

Quality Concerns in Psychotropic
Prescribing:
Reducing Use of Antipsychotics with
High or Moderate Risk of Metabolic Side
Effects in Individuals with
Cardiometabolic Risk Factors

Reference Guide



Quality Concerns in Psychotropic Prescribing: Reducing the Use of Antipsychotics with High or Moderate Risk of Metabolic Side Effects in Individuals with Cardiometabolic Risk Factors

In 2007, the NYS Office of Mental Health convened a Scientific Advisory Committee of national experts in psychopharmacology. Six workgroups (schizophrenia, depression, bipolar disorder, older adults, youth, and women) identified approximately 80 quality concerns in psychotropic prescribing that are common, costly, and measurable. This clinical module provides information on the quality domain of cardiometabolic risk, including an overview of the evidence base and definitions of each indicator.

- **Client focus:** Clients who have at least one cardiometabolic risk factor and are on a high or moderate risk antipsychotic
- **Project goal:** Switch of antipsychotic to a low-risk choice if clinically feasible following clinical evaluation, for each client meeting the criteria above
- **Cardiometabolic risk factors:** Obesity, diabetes mellitus, hyperlipidemia, hypertension, cardiovascular disease
- **High- and moderate-risk antipsychotics: for adults:** olanzapine (Zyprexa), quetiapine (Seroquel), chlorpromazine (Thorazine), thioridazine (Mellaril); **for children:** all antipsychotics except Geodon (ziprasidone) and Abilify (aripiprazole)

Brief Definitions

PSYCKES Cardiometabolic Risk Indicators	
Hypertension [HTN]	The percentage of consumers of all ages who are currently on an antipsychotic medication with a moderate- to high risk for cardiometabolic disorders among consumers currently on any antipsychotic AND who have been diagnosed with hypertension in the previous five years
Cardiovascular Disease [CVD]	The percentage of consumers of all ages who are currently on an antipsychotic medication with a moderate- to high risk for cardiometabolic disorders among consumers currently on any antipsychotic AND who have been diagnosed with acute myocardial infarction, stroke, or any ischemic vascular disease, or who have undergone a coronary artery bypass graft or percutaneous transluminal coronary angioplasty in the previous five years
Hyperlipidemia [HL]	The percentage of consumers of all ages who are currently on an antipsychotic medication with a moderate- to high risk for cardiometabolic disorders among consumers currently on any antipsychotic AND who have been diagnosed with hyperlipidemia/hypercholesterolemia, or were prescribed medications to treat those conditions in the previous five years
Diabetes/Pre-diabetes [DM]	The percentage of consumers of all ages who are currently on an antipsychotic medication with a moderate- to high risk for cardiometabolic disorders among consumers currently on any antipsychotic AND who have been diagnosed with diabetes or have had elevated blood glucose (pre-diabetes) or received medication for

PSYCKES Cardiometabolic Risk Indicators	
	diabetes or pre-diabetes in the previous five years
Obesity [Obes]	The percentage of consumers of all ages who are currently on an antipsychotic medication with a moderate- to high risk for cardiometabolic disorders among consumers currently on any antipsychotic AND who have been diagnosed with obesity or received medication for obesity in the previous five years
Cardiometabolic summary	The percentage of consumers meeting criteria for any of the cardiometabolic indicators, among those on an antipsychotic AND who have one of the specified cardiometabolic conditions

Scope of the Problem

The PSYCKES Cardiometabolic Risk indicator set focuses on the risks that antipsychotic medications can pose to the health of consumers who have pre-existing risk factors for heart attacks, peripheral vascular disease, or strokes. Among the major metabolic side effects of antipsychotics are weight gain and increased risk for diabetes, which are both already significant problems in the general population in the United States. From 1991-2001, the rate of obesity increased by 74% in the US [1]. 68% of adult Americans and 31% of children are either overweight or obese [2]. Obesity continues to increase in the US at a rate of about 1% per year, which translates into 2.4 million new individuals with obesity each year [3]. Medical costs average \$1,500 more per year for an obese person compared to someone of normal weight, and obesity results in a doubling of mortality rates from all causes [3]. Similarly, the prevalence rates of diabetes have surged by 58% in the decade between 1991 and 2001, and as of 2007, 10% of all adults and 23% of adults over 60 years had diabetes [4]. With over 40,000 new cases diagnosed each year, the health effects of diabetes are significant. Diabetes is the leading cause of blindness and kidney failure in adults, and dramatically increases rates of cardiovascular disease. In 2007, the US spent \$174 billion in a single year on the direct and indirect costs of diabetes. These medical risks are magnified for consumers with psychiatric disorders. Obesity is twice as common in this population [5], and diabetes rates are high. An analysis of New York State (NYS) Medicaid claims data suggests that diabetes is nearly twice as common in the mental health population served by OMH-licensed clinics as in the overall Medicaid population.

Smoking, hypertension, elevated cholesterol and triglyceride levels, and a sedentary lifestyle are also major modifiable risk factors for cardiovascular disease. Consumers with schizophrenia and bipolar disorder are up to three times more likely to have these risk factors. The National Association of State Mental Health Program Directors (NASMHPD) noted in a 2006 report that consumers with serious mental illness die, on average, 25 years earlier than the general population. The major cause of this increased mortality was cardiovascular disease [6]. The NASMHPD has called for people with serious mental illness to be designated as a "health disparities population" because stigma, access to care, and factors related to illness and treatment contribute to the very high risk and poor health outcomes documented. The adoption of evidence-based practices for prescription of antipsychotic medications may be an effective means to lower the risk for diabetes and cardiovascular disease in consumers with psychiatric diagnoses [7].

