All studies provided some demographic information on subjects, such as proportion of males and females, average age, socioeconomic status, and ethnicity. Most studies did not tabulate the number of participants with missing data for each variable, making it difficult to determine numbers of subjects in different analyses.

Tested for Drug Differences

Nineteen studies administered multiple antipsychotics.* Nine studies analyzed data for all drugs combined.[19,21,23,27,29,32-34,44] Ten studies tested for drug differences in cardiometabolic outcomes.† Six studies administered a single antipsychotic[25,26,30,31,37,45]; 5 administered olanzapine,[25,26,30,31,45] some to test if the mode of administration[45] or adjunct treatments minimized weight gain.[30,31]

Case-Control Comparisons

Seven studies tested if patients were different from controls at baseline with regard to weight and fat distribution and diet; indices of diabetes risk; and biochemical indices such as triglyceride, cholesterol, and cortisol levels (eTable 1). Four studies recruited patients who were antipsychotic naive[18,19,24,46]: 1 included patients within 72 hours of first exposure,[22] 1 included patients with up to 2 weeks' lifetime exposure but no more than 3 doses in the month prior to recruitment,[20] and another recruited patients with up to 16 weeks of recent exposure.[21]

RESEARCH FINDINGS

Case-Control Findings

At baseline, patients had a higher waist to hip ratio than controls in 3 studies,[18,19,24] a higher saturated fat intake,[24] and, in a study that matched on body mass index (BMI), 3 times more intra-abdominal fat,[24] but there was no elevation of intra-abdominal fat in another study that did not report matching.[19] There were no other significant weight-related differences. At baseline, patients did not have more total body fat,[24] abdominal subcutaneous fat,[19,24] unsaturated fat intake,[24] or a higher weight,[19,21,46] BMI,[19-21,24,46] or waist circumference[46] than controls.

Patients had a higher prevalence of prediabetes (elevated fasting glucose[21] or insulin[19] level) than controls in 2 studies but 1 of these included patients exposed to antipsychotics for up to 16 weeks.[21] Another study reported a 10-fold higher prevalence of diabetes in patients (5%) than controls (0.5%),[22] which may be largely independent of weight or low-density lipoprotein (LDL) cholesterol given that the relevant controls were significantly more likely to have elevated LDL cholesterol levels and to be overweight or obese (52% vs 27%, in their corrected Table 1) compared with patients. Patients did not differ from controls on trigylceride[21]; total, LDL,[22] or high-density lipoprotein (HDL) cholesterol[21,22]; insulin[21]; adiponectin; leptin; interleukin 6; vascular cell adhesion molecule 1; or E-selectin[21] levels. One study found an elevated waist to hip ratio and elevated fasting insulin level relative to controls only in female patients.[19]

Two studies used controls to test if change over time was due to factors other than treatment.[20,46] One study matched hospitalized cases and controls by sex, age, exercise and diet (basal metabolic rate), race, and socioeconomic status to match for possible confounders of natural weight gain over time.[46] Concomitant drugs that could potentially affect weight were not permitted. Patients had significantly elevated weight (4 kg) and BMI (2 kg) after 6 weeks of double-blind, randomized treatment with haloperidol, risperidone, or olanzapine compared with controls after 6 weeks of unmedicated follow-up. After 12 months of treatment with haloperidol, risperidone, olanzapine, or perphenazine, cases had a significantly greater increase in BMI (2 kg) than controls matched only for age.[20]

To control for progressive weight gain in cases over time, independent of medication, 1 study included a second control group of patients (n=7) who refused antipsychotic drug treatment for longitudinal comparison with treated patients and healthy controls.[20] The mean weight gain was 17 kg across 1 year for olanzapine, 8 kg for risperidone, 4 kg for haloperidol, 1 kg for perphenazine, 1 kg for patients who refused antipsychotics, and 1 kg for age- and sex-matched controls with no history of psychosis.

Change in Cardiometabolic Risk Factors After Treatment With Antipsychotics

Studies that administered multiple antipsychotics but analyzed data for all drugs combined[19,21,23,27,29,32-34,44] found that changes in weight, BMI, and waist circumference were evident after 1 month.[34] There was a significant increase in interleukin 12 after 6 weeks[47] and a significant increase in subcutaneous and intra-abdominal fat, a 3-fold increase in leptin level, and a significant increase in total and LDL cholesterol, triglyceride, and nonfasting glucose levels after 10 weeks.[19] Total body weight increased by 10% to 12% after 6 to 12 months.[27,29] Most of that weight change occurred in the first 6 months. At baseline, 36% to 42% were overweight or obese[21,27] (like the broader community); after 6 months, 58% to 71% were overweight or obese.[21,27]

