Prolactin-Related and Metabolic Adverse Effects of Atypical Antipsychotic Agents

David C. Henderson, M.D., and P. Murali Doraiswamy, M.D.

While there are many effective antipsychotics available to clinicians for treating schizophrenia or bipolar mania, the onset of antipsychotic-associated prolactin-related and metabolic adverse effects can diminish the effectiveness of treatment. Increased levels of prolactin (hyperprolactinemia) associated with some antipsychotics raises the risk of sexual side effects. The increased appetite and/or sedation (reduced activity levels) induced by other antipsychotics can lead to weight gain, dyslipidemia, and high blood pressure and, if unchecked, ultimately to cardiovascular disease, diabetes, and metabolic syndrome. Clinicians should take steps to help their patients avoid unnecessary risks associated with antipsychotic use. These steps include monitoring risk factors for developing these illnesses by taking careful patient histories and baseline measurements of patients' weight and blood chemistry. Patients should be made aware of potential metabolic and prolactin-related side effects, and periodic checks should also be made to watch for changes in weight, body mass index, waist size, blood pressure, fasting glucose, or lipid levels that could be harmful and may increase risk for cardiovascular disease.
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Despite the availability of many options for treating schizophrenia or bipolar disorder, the onset of prolactin-related or metabolic adverse effects can diminish the effectiveness of treatment. Second-generation antipsychotics differ in their propensity for causing hyperprolactinemia and metabolic disturbances, such as increased weight gain, increased lipid levels, or high blood sugar. Such differences may translate into differential risks for cardiovascular disease, diabetes, metabolic syndrome, osteopenia, and other adverse outcomes. Because of the uncertain long-term consequences and reported severity of some of these effects, clinicians should be prudent in both initial drug selection and ongoing monitoring for both metabolic and hormonal consequences, which will help prevent or minimize the risks for adverse events and enhance the long-term effectiveness.

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HYPERPROLACTINEMIA

Prolactin, a pituitary hormone usually associated with breast development and lactation after pregnancy, has become an important topic, not only in psychiatry but also in the fields of breast cancer, osteopenia, and platelet aggregation. Most antipsychotics inhibit the release of dopamine from the dopamine-2 (D_2) receptor, and a side effect of this D_2 receptor antagonism is the increased release of prolactin, which is usually inhibited by dopamine. This subsequent rise of prolactin in the blood can in some cases lead to symptoms of hyperprolactinemia, which include gynecomastia, galactorrhea, sexual dysfunction, infertility, oligomenorrhea, and amenorrhea.[1] Although in other cases a high prolactin level may not cause any clinically detectable symptoms,[2] researchers are investigating potential long-term consequences of hyperprolactinemia such as osteopenia and cancer risk.

Pharmacologic Causes of Hyperprolactinemia

Pharmacologic compounds that target the hypothalamic dopamine system or pituitary dopamine receptors can be associated with elevated prolactin levels, including dopamine receptor antagonists, dopamine-depleting agents, antidepressants, and some hormones. Conventional antipsychotics and some atypical antipsychotics are potent D_2 blockers and hence termed *prolactin-raising-agents*; other atypical antipsychotics have low D_2 potency or are partial

TAKE-HOME POINTS

Clinical Management of Prolactin Side Effects

- Counsel patients about all of the potential adverse effects associated with hyperprolactinemia, including sexual side effects and potential risk for cancer
- Monitor for prolactin-related symptoms, such as menstrual or breast changes; if using potent dopamine-2 (D_2) blockers, consider a magnetic resonance imaging (MRI) scan if prolactin levels are very high or pituitary symptoms emerge (such as headache or blurred/double vision)
- Consider adjusting medication dosage or switch to a prolactin-sparing medication
- Consider breast examinations for women
- Partial agonists or low D_2-affinity agents are least likely to cause persistent prolactin elevation; partial agonists may even lower prolactin levels

Clinical Management of Metabolic Side Effects

- Routinely consider the health consequences of antipsychotic treatment as part of clinical practice
- Monitor weight, waist, blood pressure, and fasting glucose and lipids
- Try to prevent side effects or, if not possible, detect side effects early and intervene to prevent side effects from becoming problematic
- Lower the threshold for switching to other agents when patients begin experiencing side effects
- Aggressively intervene when side effects are present and refer patients to other medical specialists when necessary to address weight and metabolic issues
- Routinely discuss diet, nutrition, and exercise with patients

agonists, and prolactin elevations are rare with these latter agents.