The Metabolic Syndrome

The concept of insulin resistance is essential to understanding how metabolic risk factors lead to excess cardiovascular illness and death. Insulin is the hormone the body uses to turn sugar

into energy, and insulin resistance refers to the reduced sensitivity of body tissues to insulin. Obesity contributes to insulin resistance and a cascade of other abnormalities including increased blood sugar and triglyceride levels, decreased HDL (good) cholesterol, and elevated blood pressure. Metabolic syndrome is defined as the presence of at least 3 of 5 cardiovascular disease (CVD) risk conditions. Studies have shown a threefold increase in the risk of cardiovascular disease in subjects with the metabolic syndrome as compared with health subjects [8,9].

Metabolic Syndrome Criteria*

Adults (18 and older)	Children and Adolescents
Abdominal Obesity: waist circumference \geq 40 inches in men; \geq 35 inches in women (alternate criteria: Body Mass Index (BMI) \geq 30)	Abdominal Obesity: Waist circumference \geq 90 th percentile or Body Mass Index (BMI) \geq 95 th percentile
Blood Pressure: \geq 130/85 mm Hg	Blood Pressure: \geq 90 th percentile for sex and age
Fasting Triglyceride level: \geq 150 mg/dl	Fasting Triglyceride level: \geq 110 mg/dl
Fasting HDL (good) Cholesterol: $<$ 40 mg/dl in men; $<$ 50 mg/dl in women	Fasting HDL (good) Cholesterol: $<$ 40 mg/dl in both boys and girls
Fasting Blood Glucose: \geq 110 mg/dl	Fasting Blood Glucose: $>$ 110 mg/dl

*3 or more out of 5 indicates presence of metabolic syndrome; 2 out of 5 indicates high risk for developing metabolic syndrome

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [10], a large clinical research study comparing the effectiveness and safety of several antipsychotic medications, highlighted the importance of monitoring metabolic factors in consumers with schizophrenia. Data from CATIE showed that 43% of study consumers with schizophrenia met criteria for the metabolic syndrome upon entry into the study, approximately twice the prevalence in the general population [11]. Women were more likely than men to have the metabolic syndrome. In more recent studies, high rates of metabolic syndrome have been documented in people with bipolar disorder, major depression, and post-traumatic stress disorder (PTSD). Youth and people taking antipsychotic medications for the first time appear even more likely to develop features of metabolic syndrome when taking second generation antipsychotics [12,13]. These high rates of obesity, diabetes, and metabolic syndrome in people with psychiatric disorders place consumers at risk for developing serious medical problems, which can be worsened by psychiatric medication treatment.

Quality Concerns in Cardiometabolic Risk and Antipsychotic Prescribing

The cardiometabolic quality indicators developed by PSYCKES target the prescription of antipsychotics to consumers who have at least one of the criteria for metabolic syndrome or have pre-existing cardiovascular disease. Short- and long-term studies have shown that individual antipsychotic medications have differential effects on these risk factors. Among the first generation antipsychotics, it has long been known that chlorpromazine (Thorazine) and thioridazine (Mellaril) are associated with significant rates of weight gain and insulin resistance [14]. Recent research has focused on weight gain of 2 to over 8 lbs associated with short-term treatment with second generation antipsychotics [15]. Data from studies lasting one year or more showed that aripiprazole (Abilify) and ziprasidone (Geodon) had the lowest risk for weight gain (average 2 lbs); risperidone (Risperdal) and quetiapine (Seroquel) showed an average of

4.4 to 6.6 lbs increase; and olanzapine (Zyprexa) had an average weight gain of over 13 lbs for doses of 17.5 mg or less, and 22 pounds at doses over 17.5 mg. Olanzapine trials of up to one year showed that weight gain does not plateau but continues to increase throughout the year.

In the CATIE study [16] the switch from a first generation antipsychotic perphenazine (Trilafon) to either olanzapine or quetiapine was associated with significant increases in cholesterol and triglyceride levels. Similar findings were noted in a study of young adult consumers early in the course of a psychotic illness who were randomly assigned to receive olanzapine, risperidone, or quetiapine [17]. After 1 year of treatment, consumers taking olanzapine and quetiapine were shown to have significantly greater increases in cholesterol as compared to those taking risperidone. Other studies of first episode psychosis have demonstrated more sensitivity to metabolic effects of antipsychotic medications early in the course of illness [18].

Cardiometabolic effects are of special concern in children and adolescents. Studies have shown the metabolic effects of second generation antipsychotic agents seen in adults may be magnified in children and adolescents [19]. Although there is much less known about antipsychotic agents and the metabolic syndrome in children and adolescents, ongoing research indicates that youth taking these medications are at least as likely to develop metabolic abnormalities as adults [20]. In a study of early onset schizophrenia treatment, the olanzapine treatment arm was prematurely discontinued due to the absence of superior benefit and evidence of increased cardiovascular risk related to high levels of blood glucose and triglycerides [21]. Despite these concerns, NYS Medicaid data suggest that although children and adolescents are more vulnerable to metabolic side effects, they are less likely than adults to be monitored for them.