There was a significant change in total,[21,29,44] LDL,[21,44] and HDL cholesterol,[29] triglyceride,[29,44] fasting insulin and glucose, leptin, E-selectin, and adiponectin levels by 6 months.[21] Weight gain continued for at least 3 years.[43] Those who had taken antipsychotics continuously over 2.5 years had nonsignificantly more weight gain (13 kg) than those who had not (7 kg).[23] Genotype may also play a role. The wild-type variant of the 5HT2C receptor gene

References 18-21, 23, 24, 27-29, 32-36, 38, 40-42, 44.
†*References 18, 20, 24, 28, 35, 36, 38, 40-42.*

regulatory region was associated with significantly more weight gain after 10 weeks taking risperidone or chlorpromazine than the –759 C/T polymorphism in a Han Chinese cohort.[32] This finding was replicated in a Spanish cohort treated with a different combination of antipsychotics and in the subset of those given olanzapine.[33]

In studies that administered multiple antipsychotics and tested for differences in cardiometabolic outcomes across drugs,‡ the combination of drugs studied and the follow-up interval varied (eTable 1), which is important because the trajectory of weight gain varies across different drugs. We therefore summarize results by follow-up point to better show the pattern of findings that emerges across studies.

By 6 to 8 Weeks. Weight gain was significant. The average weight gain after 6 to 8 weeks taking olanzapine was 5 to 6 kg,[18,26,45] which was significantly higher than the average weight gained while taking risperidone (4 kg) or haloperidol (3 kg).[18] In another study, means were not reported but the rank order of weight gain by drug administered was the same.[36] There was a significant increase in fasting and postprandial blood glucose levels and the incidence of diabetes after 6 weeks in male patients.[39] The largest effects were seen for olanzapine, then risperidone and haloperidol. At 8 weeks, there was a significant increase in insulin level, insulin resistance, and glucose, cholesterol, triglyceride, and C peptide levels across clozapine, olanzapine, risperidone, and sulpiride combined but no significant difference between drugs.[28]

By 3 to 4 Months. Olanzapine was associated with significantly more weight gain (7-9 kg)[26,41,48] than haloperidol (3-4 kg)[41,48] but not risperidone (6 kg).[48] Risperidone was associated with significantly more weight gain than haloperidol (5 kg vs 3 kg).[38] Other results were less consistent. A significant increase in cholesterol and fasting insulin levels was found after 3 to 4 months taking olanzapine in 1 study[26] but not another.[25] No significant increase was found in fasting triglyceride, glucose,[26] or leptin[25] levels but there was a significant increase in absolute fat mass; percentage of body fat and waist to hip ratio, suggesting central deposition of body fat; and C peptide level while taking olanzapine.[25]

By 6 Months. Gain in intra-abdominal fat was nonsignificantly higher with risperidone (27 cm^2) than olanzapine (18 cm^2).[24]

By 1 Year. There was no significant difference in weight gain across different antipsychotics.[20,35,38,40,48] Two studies did not report pairwise drug comparisons, just 4- and 5-way comparisons.[20,40] The rank and range of average weight gain reported after 1 year taking antipsychotics for each drug across informative studies is olanzapine, 11 to 14 to 17 kg[20,40,48]; amisulpride, 10 kg[40]; clozapine, 10 kg[35]; quetiapine fumarate, 10 kg[40]; risperidone, 8 to 9 kg[20,48] and at 2 years, 7 kg[38]; haloperidol, 4 to 7 to 11 kg[20,40,48] and at 2 years, 6 kg[38]; chlorpromazine, 6 kg[35]; ziprasidone hydrochloride, 5 kg[40]; and perphenazine, 1 kg.[20]

‡*References 18, 20, 24, 28, 35, 36, 38, 40-42.*

This ranking of antipsychotics was reflected in other weight-related changes, such as 4-kg or more weight increase,[36] 7% or more weight increase,[42,46] increasing BMI,[41,48] and the incidence of metabolic syndrome,[49] but not for intra-abdominal fat.[24] Orally disintegrating tablets of olanzapine were associated with significantly less weight gain than standard tablets,[45] as was adjunctive reboxetine[31] but not fluoxetine.[30]

At 12 months, there was a significant increase in insulin level, insulin resistance, and total and LDL cholesterol, triglyceride, leptin, and ghrelin levels,[40,50,51] an elevation in fasting glucose level in 1 study[40] but not in 2 others,[35,50] and weight gain significantly correlated with insulin and leptin levels.[51] No significant differences were found across haloperidol, olanzapine, or risperdione.[51] No significant differences were found across haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone.[40] A comparison of olanzapine, risperidone, and quetiapine in another of the larger samples did find significant differences at 12 months: olanzapine and quetiapine were associated with a greater elevation in triglyceride level and systolic blood pressure than risperidone; olanzapine was associated with a greater elevation in diastolic blood pressure than risperidone; quetiapine was associated with a greater elevation in cholesterol level than risperidone; and olanzapine was associated with a greater reduction in HDL cholesterol level than quetiapine or risperidone.[42] This is consistent with the earlier-mentioned ranking for weight, with olanzapine over quetiapine over risperidone.