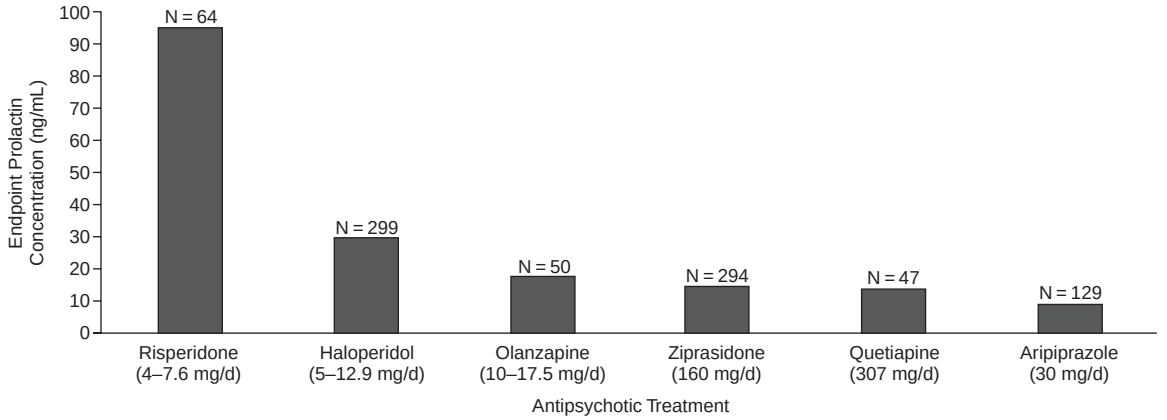
Specifically, amisulpride and risperidone are associated with substantially higher levels of prolactin in the blood compared with clozapine, olanzapine, ziprasidone, quetiapine, and aripiprazole.[1] Perkins[3] reviewed available direct and indirect comparisons and suggested that the level of risperidone-associated prolactin elevation was several times (even as much as 10 times) higher than that of aripiprazole-associated prolactin changes (Figure 1). Other studies have found that both risperidone[4,5] and amisulpride[4,6] increased prolactin levels in patients with schizophrenia or bipolar disorder, and some studies suggest that prolactin may be elevated in nearly 75% of patients taking potent D_2 blockers.[6] Women are more likely to be affected than men.[2,4] According to one study, the elevated prolactin resulting from risperidone use may be associated with 9-hydroxyrisperidone, an active metabolite of risperidone.[7,8] The 9-hydroxyrisperidone metabolite, currently marketed as the atypical antipsychotic paliperidone, is also associated with increased levels of prolactin.[9–12]

Diagnosing Hyperprolactinemia

Normal serum levels for prolactin are roughly 10 to 25 μg/L in women and 10 to 20 μg/L in men; for postpubertal women, the numbers are slightly higher. These levels peak during rapid eye movement (REM) sleep and at early morning. Levels rise after exercise, meals, sexual intercourse, and acute stress; pregnancy elevates prolactin. Thus, levels should be ideally measured under nonstressful conditions in the fasting state. Hyperprolactinemia (based on historical concern for a functional pituitary tumor) is usually denoted as levels > 100 μg/L, but there is wide variation. In addition to antipsychotics, a number of other triggers, such as hypothyroidism or oral contraceptives, can also cause hyperprolactinemia. Clinical symptoms of hyperprolactinemia have been noted to manifest even when prolactin values are lower, such as between 60 to 100 μg/L,[13] and the rapidity of change and degree of change are other factors that can influence symptomatology. For example, in one person whose baseline prolactin levels are 8 μg/L, a 5-fold increase to 40 μg/L following treatment may be sufficient to produce symptoms. Another person with a prolactin level of 80 μg/L may not report any symptoms. Thus, the relation between absolute prolactin levels and adverse effects can vary with genetic status and other factors not yet fully understood.[14]

Symptoms of hyperprolactinemia vary between women and men. Women may present with symptoms such as oligomenorrhea, amenorrhea, infertility, decreased libido, habitual abortion, and galactorrhea.[15] In men, symptoms include infertility associated with decreased sperm

Figure 1. Mean Plasma Prolactin Levels After 4 to 8 Weeks of Antipsychotic Treatment[a]



[a]Reprinted with permission from Perkins.[3]

production, galactorrhea, gynecomastia, decreased libido or potency, and reduced muscle mass.[15] With prolonged hyperprolactinemia, both women and men may develop osteopenia.[16] Additionally, there may be a relationship between sustained chronic hyperprolactinemia and increased risk for breast cancer,[17–21] endometrial cancer,[22,23] and increased platelet aggregation,[24,25] which might be a risk factor for cardiovascular disease. These relationships have not yet been proven in humans.