Classification of Antipsychotics and Cardiometabolic Risk

Cardiometabolic risk and metabolic syndrome are serious quality concerns for individuals receiving antipsychotic medications; different medications present different levels of risk. In order to assess the metabolic impact of antipsychotic medications, the PSYCKES project's Scientific Advisory Committee Schizophrenia sub-group reviewed the American Psychiatric Association (APA) Practice guidelines for the Treatment of Patients with Schizophrenia (2nd edition)[22] the American Diabetes Association-APA Consensus Statement on Antipsychotic Drugs and Obesity and Diabetes [23], and recent research including CATIE-based studies.

Although risperidone (Risperdal) and quetiapine (Seroquel) were grouped together by the Schizophrenia Practice Guideline and the ADA-APA Consensus statement, the Scientific Advisory Committee Schizophrenia subgroup recognized that recent evidence suggests that the metabolic side effects of risperidone, particularly pertaining to changes in lipids, are not as marked as those of quetiapine. The Schizophrenia subgroup also identified two first-generation antipsychotic medications, chlorpromazine and thioridazine, that also have potentially problematic weight gain and metabolic effects. Therefore, the Scientific Advisory Committee Schizophrenia subgroup recommended that chlorpromazine, thioridazine, and quetiapine be identified as moderate-risk medications for metabolic abnormalities and risperidone be assigned to a lower-risk category. Although the Scientific Advisory Committee Schizophrenia sub-group recognized that clozapine (Clozaril) is a high-risk medication for causing metabolic abnormalities, the subgroup recommended that clozapine be excluded from review under this indicator. The drug's demonstrated superior efficacy in treatment-resistant illness and suicide prevention, along with the repeated treatment failures that typically precede a clozapine trial, provide clinical justification for continuation despite cardiometabolic risk. Newly-approved antipsychotic medications asenapine (Saphris) and iloperidone (Fanapt) have not been

classified due to limited data regarding metabolic and other cardiovascular effects of these agents.

Cardiometabolic Risk Classification of Antipsychotic Medications for Adults

High Risk	Moderate Risk	Low Risk
Olanzapine (Zyprexa)	Quetiapine (Seroquel) Chlorpromazine (Thorazine) Thioridazine (Mellaril)	Aripiprazole (Abilify) Paliperidone (Invega) Risperidone (Risperdal) Ziprasidone (Geodon) All first-generation (conventional) antipsychotics except chlorpromazine (Thorazine) and thioridazine (Mellaril)

*Clozapine not included in PSYCKES cardiometabolic indicator

For children and adolescents, there is less evidence regarding the use and adverse effects of these medications. The cardiometabolic risk categories below are based on clinical experience as well as available scientific data.

Cardiometabolic Risk Classification of Antipsychotic Medications for Children and Adolescents

Highest Risk	Higher Risk	Moderate Risk	Lower Risk
Olanzapine (Zyprexa)	Quetiapine (Seroquel) Paliperidone (Invega) Risperidone (Risperdal)	All first-generation (conventional) antipsychotic medications except molindone (Moban)+	Aripiprazole (Abilify) Molindone (Moban)+ Ziprasidone (Geodon)

*Clozapine not included in PSYCKES cardiometabolic indicator +Moban may not be available in the US.

Clinical Recommendations for Reducing Cardiometabolic Risk

1. Consumers with cardiometabolic conditions who are currently receiving high or moderate risk antipsychotic medications should be **engaged by their prescribers in a conversation** about the cardiometabolic risks associated with their regimen, and the benefits of making a change. A **switch to a medication posing a lower risk** for cardiometabolic complications should be considered if clinically appropriate.
2. **Consumers with preexisting cardiometabolic risks** should be started initially on low risk medications.
3. **Alternate non-antipsychotic treatments should be considered for children and adolescents** with cardiometabolic risk. If an antipsychotic medication is indicated, a low risk medication is the first-line choice. Emphasize to the clinical staff the importance of asking consumers about both their **medical and family history of cardiometabolic disease** at intake.
4. **Psychoeducation** in varied formats should be available to all consumers. Brochures, scientific summaries, information sessions, and ongoing medication education groups can be helpful in providing information helpful to consumers and promote dialogue with prescribers.
5. **Cross tapers are recommended** when switching medications. To decrease the risk of relapse, the new antipsychotic drug should be started first and titrated to a therapeutic

dose (if tolerated) before beginning the taper of the first medication. Medication changes are tolerated best by consumers when the changes start low and go slow. A common clinical practice is to change a medication by no more than 1/3 of the current dose, no more frequently than every 2-3 weeks.

6. Consumers and families will benefit from **supportive services** from the clinic during periods of medication change. These services may include frequent check-in calls with the clinic nurse, increased appointment frequency with the prescriber and therapist, medication groups with other consumers, and psychoeducation about side effects or symptoms likely to be experienced. Specific interventions for management of common difficulties including sleep problems, anxiety, and other changes in wellbeing may be developed by the clinical staff to **provide clients with tools** to use during the change.
7. **Rating scales** filled out by the client can be very helpful during medication changes. Rating scales can educate consumers in understanding and observing symptom constellations over time; and provide clinicians with accurate longitudinal information about the effect of medication change or discontinuation on symptoms and function.
8. Clinics should develop processes to **liaise with primary care providers**, including facilitation of appointment scheduling for clients who have not had regular medical consultation.