Baseline Predictors of Cardiometabolic Outcomes

Lower pretreatment BMI,[20,44,46] younger age,[20,44] triglyceride level,[44] more negative symptoms,[20] and more comedications and antidepressants[20] predicted weight gain after antipsychotic treatment. In 1 study, women (but not men) starting with a normal BMI gained a significantly higher percentage of body weight (mean, 18%) than those starting with an overweight BMI (mean, 2%).[27]

COMMENT

Drawing definitive conclusions about the impact of antipsychotics on cardiovascular risk factors in patients with a first episode of treated psychosis is not currently possible. Some drug comparisons are entirely lacking, and others appear underpowered. Sample sizes varied widely but most were small. Only 4 studies ascertained more than 200 patients. Most studies do not describe their patient or control samples well enough to gauge representativeness. Medication compliance is rarely assessed and never explicitly factored into analyses, even in formal treatment trials. Dropout rates in the longer trials were as high as 80% to 90%,[41,52] which limits conclusions about longer-term outcomes. Given the sparseness of cardiometabolic outcome data beyond 1 year, a commonly used method for handling missing data (last observation carried forward) may underestimate weight gain and associated parameters in patients compliant with antipsy-

chotic use for much longer than average periods by as much as 50%.[52]

The results of the studies reviewed herein point toward 2 important hypotheses that need further research:

1. In general, there is no difference in cardiometabolic indices between patients and controls prior to treatment with antipsychotic drugs. Caveat: Prior to first exposure to antipsychotics, patients may have a higher waist to hip ratio and more intra-abdominal fat relative to BMI than controls but adequate control matching may be required to detect these early differences.
2. Risk for cardiovascular disease, indexed by weight and other metabolic indices, increases after first exposure to any antipsychotic. Caveat: After 1 year of antipsychotic drug treatment, a rank order of drugs can be derived across all studies reviewed herein but there is no evidence of significant differences between first- and second-generation antipsychotics. Weight gain after 1 year taking risperidone, for example, was very similar to weight gain after 1 year taking haloperidol or chlorpromazine. Variance in adverse cardiometabolic effects within each class indexes the most meaningful source of variance. Weight gain while taking olanzapine, for example, was much higher than weight gain while taking ziprasidone.

SUGGESTIONS FOR FUTURE DIRECTIONS

Weight gain may be the most visible of the adverse cardiometabolic effects of antipsychotic drugs but tracking less visible risk factors is just as important. Elevated LDL cholesterol level is the main target for primary prevention of heart disease[2] but it is not clear whether changes in LDL or HDL cholesterol, triglyceride, or serum glucose levels or insulin resistance in the first treated episode of psychosis are independent of weight changes. More research in this area is needed to determine which cardiometabolic indices are most strongly affected by which antipsychotics and what the long-term consequences of this are.

As many as 39% of patients are nonadherent and 20% inadequately adherent[53] in their first year of antipsychotic drug treatment but many studies do not assess or analyze medication compliance. Assessment of serum levels of antipsychotics is important because compliance with a prescription does not ensure a therapeutic dose and that is ultimately the point of tracking adherence with prescribed medication in relation to outcomes. Some antipsychotics do not even have a known therapeutic window, especially for youth.[54] This is an important unsolved problem. Dosage effects on the efficacy of antipsychotics for psychotic symptom reduction and the emergence or exacerbation of cardiometabolic risk factors, and their relationship, should be tested.

Comorbidity, sex, age, and genetic makeup may all affect treatment efficacy and adverse effects. Exclusion criteria in drug trials often include substance abuse and depression or other medical conditions, even minor cardiometabolic abnormalities. Recreational drug use, drug abuse, and depression are all common in cohorts of patients with a first treated episode of psychosis[55-57] and increase risk for cardiovascular disease,[58,59] but we do not know if they moderate cardiovascular risk during treatment with antipsychotics.