Because symptoms of hyperprolactinemia may be seen as personal, embarrassing, or sensitive, patients may not readily volunteer information. Further, patients may not associate symptoms of hyperprolactinemia with antipsychotic use. Some evidence suggests that less than a quarter of women may report galactorrhea.[15] The estimated prevalence of adverse events associated with antipsychotics can range widely depending on many factors (e.g., menstrual abnormalities have been reported in 15% to 90% of antipsychotic users[6]). While asking every patient about all potential side effects related to prolactin elevation may be impractical, it is good practice to educate all patients about such effects before starting therapy. The differential diagnosis of sexual side effects such as diminished libido must also consider the many other potential contributing factors that can exist in psychiatric patients. Although there is a relationship between elevated prolactin and the suppression of estrogen and testosterone,[26] clinicians may often consider negative symptoms, a mood disorder such as depression, or an adverse effect of selective serotonin reuptake inhibitor use as a contributing factor to a patient's diminished libido instead of considering an association with prolactin elevation.

While this review is primarily focused on adults, it should be noted that prolactin also affects pubertal maturation in adolescents. Hyperprolactinemia associated with D_2 blockers could inhibit gonadal function, which in theory may slow growth or sexual development. Likewise, it should also be noted that dopamine agonists can suppress prolactin levels. It is reassuring that a pooled analysis of 5 studies of 700 children (aged 5 to 15 years) treated with risperidone for about 1 year found no adverse effects on growth.[27] But this issue is under further study and longer follow up may be needed for conclusive answers.

Managing Hyperprolactinemia

Case report 1. Ms. A, a 40-year-old woman with first-episode psychosis was treated with risperidone, citalopram, and topiramate. Six months later, she complained of galactorrhea, headaches, and seeing colored shapes. Her prolactin levels were elevated at 72 µg/L. The increased prolactin prompted an imaging study that showed a pituitary microadenoma. Her medications were tapered off, and she was switched to aripirazole, which was gradually raised to 30 mg daily. After 2 weeks, her galactorrhea had resolved, and after 1 month, her prolactin levels had dropped to 1.8 µg/L. At subsequent follow-up, her visual symptoms were reported to have resolved as well. The link between pituitary tumor and hyperprolactinemia is uncertain since a second imaging study was not done. But this case illustrates how judicious switching benefited one individual.[28]

Because switching medications can increase the risk of a flare-up of the underlying symptoms being treated, such as psychosis or bipolar disorder, clinicians must be extremely careful to weigh the decision to switch. Elevation of prolactin in one patient can have different effects than in another, such as when a tumor is present. Treatment choices or approaches will, therefore, differ. One approach could be to first lower the dose of risperidone and then monitor for a decrease in prolactin levels. However, if a symptomatic pituitary adenoma is present, such as one pressing on the optic chiasm, the tumor should be the

Table 1. Frequency of Adverse Event Reports by Antipsychotic[a]

Drug	Pituitary Tumor[b]	Hyperprolactinemia[b]	Galactorrhea	Amenorrhea	Gynecomastia[b]	Total[c]
Risperidone	54	702	530	445	118	1247
Olanzapine	11	37	17	21	23	93
Haloperidol	9	32	49	24	28	104
Ziprasidone	6	12	13	2	4	30
Clozapine	4	15	16	17	7	46
Quetiapine	1	13	12	3	5	28
Aripiprazole	0	5	5	2	4	16
Total[c]	77	796	630	503	186	1530

[a]Reprinted with permission from Szarfman et al.[29]
[b]Adverse events were studied by combining several event codes.
[c]Totals are not the sum of the preceding columns or rows; a single report may mention > 1 event and/or > 1 antipsychotic drug.

primary concern. It is possible that high potency D_2 blockers, such as risperidone, exacerbate undetected benign pituitary adenomas.

Few antipsychotics are associated with conditions related to increased prolactin, such as pituitary adenomas, hyperprolactinemia, galactorrhea, amenorrhea, and gynecomastia. Risperidone, however, appeared to have an increased association with all 5 of these conditions in a retrospective pharmacovigilance study of prolactin-associated adverse events (Table 1) conducted by Szarfman et al.[29] This study analyzed data from the Adverse Event Reporting System database at the U.S. Food and Drug Administration (FDA), which contains reports submitted by consumers, doctors, hospitals, and pharmaceutical companies. A data-mining algorithm was used to calculate adjusted observed-expected ratios of drug-adverse event associations with haloperidol and the atypical antipsychotics risperidone, olanzapine, ziprasidone, clozapine, quetiapine, and aripiprazole. Risperidone was found to have the greatest association with the development of pituitary tumors compared with the other antipsychotics studied; of the 77 tumor reports associated with antipsychotic use, 54 were associated with risperidone use. Szarfman et al.[29] also found a correlation between the potency with which a drug can elevate prolactin levels and the drug's propensity for being associated with pituitary tumors. For risperidone use, there was almost a 20-fold greater association with pituitary tumors than would have been predicted.