Annotated Bibliography for Cardiometabolic Risk in Adults and Youth

These papers have been selected and briefly summarized to provide clinicians and CQI teams with key evidence from the scientific literature which may be helpful in informing clinical practice and working with clients to reduce their health risks from psychotropic medications. The scientific summaries located on the [PSYCKES website](#) provide more in-depth information and critical review of important scientific articles.

Research Studies

1. **Padmavati R, McCreddie RG, Tirupati S. Low prevalence of obesity and metabolic syndrome in never-treated chronic schizophrenia.** *Schizophrenia Research* 2010, vol 121 pp 199-202
Researchers and clinicians have wondered whether people with schizophrenia have an increased risk for developing obesity and metabolic abnormalities independent of treatment with medications. This case-control study was done in India with 51 people with never-treated schizophrenia and 51 normal controls. 96% were vegetarians. People with schizophrenia were more likely to be unmarried and unemployed but all subjects and controls lived in extended family groups.
 - BMI was higher in the control group than the schizophrenia group.
 - Waist circumference, blood pressure, glucose, triglyceride and HDL cholesterol levels were not different between the two groups.
2. **De Hert M, Hanssens L, Van Winkel R et al. Reversibility of Antipsychotic Treatment-Related Diabetes in Patients With Schizophrenia.** *Diabetes Care* 2006, Vol 29, no 10, p2329-2330 (letter).
While the clinical concerns related to metabolic effects of antipsychotic treatment have been well-documented, scientific evidence regarding effect of medication changes on medical illness is just emerging. This case series reports on 7 patients who were switched from other high and moderate risk antipsychotics to aripiprazole (Abilify) after the new onset of diabetes, determined by glucose tolerance testing and fasting glucose levels.

There was reduction at 3 months of glucose values at all times in the OGTT, fasting insulin, glycosylated hemoglobin, weight, waist circumference, and BMI. This prospective case series provides evidence that diabetes can be reversed with a change in antipsychotic medication.

3. **Ray WA, Chung CP, Murray KT: Atypical antipsychotic drugs and the risk of sudden cardiac death.** *New England Journal of Medicine* 360 (3):225-235, 2009
 - This study, conducted in Tennessee, found that current users of typical and atypical antipsychotic drugs had a similar, dose-related increased risk of sudden cardiac death.
 - Adjusted IRR for sudden cardiac death in relation to antipsychotic treatment was: typicals 1.99 (95% CI 1.68,2.34); atypicals 2.26 (95% CI 1.88,2.72).
4. **Baker RA, Pikalov A, Tran QV, et al: Atypical antipsychotic drugs and diabetes in the US food and drug administration adverse event database: a systematic bayesian signal detection analysis.** *Psychopharmacology Bulletin* 42(1):11-31,2009
 - In the FDA AERS database, higher associations with diabetes-related adverse events were found for olanzapine, risperidone, clozapine, and quetiapine.
 - Lower associations with diabetes-related adverse events were found with haloperidol, aripiprazole, and ziprasidone.
 - These findings support differential risk of diabetes across atypical antipsychotics and reinforce the need for metabolic monitoring of patients taking antipsychotics.
5. **Weiden PJ, Newcomer JW, Loebel AD, et al: Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone.** *Neuropsychopharmacology* 33:985-994, 2008
 - Clinically significant sustained improvements in weight, BMI, total cholesterol, and triglycerides were found in patients switched to ziprasidone from risperidone or olanzapine.
6. ***Correll CU, Frederickson AM, Kane JM, et al: Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics.** *Bipolar Disorders* 10:788-797, 2008
 - Patients with bipolar disorder and schizophrenia who are treated with SGAs have similarly high rates of metabolic syndrome.
 - These findings suggest a shared susceptibility to antipsychotic related metabolic dysregulation that is not primarily related to psychiatric conditions or concomitant mood stabilizer treatment.
7. **Kreyenbuhl J, Medoff JR, Seliger SL, et al: Use of medications to reduce cardiovascular risk among individuals with psychotic disorders and type 2 diabetes.** *Schizophrenia Research* 101:256-265, 2008
 - Use of cardioprotective medications in patients with diabetes and serious mental illness increased over the study period. However, a considerable number of patients remained inadequately managed despite considerable cardiac risk.
 - African Americans were less likely than Caucasians to receive statins but more likely to receive ACE-inhibitors or ARB's.
8. **Haupt DW, Fahnstock PA, Flavin KA et al: Adiposity and insulin sensitivity derived from intravenous glucose tolerance tests in antipsychotic-treated patients.** *Neuropsychopharmacology* 32:2561-2569, 2007