The age distribution in cohorts of patients with a first treated episode of psychosis varies by sex because of sex differences in the age at onset of psychosis.[13] Patients with first-episode psychosis are composed of younger men and older women unless artificially constrained to ascertain a specific age range via a youth service. This means that the prevalence of schizophrenia in first-episode cohorts will be much higher in youth and young adults than in those unselected for age.[13] Tests for sex differences should therefore control for age effects[60] and all studies should report any age limits on ascertainment and intake/outcome diagnosis. Diagnosis is important because large population-based studies have shown that different psychosis subtypes index partly distinct risk factors,[61] which may prove to be related to comorbidity with physical disease. There is no a priori reason to assume that treatment effects are unrelated to risk factors for psychosis or cardiovascular disease.

Women may be more sensitive to the effects of antipsychotics[60] and their increased risk for central obesity may be evident early.[19] After 3 to 6 months of treatment, women had waist circumference measures in the high-risk range.[29] Hypoadiponectinemia induced by visceral fat accumulation may be a strong risk factor for metabolic and cardiovascular diseases and some cancers.[62] Central obesity early in the course of treated illness may therefore predict later physical disease. Efforts to evaluate interventions that target emerging central obesity, especially in women, should be a clinical research priority.

Adoption of both the CONSORT guidelines for randomized controlled trials and the STROBE guidelines for observational (cohort) studies will increase the accuracy of reporting and interpretation of future studies of cardiometabolic outcomes of the first treated episode of psychosis. Beyond the implementation of these guidelines we recommend future studies:

1. Provide a more detailed characterization of the primary exposure—medication—by assessing and analyzing medication compliance by identifying the therapeutic window for antipsychotic drugs in adults and youth and by evaluating dosage effects.
2. Undertake a comprehensive assessment of cardiometabolic risk factors following, at the very least, recommended monitoring guidelines.[63] Long-term follow-up will be required to accurately document the emergence of some outcomes, such as diabetes.
3. Examine whether cardiovascular outcomes are moderated by (1) demographic characteristics (sex and age at a minimum); (2) clinical characteristics; and (3) genetic factors.

CLINICAL IMPLICATIONS

Individuals treated with antipsychotics should be assessed before (or very soon after) first exposure to antipsychotics to determine baseline cardiovascular risk. Regular monitoring is then recommended using consensus guidelines.[63] Any clinically significant changes should

be dealt with following recommended protocols and referral to a primary care physician or appropriate specialist.[64] Information from monitoring should guide the selection (and switching) of antipsychotic agents,[63] but in practice, regular monitoring is rarely conducted.[65] We have found that general nurses can conduct monitoring in a first-episode psychosis service,[66] but in other settings, and outside of the rigorous protocols of research studies, cardiometabolic monitoring is still not routinely implemented.[67] This is an important failure of care.

LIMITATIONS

There are many unresolved issues. Contrary to expectations, in all but 1 of the largest studies,[42] cardiometabolic outcomes were not significantly different across different antipsychotics at study end points. This may reflect low power to detect true differences given currently attainable sample sizes relative to the number of antipsychotics administered. A recent meta-analysis of weight gain following first exposure to antipsychotics in the absence of any concomitant medications that may affect weight did not find any significant differences across antipsychotics[5] because, the authors concluded, there were insufficient data. Different second-generation antipsychotics are associated with significantly different cardiometabolic profiles in samples that are not restricted to the first treated episode.[68] Olanzapine causes more weight gain than all other second-generation antipsychotics except clozapine. Clozapine causes more weight gain than risperidone, risperidone more than amisulpride, and sertindole more than risperidone. Olanzapine elevates cholesterol level more than aripiprazole, risperidone, and ziprasidone but not amisulpride, clozapine, and quetiapine. Quetiapine elevates cholesterol level more than risperidone and ziprasidone. Olanzapine elevates blood glucose level more than amisulpride, aripiprazole, quetiapine, risperidone, and ziprasidone but not clozapine. Key unanswered questions concern the strength of the association between antipsychotic exposure and adverse cardiometabolic effects for each antipsychotic, which can only be estimated with previously antipsychotic-naive patients, the timing of the emergence of these effects, and their trajectory, not if they eventually occur. An observed temporal relationship does not prove a causal relationship exists, and lifestyle factors associated with psychosis may play a part, but systematic differences in the pattern and timing of the adverse cardiometabolic outcomes of different antipsychotics in randomized trials are consistent with a causal link. Possible modifiers of the observed association, its effect size and trajectory, are important to evaluate because treatment is correlated with length and severity of illness. Longitudinal investigation of patients who refuse antipsychotics or become noncompliant is therefore required to test if risk is concentrated in those who are compliant with their antipsychotic medication.

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