Risperidone also had an increased association with other prolactin-related conditions when compared with other antipsychotics.[29] Of 796 total reports of hyperprolactinemia, risperidone was associated with 702 reports; of 630 total reports of galactorrhea, risperidone was associated with 530 reports; of 503 total reports of amenorrhea, risperidone was associated with 445 reports; and of 186 total reports of gynecomastia, risperidone was associated with 118 reports. Out of a combined total of 1530 reports of these adverse events, risperidone was associated with 1247 reports. By comparison, olanzapine was only associated with 93 reports, haloperidol with 104 reports, ziprasidone with 30 reports, clozapine with 46 reports, quetiapine with 28 reports, and aripiprazole with 16 reports.

Some caveats must be made about the study's findings.[29] First, the above numbers may underestimate actual events associated with antipsychotic use. Because the FDA data are based on voluntarily submitted adverse event report forms, only a small fraction of nonserious events that ever occur in the community are reported. To get more accurate data, a prospective trial would be needed. Second, there are reporting and detection biases. An example of a reporting bias is that fewer side effects may be reported for haloperidol since doctors in general tend to report fewer side effects for older drugs. Additionally, haloperidol was launched many years prior to the introduction of the term *pituitary tumor* in this database. Detection bias can occur if patients given one drug are more likely to receive magnetic resonance imaging (MRI) scans than patients given other antipsychotics and incidental tumors are incorrectly linked to the drug. Publicity, such as newspaper stories or journal articles, can lead to increased reporting. Case reports tend to be heterogeneous and the term *pituitary tumor* includes a range of conditions from benign hyperplasia to functional adenomas and large tumors causing optic compression. Further, differences in prescription volume, patient populations, or comorbid conditions can also lead to reporting and detection biases. On the other hand, the main strength of spontaneous reporting is that it may provide early signals for events that have been missed in short-term clinical trials and have become more apparent once the drug is used in real world settings.

Thus, the findings from Szarfman et al.[29] must be interpreted in this context, and the strength of the association between risperidone and hyperprolactinemia is consistent with other studies. In this database, high tumor numbers were not seen with other drugs used to treat conditions such as brain tumors or multiple sclerosis for which patients routinely get brain MRI scans. Of all 4000 drugs in the database, risperidone had the second highest association with pituitary tumors, after growth hormone.

Additionally, one study[30] has shown that a dopamine agonist can shrink pituitary tumors, so it is possible to hypothesize that a potent dopamine antagonist could cause or enlarge pituitary tumors. Nevertheless, because database analysis is retrospective and cannot prove causality, prospective clinical trials are needed.

Clinicians should take steps to help their patients avoid and manage the risks associated with antipsychotic use and hyperprolactinemia. To help patients avoid hyperprolactinemia, clinicians should recognize that some antipsychotics they prescribe are potent D_2 blockers and are more likely to elevate prolactin than other antipsychotics. But if a dopamine antagonist is needed to treat a patient, clinicians can take several steps to avoid or minimize the potential adverse effects of the treatment.[13] First, clinicians need to educate their patients about the risks associated with the drug and about potential side effects that patients should watch for. Additionally, clinicians should be on the lookout for clinically significant adverse effects, and if adverse effects are present, a determination should be made as to whether they are of sufficient magnitude or chronicity to raise other health concerns, such as osteoporosis. Lastly, clinicians can consider monitoring the prolactin levels of their patients, starting with a baseline measurement upon treatment initiation. If prolactin levels and/or side effects become unacceptably high, clinicians should reassess treatment risks and benefits and consider options such as reducing the dosage of the antipsychotic or switching to a prolactin-sparing atypical antipsychotic.[31] An MRI scan should be considered if a pituitary adenoma is suspected. In some cases, this decision may even include endocrine consultation and possibly giving the patient a prolactin-lowering dopamine agonist,[32] such as bromocriptine. This is a decision that must be based on clinical judgment. A recent study[33] examined 55 patients with haloperidol-associated hyperprolactinemia and found that the addition of aripiprazole (up to 30 mg/day) normalized 88.5% of patients at week 8 compared to 3.6% of patients receiving placebo. The effect was seen in both sexes. In this study, 7 of 11 women with menstrual problems regained menstruation with the addition of aripiprazole.

WEIGHT GAIN AND METABOLIC EFFECTS

Antipsychotic use has long been associated with some weight gain, which was first reported as an effect of conventional agents, such as chlorpromazine,[34] and has subsequently been observed for atypical antipsychotic agents in variable degrees.[35] Some antipsychotic agents, such as low-potency phenothiazines[34] and the atypical antipsychotics clozapine[35,36] and olanzapine,[35,36] can induce significant weight gain. Substantial weight gain can lead to obesity and a subsequent elevation of cholesterol and glucose levels, which increases the risk for several health problems,[37,38] such as cardiovascular disease, stroke, type 2 diabetes, and peripheral vascular disease, and even some cancers such as breast, prostate, and colon cancer.