- This study used IV glucose tolerance tests to quantify whole-body insulin sensitivity in patients treated with either an FGA or an SGA.
 - Adiposity levels occurring during antipsychotic treatment are strongly related to insulin resistance. This confirms that antipsychotic-induced weight gain can contribute to increased cardiometabolic risk in patients with schizophrenia and schizoaffective disorder.
 - There were no consistent effects of medication group on either insulin sensitivity or secretion, independent of adiposity.
9. **Goethe JW, Szarek BL, Caley CF, et al: Signs and symptoms associated with the metabolic syndrome in psychiatric inpatients receiving antipsychotics: a retrospective chart review.** *Journal of Clinical Psychiatry* 68:22-28, 2007
- 69.3% of the study sample had at least one correlate of metabolic syndrome (BMI >30 kg/m², dyslipidemia, and/or a diagnosis of hypertension or diabetes).
 - The risk for symptoms of metabolic syndrome is particularly high in those >50 years, those taking clozapine, or those on more than one antipsychotic.
 - These findings support the call for routine screening for metabolic syndrome in patients on antipsychotics.
10. **Bobes J, Arango C, Aranda P, et al: Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS study.** *Schizophrenia Research* 90:162-173, 2007
- Patients treated with antipsychotics (either an SGA or haloperidol) had CHD risk and prevalence of metabolic syndrome in the same range as the Spanish general population who were 10-15 years older than the study population.
11. **Correll CU, Frederickson AM, Kane JM, et al: Does antipsychotic polypharmacy increase the risk for metabolic syndrome?** *Schizophrenia Research* 89:91-100, 2007
- Antipsychotic polypharmacy was present in 19.2% of the study population.
 - Compared to patients receiving monotherapy, patients on antipsychotic polypharmacy have higher rates of metabolic syndrome and lipid markers of insulin resistance.
 - Logistic regression analysis showed that metabolic syndrome was significantly associated with co-treatment with an FGA (p<.0001).
 - However, antipsychotic polypharmacy dropped out of multivariate regression models, indicating that antipsychotic polypharmacy is not independently associated with the prevalence of metabolic syndrome and lipid markers of insulin resistance, which are related to known demographic, clinical, and anthropometric risk factors.
12. **Citrome LL, Holt RIG, Zachry WM, et al: Risk of treatment-emergent diabetes mellitus in patients receiving antipsychotics.** *Annals of Pharmacotherapy* 41:1593-1603,2007
- This was a Medline and PSYCInfo search for antipsychotics and diabetes that was undertaken for the years 1966-2005.
 - Comparing antipsychotics and diabetes, little observable difference was noted between individual SGAs vs. FGAs.
 - Avoidance of diabetes as an outcome cannot be predictably achieved with precision by choice of an SGA vs. an FGA.

- Risk assessment for new-onset diabetes requires assessment of established risk factors (family history, non-white ethnicity, diet, central obesity, level of physical activity).

13. Strassnig M, Miewald J, Keshavan M et al: Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one year analysis.

Schizophrenia Research 2007, 93(1-3): 90-98

In the CATIE trial patients had on average been on antipsychotics for 14 years. This study demonstrates that antipsychotic naïve people treated for the first time for psychosis with antipsychotic medications are significantly more susceptible to weight gain. This data comes from an ongoing study of first episode psychosis at the University of Pittsburgh. There were 98 subjects, including patients with and without mood symptoms, and 30 controls matched for age and gender. There was a small group of people with first episode of psychosis on no medication. Average antipsychotic exposure was 303 days, and there was no antipsychotic polypharmacy. Excessive weight gain was defined as an increase of $\geq 7\%$ of body weight.

- Factors associated with more weight gain: younger patients, more negative symptoms.
- Increases after one year in body weight by drug: olanzapine 37 lbs, risperidone 28 lbs, haloperidol 9 lbs, perphenazine 3.4 lbs, psychotic on no meds 3.3 lbs, healthy controls 2.4 lbs.
- Regarding polypharmacy, the total number of medications (regardless of class) and the use of antidepressants were predictors of weight gain.

14. Joukaama M, Heliövaara M, Knecht P, et al: Schizophrenia, neuroleptic medication, and mortality. *British Journal of Psychiatry* 188:122-127, 2006

- This study utilized comprehensive medical exams at baseline and at 17 year follow-up.
- The number of neuroleptics used at baseline survey showed a graded relationship to mortality. Adjusted for age, gender, somatic diseases, and other potential risk factors for premature death, RR was 2.50 (95% CI 1.46,4.3) per increment of neuroleptic.

15. Honer WG, Thornton AE, Chen EY, et al: Clozapine alone vs. clozapine and risperidone with refractory schizophrenia. *New England Journal of Medicine* 354(5):472-82, 2006

- In this randomized, double-blind study, patients with schizophrenia and poor response to clozapine received augmentation with risperidone.
- Addition of risperidone to clozapine did not improve symptoms in patients with severe schizophrenia.
- There was an increase in fasting blood glucose in the group treated with risperidone.

16. Citrome L, Jaffe A, Levine J, et al: Incidence, prevalence, and surveillance for diabetes in New York State psychiatric hospitals 1997-2004. *Psychiatric Services* 57:1132-1139, 2006

- From 1997-2004, the doubling of the IR of treated diabetes (from 0.9% to 1.8%; RR=2.03, 95% CI 1.51,2.73), and the increased prevalence of identified diabetes cases (from 6.9% to 14.5%; RR=2.11, 95% CI 1.93,2.31) among psychiatric inpatients in NYSOMH facilities mirrors that of the general population, but at higher absolute rates.

17. **Citrome L, Jaffe A, Levine J, Allingham B, Robinson J: Relationship between medication treatment and new cases of diabetes among psychiatric inpatients.** *Psychiatric Services* 55:1006–1013, 2004
- Exposure to SGA polypharmacy, to clozapine monotherapy, or to quetiapine monotherapy significantly increased risk of treatment emergent diabetes.

