Chapter 3. Quality Concerns in Psychotropic Prescribing:
Reducing Use of Antipsychotics with High or Moderate Risk of Metabolic Side Effects in Individuals with Cardiometabolic Risk Factors
Quality Concerns in Psychotropic Prescribing

Introduction

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. With input from the PSYCKES Stakeholder Advisory Committee of consumers, families, providers, and government agencies, OMH identified two initial sets of quality concerns focused on polypharmacy and cardiometabolic risk. Two additional sets of quality concerns focused on dose and on youth have been selected as options for clinics beginning Phase II of the PSYCKES-CQI Initiative. This chapter of the Handbook provides information on each quality domain, including an overview of the evidence base and definitions of each indicator set.

Recommendations for QI Teams Working to Improve Psychotropic Prescribing

1. **Consult with prescribers** individually or as a group to determine what additional supports they believe would be helpful to clients and their families during medication changes. Additional clinical support is likely to reduce anxiety and provide a better safety net for symptom monitoring and management.

2. **Provide prescribers with indicator descriptions** and scientific summaries, and encourage them to contact your agency CQI team or PSYCKES-Help with any questions or concerns. **Ask prescribers** periodically what you can do to help facilitate their contribution to the QI project.

3. **Track barriers** to medication change and engage therapists and other clinicians in developing nonpharmacologic therapy and supports which address common barriers. For example, consider supporting therapist training in CBT for insomnia, or develop anger management groups.

4. In addition to psychotherapy, **psychosocial interventions** including nurse appointments, medication groups, and peer supports can be instrumental in assisting client in reducing their medication burden. These strategies may also improve the comfort level of prescribers in the process.

5. **Communicate back to prescribers** about success stories. Collect and share stories about clients who were successful in changing medications with the clinical staff.

OMH continues to develop clinical and other resources to support clinics in implementing the CQI project, including summaries of scientific articles, web-based training and Continuing Medical Education modules, and consultation opportunities with adult and child psychiatrists. For more information about these resources, or to suggest additional supports that would be helpful, please visit the PSYCKES-Medicaid website at [www.psyckes.org](http://www.psyckes.org) or e-mail the PSYCKES team at PSYCKES-Help@omh.state.ny.us.
Quality Concern: Reducing the Use of Antipsychotics with High or Moderate Risk of Metabolic Side Effects in Individuals with Cardiometabolic Risk Factors

- **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:** olanzapine (Zyprexa), quetiapine (Seroquel), chlorpromazine (Thorazine), thioridazine (Mellaril)

<table>
<thead>
<tr>
<th>PSYCKES Cardiometabolic Risk Indicators</th>
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<tr>
<td>Hypertension [HTN]</td>
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<tr>
<td>Cardiovascular Disease [CVD]</td>
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<td>Hyperlipidemia [HL]</td>
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<td>Diabetes/Pre-diabetes [DM]</td>
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<tr>
<td>Obesity [Obes]</td>
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<tr>
<td>Cardiometabolic summary</td>
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Scope of the Problem

The PSYCKES Cardiometabolic Risk project 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*

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

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
<th>Low Risk</th>
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<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Quetiapine (Seroquel) Chlorpromazine (Thorazine) Thioridazine (Mellaril)</td>
<td>Aripiprazole (Abilify) Paliperidone (Invega) Risperidone (Risperdal) Ziprasidone (Geodon) All first-generation (conventional) antipsychotics except chlorpromazine (Thorazine) and thioridazine (Mellaril)</td>
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</table>

*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**

<table>
<thead>
<tr>
<th>Highest Risk</th>
<th>Higher Risk</th>
<th>Moderate Risk</th>
<th>Lower Risk</th>
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<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Quetiapine (Seroquel) Paliperidone (Invega) Risperidone (Risperdal)</td>
<td>All first-generation (conventional) antipsychotic medications except molindone (Moban)+</td>
<td>Aripiprazole (Abilify) Molindone (Moban)+ Ziprasidone (Geodon)</td>
</tr>
</tbody>
</table>

*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 (www.psyckes.com) under the Education and Training tab provide more in-depth information and critical review of important scientific articles.


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, and 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.


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 ≥7% of body weight. Factors associated with more weight gain: younger patients, more negative symptoms.
4. 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, and 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.

3. 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.


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

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<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
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<th>Quarterly</th>
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<tr>
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<td>Fasting blood glucose</td>
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Association of medications with cardiac risk factors and metabolic syndrome is not limited to antipsychotics. Evidence has been emerging over the past 3 years linking these side effects with treatment for anxiety and mood disorders in addition to psychotic disorders. Antidepressant medications have been known to affect glucose regulation. This case-control study done in the U.K. used a cohort of 165,000 patients at least 30 years old who received at least one prescription for an antidepressant and did not have diabetes. 2,432 cases of diabetes were identified and were matched with 8,963 controls.

- Recent use of moderate- or high-dose antidepressants was associated with an 84% increased risk for developing diabetes. (The risk of DM in people with depression is 35%). Moderate/high dose was defined as equivalents to 20 mg of fluoxetine (Prozac).
- Shorter duration of use (less than 1 year) and very low dosing was not associated with the development of diabetes.
- The risk was the same for SSRIs and TCAs.
- For individual drugs, increased risk was observed for amitriptyline, fluvoxamine, paroxetine, and venlafaxine. The number of subjects for fluvoxamine and venlafaxine was small.


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.


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.


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.

References