Diagnosing Weight Gain and Metabolic Effects

Clinicians can begin by being aware of their patients' potential risks for developing illnesses by taking careful patient personal and family histories and by taking baseline measurements of their patients' weight and blood chemistry. Periodic checks should be made to monitor changes in weight, body mass index (BMI), waist size, or fasting glucose and lipid levels that are potentially harmful and can lead to serious health problems.[38]

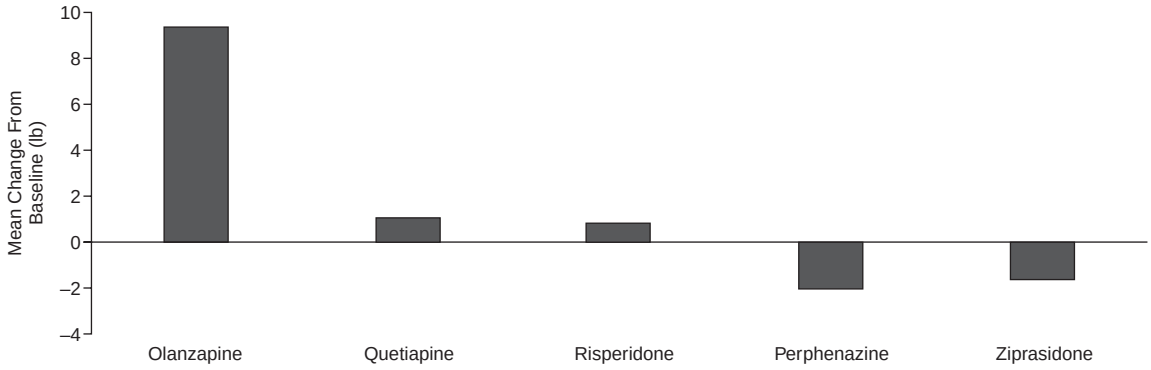
> ***Case report 2.*** Ms. B is a 27-year-old African American woman with a history of chronic schizophrenia and poor medication compliance; she had stopped taking her medication. She presented with psychotic symptoms including hallucinations, paranoia, and delusions, as well as poor insight and poor judgment. She has a family history of type 2 diabetes and smokes 1 pack of cigarettes per day. Her baseline data showed slightly elevated blood pressure (130/90 mm Hg), a BMI of 27, and a waist measurement of 33 inches. Her total cholesterol was 180 mg/dL, her fasting triglycerides were 141 mg/dL, her high-density lipoprotein (HDL) was 47 mg/dL, her low-density lipoprotein (LDL) was 111 mg/dL, and her fasting glucose was at 93 mg/dL.
>
> Ms. B responded well to antipsychotic treatment but gained 20 lb over a 10-week period, which resulted in an increased BMI of 31 and a waist measurement of 36 inches. Her blood pressure increased to 140/95 mm Hg, her total cholesterol increased to 190 mg/dL, her fasting triglycerides increased to 199 mg/dL, her HDL lowered to 42 mg/dL, her LDL increased to 121 mg/dL, and her fasting glucose increased to 98 mg/dL.

Managing Weight Gain

Patients should be screened at the beginning of treatment to check for risk factors such as a family history of obesity, cardiovascular disease, or diabetes. If risk factors are present, then these patients should be educated about diet, nutrition, and exercise, and monitored carefully during treatment. Pharmacologic agents chosen at the start of treatment should be selected with the prevention of weight gain in mind. Some drugs can increase appetite, which can increase food intake, while at the same time causing a sedating effect; patients given those drugs will subsequently decrease their level of activity and energy expenditure while increasing their food intake, creating a perfect setting for weight gain. Because it is easier to prevent weight gain than to reverse it, patients given weight-inducing drugs need to be extra watchful of eating a reasonable amount and maintaining a healthy level of activity.

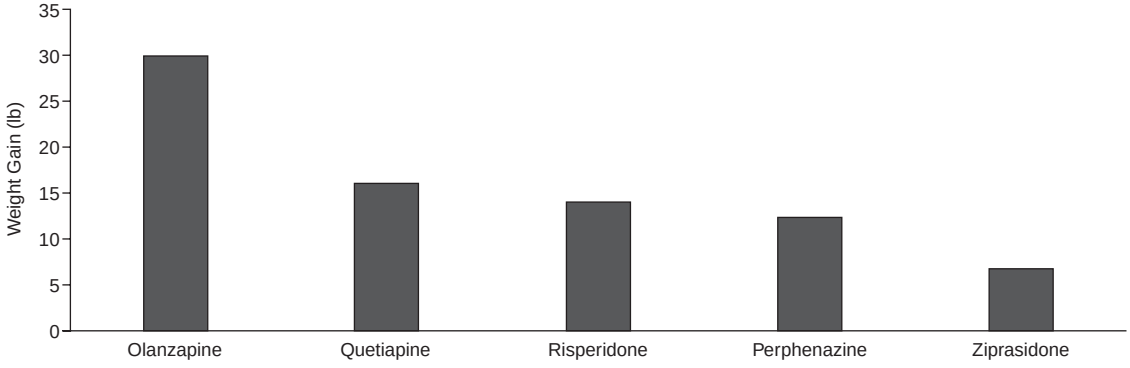
A patient can gain weight but still have a good clinical response to antipsychotic treatment. Regardless of response, clinicians should intervene if weight gain appears to be a developing problem. If the initial treatment be-