Reviews and Metanalyses

1. **Newcomer JW: Antipsychotic medications: metabolic and cardiovascular risk.** *Journal of Clinical Psychiatry* 68(Suppl 4):8-13, 2007
 - This article reviews evidence in the literature for increased mortality, cardiovascular risk factors, diabetes, obesity, and metabolic syndrome in people with serious mental illness and the associations of antipsychotics with these health problems.
 - Also provides a discussion on various strategies for monitoring cardiometabolic risk factors in patients with mental illness.
2. **Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence.** *Journal of Clinical Psychiatry* 68(suppl):20-27, 2007
 - There is a critical need for psychiatrists and primary care professionals to increase awareness of and attention to the physical health problems of people with mental illness, including appropriate management of metabolic adverse effects associated with psychiatric medications.
3. **Cohn TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications.** *Canadian Journal of Psychiatry* 51:492-501, 2006
 - This is a review of major published consensus guidelines for metabolic monitoring of patients treated with antipsychotics.
 - Also provides a selective review of practice guidelines for management of diabetes, dyslipidemia, and hypertension.
 - There is considerable consensus in the published guidelines.
 - Monitoring, but not necessarily treatment, falls within the scope of psychiatric practice and should include screening for metabolic disorders and tracking of effects of antipsychotic treatment.
4. **Hennekens CH, Hennekens AR, Hollar S: Schizophrenia and increased risks of cardiovascular disease.** *American Heart Journal* 50:1115-21, 2005
 - This article reviews absolute and relative impacts of major causes for mortality among patients with schizophrenia.
 - The chief cause of premature mortality among patients with schizophrenia is CHD, caused mainly by increased adverse risk profiles.
 - Patients with schizophrenia have a 20% decreased life expectancy compared to the general US population.
 - More than two-thirds of patients with schizophrenia die of CHD, compared to one-half of the US population.
5. **Newcomer JW: Second generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review.** *CNS Drugs* 19(suppl):1-94, 2005
 - This review covers eight separate SGAs available in USA or Europe.

- Clozapine and olanzapine are associated with the greatest risk of clinically significant weight gain, as well as the greatest risk of diabetes and dyslipidemia.
- Limited controlled studies support the hypothesis that clozapine and olanzapine may have a direct effect on glucose regulation independent of adiposity.
- The rank order of risk observed for SGAs suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of insulin resistance, dyslipidemia and hyperglycemia between SGAs.

Pediatrics (Cardiometabolic)

1. **Fraguas D, Merchan-Naranjo J, Laita P et al: Metabolic and hormonal side effects in children and adolescents treated with second generation antipsychotics.**

Journal of Clinical Psychiatry 69: 1166-1175, 2008

- After six months of treatment with either risperidone, olanzapine, or quetiapine, the number of patients at risk for adverse health outcomes increase from 16.7% (n=11) to 37.9% (n=25, p=.018). The number of subjects at risk for adverse health outcomes increased significantly only for olanzapine (p=.012).
- Total cholesterol increased significantly for patients receiving olanzapine (p=.047) and quetiapine (p=.016)
- At six month follow-up, 50% (n=33) of subjects showed significant weight gain. Significant increases in BMI z scores were seen in those treated with olanzapine and risperidone.
- Metabolic and hormonal side effects of SGAs in children and adolescents should be carefully monitored when prescribing these drugs.

2. **McIntyre RS, Jerrell JM: Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents.** *Archives of Pediatric and Adolescent Medicine* 162(10):929-935, 2008

This rich study highlights the increased effects of both antipsychotic polypharmacy as well as polypharmacy involving antipsychotic plus another class of medication on cardiovascular and metabolic illness in youth under 18. It is designed as a retrospective cohort study using Medicaid data in a single state (SC), and compares the incidence/prevalence of metabolic, cardiovascular, and cerebrovascular events in a group of youths treated with antipsychotics (n=4140) to a random sample of youth (n=4500) without antipsychotic exposure over a 10 year period. The study compared risks between the exposed and unexposed groups, and then looked at which factors increased the risk of cardiometabolic health problems in both groups. Potential factors examined including gender, ethnicity, age, antipsychotic polypharmacy, and other drug classes prescribed concomitantly with the antipsychotic. Preexisting cardiovascular, cerebrovascular, and metabolic disorders were factored out.

- 42% of individuals youth received **antipsychotic polypharmacy**.
- The antipsychotic-treated cohort had higher prevalence of **obesity** (OR 2.13), **type 2 diabetes** (OR 3.23), and **cardiovascular conditions** (OR 2.70). The control sample, interestingly, had a higher prevalence of dyslipidemia (OR 3.01) and hypertension (OR 2.35)
- Odds of **obesity and/or weight gain** were greatest for youth receiving **antipsychotic polypharmacy** (OR 2.28), **polypharmacy including mood stabilizers** (OR 1.78), **polypharmacy including high risk antidepressants**

- (amitriptyline, nortriptyline, mirtazapine, and paroxetine)(OR 1.66). Female gender (OR 1.75), and for youth ≥ 13 (OR 1.34) were also significant.
- The odds of developing **Type 2 diabetes** were higher for youth on **antipsychotic polypharmacy** (OR 2.36), **for girls** (OR 1.79), and **youth ≥ 13** (OR 1.52)
 - The mean age of **initiation of antipsychotic treatment was 11.4**; the mean **age of onset of incident type 2 diabetes was 13.8**. Youth taking aripiprazole (Abilify), compared to other psychotropics had significantly longer time to diagnosis of DM (OR 35.92).
 - Odds of **dyslipidemia** were higher for **antipsychotic polypharmacy** (OR 5.26), girls (OR 2.08) and youth ≥ 13 .
 - Hypertension was unrelated to which antipsychotic was used.
 - **Incident cardiovascular conditions** were more likely with the use of **haloperidol** (Haldol)(OR 4.34) and **multiple antipsychotics** (OR 1.57).
3. **Correll CU: Monitoring and management of antipsychotic-related metabolic and endocrine adverse events in pediatric patients.** *International Review of Psychiatry* 20(2):195-201, 2008
- Children and adolescents may be more sensitive to antipsychotic-related adverse events than adults.
 - Proactive monitoring and management of antipsychotic-related side effects should be part of clinical practice.
 - It is important to use age-appropriate thresholds for weight and metabolic measures.
4. **Correll CU: Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes.** *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(1):9-20, 2008
- This article reviews available data on antipsychotic-related adverse effects and provides a guide for evaluation and management of antipsychotic-related adverse effects in children and adolescents.
 - Antipsychotics are being used in larger and increasing quantities for a wide range of disorders in children (including psychotic, mood, and disruptive behavior disorders), and in adolescents (to treat irritability related to autism, tic disorders, OCD, PTSD, and aggression).
 - Most randomized controlled data for this population is only available for risperidone.
 - The article also has a comprehensive table that provides a comparative overview of side effects profiles for SGAs in children and adolescents, as well as suggested monitoring and management strategies in pediatric patients treated with antipsychotics.
5. **Correll CU, Carlson HE: Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents.** *Journal of the American Academy of Child and Adolescent Psychiatry* 45:771-793, 2006
- This is a selective review of endocrine and metabolic effects of psychotropic medications in the pediatric population with a focus on monitoring and management strategies.
 - Children and adolescents are at increased risk than adults for antipsychotic-induced hyperprolactinemia, weight gain, and related metabolic abnormalities.

6. **Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents.** *JAMA*, 302(16) pp1765-1773, 2009. This research study (SATIETY) was conducted in the NYC metropolitan area and included 338 youth aged 4-19 with 1 week or less of prior antipsychotic medication exposure. Diagnoses were mixed: mood 48%, schizophrenia spectrum 30%, and disruptive behavior spectrum 22%. Antipsychotics were determined by prescriber choice. 47 youth received aripiprazole, 52 olanzapine, 45 quetiapine, and 168 risperidone. 20 received no antipsychotic and served as a small comparison group. The study continued for 12 weeks. The main outcome measures were weight gain and changes in lipid and metabolic parameters.
- Weight increased significantly in all treatment groups with olanzapine>quetiapine>risperidone>aripiprazole.
 - Olanzapine and quetiapine were associated with significant increases in total cholesterol and triglycerides. Risperidone-treated individuals had a significant increase in triglycerides. Though weight gain was significant with aripiprazole there were no associated changes in metabolic parameters.
7. **Correll CU, Frederickson AM, Kane JM, et al. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics.** *Bipolar Disorders* 10:788-797, 2008
- Clinicians have wondered if patients with bipolar disorder have similar metabolic responses to second generation antipsychotics. This study compares the rates of metabolic syndrome between adult patients with bipolar disorder and those with schizophrenia. A retrospective chart review was conducted of 249 inpatients treated with SGAs at the time of admission. Complete family history, demographic information, physical examination and laboratory testing was obtained at admission. 75 patients had bipolar disorder, and 174 had schizophrenia. Of note, bipolar patients had a significantly lower BMI. Treatment with clozapine was more often prescribed to the schizophrenia group, and mood stabilizers to the bipolar group, especially lithium.
- Patients with bipolar disorder and schizophrenia who are treated with SGAs have similarly high rates of metabolic syndrome: 54% in each diagnostic group.
 - Low HDL cholesterol, high blood pressure, and elevated triglycerides were the most common elements of metabolic syndrome in this cohort.
 - The presence of metabolic syndrome was **not** associated with gender, or treatment with lithium or valproate.
 - These findings suggest a shared susceptibility to antipsychotic related metabolic dysregulation that is not primarily related to psychiatric conditions or concomitant mood stabilizer treatment.

Guidelines, Consensus Statements, Treatment Recommendations

1. **American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists: Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.** *Journal of Clinical Psychiatry* 65(2): 267-272, 2004 Also published in: *Diabetes Care* 27:596-601, 2004
- This consensus statement of physician stakeholder groups provides consensus opinion on current use of antipsychotics and prevalence of obesity, pre-diabetes, and diabetes in the SGA population; the relationship between SGAs and obesity and diabetes; and the monitoring of these problems.

- The prevalence of obesity, diabetes, and dyslipidemia differs depending on SGA.
- Clozapine and olanzapine are associated with the greatest weight gain and highest occurrence of diabetes and dyslipidemia. Risperidone and quetiapine have discrepant effects. Aripiprazole and ziprasidone have little or no significant weight gain, diabetes, or dyslipidemia.
- Appropriate monitoring for metabolic syndrome in people taking antipsychotic medication is outlined.