Figure 2. CATIE Results: Mean Weight Change From Baseline[a]



[a]Data from Lieberman et al.[43] $p < .001$.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Figure 3. CATIE Results: Mean Weight Gain per Month of Treatment[a]



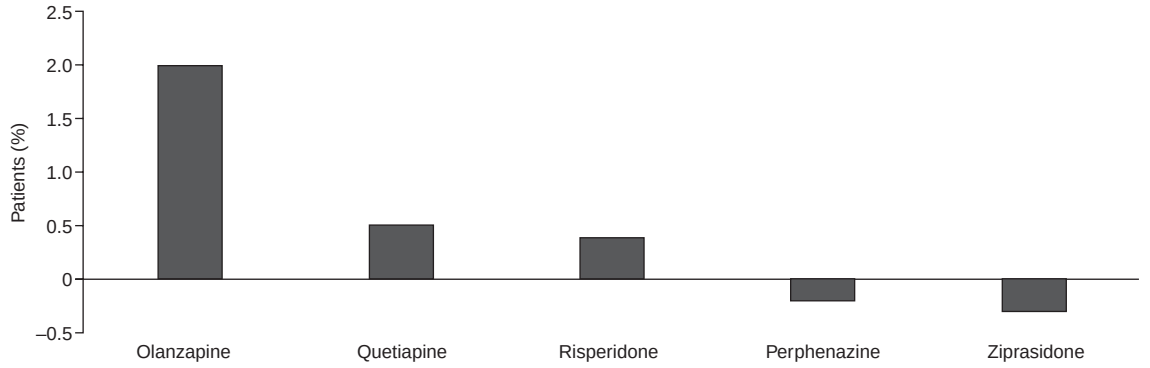
[a]Data from Lieberman et al.[43] $p < .001$.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

comes problematic, the patient can be switched to a different agent so that the patient might lose weight.[31,39] For patients who have trouble losing weight, some drugs that have a modest effect on weight include sibutramine,[40] orlistat,[40] amantadine,[41] topiramate,[35] bupropion,[42] and antihistaminic agents.[35] The risk-benefit ratio of these putative weight loss agents is not well established for this use in this setting and so clinical judgment should guide treatment choice.

Findings of weight gain in the CATIE trial. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[43] was a multisite, double-blind study conducted by the National Institute of Mental Health. This trial compared the atypical antipsychotic agents olanzapine, quetiapine, risperidone, and ziprasidone with each other and with perphenazine, a conventional neuroleptic. The trials have provided important data on metabolic side effects associated with antipsychotic use. Aripiprazole and paliperidone were not approved for use in the United States when the CATIE trial was initiated, and ziprasidone was approved after the trial had begun.

The trial[43] data highlighted the differences in both the mean weight change from baseline and the percentage of patients who gained 7% or more of their total body weight, which the FDA has set as a clinically relevant weight gain. Subjects who took olanzapine had a higher mean weight gain from baseline than subjects treated with the other drugs studied (Figure 2). Likewise, a greater percentage of patients (30%) gained 7% or more of their total weight with olanzapine than subjects treated with quetiapine, risperidone, perphenazine, or ziprasidone (Figure 3). The CATIE results also showed that when quetiapine doses were raised to efficacious levels, substantial weight gain and metabolic changes were produced, although quetiapine has not been widely thought to cause those problems. Any drug, however, that can cause sedation can lead to decreased activity and energy expenditure and increased weight. Olanzapine was found to lead other antipsychotics

Figure 4. CATIE Results: Mean Weight Gain ≥ 7%[a]



[a]Data from Lieberman et al.[43] $p < .001$.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

in weight gain per month by approximately 2 lb, followed by quetiapine and risperidone, which were both substantially lower (Figure 4). These findings showed that olanzapine had the greatest amount and the greatest rate of weight gain.

Trajectory of weight gain. Both long-term and short-term weight gain must be addressed; short-term weight gain should not be easily dismissed as a minor problem. Many patients may ignore short-term weight gain as a temporary problem that will go away. Two studies[44,45] continued to show that patients gained weight with olanzapine for up to 1 year, while weight with aripiprazole[46] and ziprasidone[47] treatment stayed relatively close to baseline, and quetiapine[48] and risperidone[49] showed slightly increasing rates of weight gain at 1 year. These data highlight the importance of addressing weight gain when it first occurs due to the potential for sustained weight gain and subsequent adverse effects to the patient's health.

Diagnosing Metabolic Syndrome

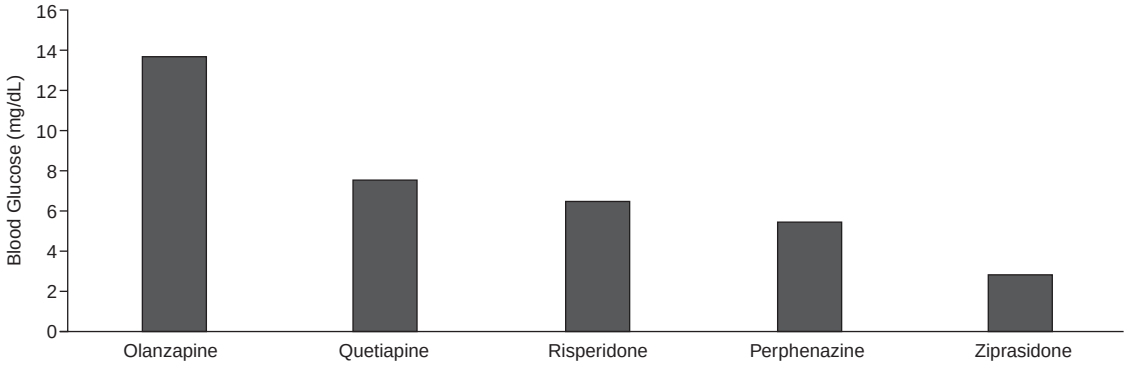
Weight gain is an important component of metabolic syndrome, which has received much attention as a predictor of cardiovascular disease, stroke, and type 2 diabetes. A diagnosis of metabolic syndrome is based on the presence of at least 3 of the following 5 components, which clinicians should track when prescribing antipsychotic medications that are prone to cause weight gain: abdominal obesity, high triglycerides, low HDL cholesterol, high blood pressure, and high fasting blood glucose.[50] First, men must have a waist circumference of more than 40 in. and women must have a waist circumference > 35 in. Second, triglyceride levels—not total cholesterol—must be ≥ 150 mg/dL. Third, HDL must be < 40 mg/dL in men and < 50 mg/dL in women. Fourth, blood pressure must be ≥ 130/85 mm Hg, and fifth, fasting blood glucose must be ≥ 100 mg/dL.

Although BMI can aid clinicians as they monitor the components of the metabolic syndrome, waist circumference is a better predictor of cardiovascular disease, stroke, and diabetes risk than BMI because BMI calculations can be affected by muscle mass. For example, an athletic individual or someone who goes to the gym every day could have increased BMI values due to increased muscle mass and not increased adiposity, which may be misleading. It is important to get accurate waist measurements in order to watch for abdominal adiposity. A combination of measures is probably the most accurate method for monitoring patients; therefore, taking weight and waist measurements and BMI can all be useful.

Findings of metabolic syndrome in the CATIE trial. Rates of metabolic syndrome based on the fasting values of a subsample of patients in the CATIE trial[43] were compared with data from the general population in the National Health and Nutrition Examination Survey (NHANES).[51] The results of that study[51] found not only that patients with schizophrenia had elevated rates of metabolic syndrome, but that each of the components of the metabolic syndrome was significantly elevated in comparison with that of the general population. In women with schizophrenia, some of the components used as criteria for assessing risk for metabolic syndrome were at higher levels than in men with schizophrenia (waist circumference, HDL cholesterol, and fasting blood glucose). Women also had a greater frequency of metabolic syndrome than men in both populations.[43,51]

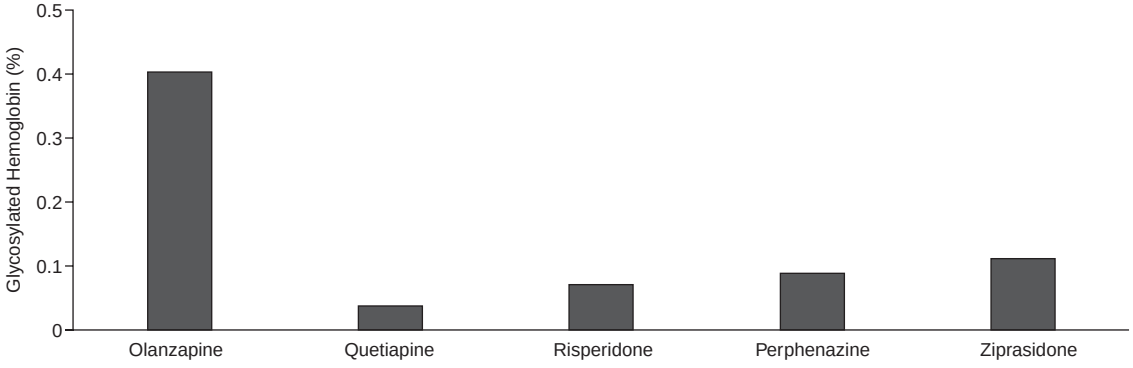
The CATIE trial[43] found significant changes in blood glucose and hemoglobin A_{1c} specific to certain antipsychotics. All of the antipsychotics showed an increase in glucose levels, with olanzapine having the highest increase, followed by quetiapine, risperidone, perphenazine, and ziprasidone (Figure 5). Likewise, olanzapine had a significantly higher percentage of glycosylated hemoglobin compared with the other antipsychotics (Figure 6). Elevated levels of cholesterol and triglycerides were found with olanzapine, quetiapine, and perphenazine, but