ADA/APA Monitoring Protocol for Clients on Second Generation Antipsychotics

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X					X	
Blood Pressure	X			X		X	
Fasting blood glucose	X			X		X	
Fasting lipid profile	X			X			X

CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Study

1. **Covell NH, Finnerty MT, Essock SM: Implications of CATIE for mental health services researchers. *Psychiatric Services* 59: 526-29, 2008**
 - The implications of CATIE for mental health services researchers are the need to monitor and change prescriber behavior to encourage informed medication selection.
 - The CATIE findings highlight the prevalence of cardiac and metabolic disorders among treatment populations and the potential impact of antipsychotics on these conditions.
 - Services researchers should use secondary data to monitor whether prescribers are providing appropriate screening and treatment.
2. **Meyer JM, Davis VG, Goff DC, et al: Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE schizophrenia trial: prospective data from phase I. *Schizophrenia Research* 101:272-286, 2008**
 - The CATIE results confirm differential metabolic effects between antipsychotics.
 - At three months, metabolic syndrome increased for olanzapine but decreased for ziprasidone. Olanzapine and quetiapine had the greatest increase in waist circumference, followed by risperidone. There was no change in waist circumference for ziprasidone, and there was a decrease with perphenazine.
 - Clinicians should monitor all metabolic parameters (waist circumference, HDL, serum triglycerides), during antipsychotic treatment.
3. **Daumit GL, Goff DC, Meyer JM et al: Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia Research* 105:175-187, 2008**
 This paper, from Phase 1 of the CATIE trial, followed 1125 patients randomized to different antipsychotics (perphenazine, risperidone, olanzapine, quetiapine; ziprasidone added in 2002) for 18 months or treatment discontinuation. The primary outcome was

the change in 10 year CHD risk using the Framingham Heart Study formula. Inputs to the equation include age, total and HDL cholesterol, blood pressure stage, presence of diabetes, presence of smoking. Results were stratified by race and gender.

- The impact on 10-year CHD risk differs significantly between antipsychotics after only a few months of exposure. In this cohort the differences between drugs is due principally to changes in total and HDL cholesterol.
 - Olanzapine produces the largest increase in CHD risk (0.5%, SE 0.3), followed by quetiapine (0.3%, SE 0.3).
 - Risk for females was 40% lower than for men, due to lower smoking rates and higher HDL.
 - There was a risk interaction between treatment and race. Perphenazine increased HDL in Caucasians and decreased in other races. Ziprasidone decreased HDL in non-whites significantly.
 - For consumers with >10% CHD risk, perphenazine, risperidone, and ziprasidone were beneficial.
4. **Nasrallah HA, Meyer JM, Goff DC, et al: Low rates of treatment for hypertension, dyslipidemia, and diabetes in schizophrenia: data from CATIE.** *Schizophrenia Research* 86:15-22, 2006
- At baseline, rates of nontreatment for diabetes, hypertension and dyslipidemia were 30.2%, 62.4%, and 88.0%, respectively.
 - There is a high likelihood that metabolic disorders are not treated in patients with schizophrenia, especially hypertension and dyslipidemia.
 - Nonwhite women may be especially vulnerable to undertreatment of dyslipidemia and diabetes compared to nonwhite men.
5. **Lieberman JA, Stroup TS, McEvoy JP, et al (CATIE investigators): Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.** *The New England Journal of Medicine* 353(12):1209-23, 2005
- Olanzapine was most effective, in terms of rates of discontinuation.
 - The efficacy of perphenazine appeared similar to quetiapine, risperidone, and ziprasidone.
 - Olanzapine was associated with greater weight gain and increase in measures of glucose and lipid metabolism.
6. **McEvoy JP, Meyer JM, Goff D, et al: Prevention of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III.** *Schizophrenia Research* 80:19-32, 2005
- Metabolic syndrome is highly prevalent in US schizophrenia patients and represents an enormous source of cardiometabolic risk, especially for women.
 - Clinical attention needs to be given to monitoring for metabolic syndrome and minimizing metabolic risks associated with antipsychotic treatment.
 - In a logistic regression model using age, race and ethnicity as covariates, CATIE males were 138% more likely to have metabolic syndrome than the NHANES matched control. CATIE women were 251% more likely to have metabolic syndrome than NHANES counterparts.
 - Controlling for BMI in the logistic regression model, males were still 85% more likely and females were 137% more likely to have metabolic syndrome than NHANES counterparts.

TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders)

1. **Sikich L, Frazier JA, McClellan J, et al: Double-blind comparison of first- and second- generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study.** *American Journal of Psychiatry In Advance* 1-13, Sept. 15, 2008
 - Risperidone and olanzapine did not demonstrate superior efficacy over molindone for treating early onset schizophrenia and schizoaffective disorder.
 - Adverse effects were frequent and differed among antipsychotics.
 - Olanzapine and risperidone were associated with significantly greater weight gain.
 - Olanzapine showed the greatest risk of weight gain and significant increases in fasting cholesterol, low density lipoprotein, insulin, and liver transaminase levels.
 - These results challenge the nearly exclusive use of SGAs to treat early onset schizophrenia and schizoaffective disorder.

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