Figure 5. CATIE Results: Blood Glucose Exposure-Adjusted Mean Change From Baseline[a]



[a]Data from Lieberman et al.[43] p = .59.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Figure 6. CATIE Results: Glycosylated Hemoglobin Exposure-Adjusted Mean Change From Baseline[a]



[a]Data from Lieberman et al.[43] p = .01.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

these levels decreased with risperidone and ziprasidone (Figure 7).

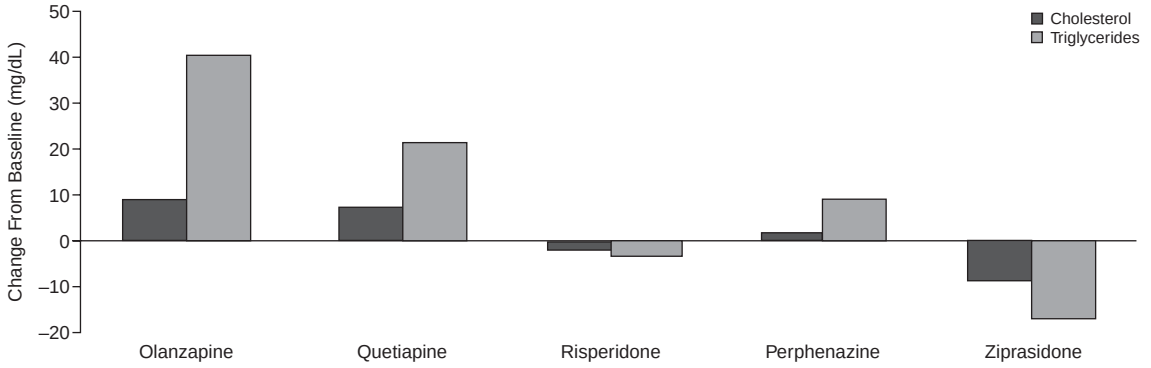
Post-CATIE antipsychotics. Even though aripiprazole was not included in the CATIE trial, another study[52] found that, after 26 weeks, aripiprazole was associated with a lower incidence of metabolic syndrome than olanzapine or placebo. A double-blind, 26-week comparison[53] of weight change with olanzapine and aripiprazole showed a 7% or greater increase in body weight in 37% of patients taking olanzapine and 14% of patients taking aripiprazole. The newest antipsychotic, paliperidone, has shown no significant changes in serum lipid or glucose levels but was associated with dose-related increases in body weight (< 2 kg) over 6 weeks.[10] Like risperidone, paliperidone also elevates prolactin levels.

Managing Metabolic Syndrome Components

Managing triglyceride levels is important because high triglyceride levels correlate more strongly with insulin resistance and metabolic syndrome than total cholesterol, and an elevation in triglyceride levels can also increase the risk for pancreatitis. Clinicians should monitor all 5 of the components of metabolic syndrome. Usually, increased weight will increase the risk for insulin resistance, but a study[54] of patients with schizophrenia given clozapine, olanzapine, or risperidone found that patients who were not obese may be at risk for insulin resistance. The patients did not gain a significant amount of weight; the mean BMI in the 3 groups was 25 kg/m^2. However, a frequently sampled intravenous glucose tolerance test found these patients, when given clozapine and olanzapine, had significantly higher levels of insulin resistance compared to risperidone-treated patients. This finding suggests that some factor other than obesity may drive insulin resistance.

The ADA Consensus Statement on Antipsychotic Drugs, Obesity, and Diabetes outlined by the American Diabetes Association (ADA), the American Psychiatric Association, the American Association of Clinical

Figure 7. CATIE Results: Cholesterol and Triglyceride Exposure-Adjusted Mean Change From Baseline[a]



[a]Data from Lieberman et al.[43] Value for both cholesterol and triglycerides was $p < .001$.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Table 2. Atypical Antipsychotics and Metabolic Abnormalities[a]

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Reprinted with permission from American Diabetes Association.[36]
[b]Newer drugs with limited long-term data.
Abbreviations: + = increase effect; – = no effect; D = discrepant results.

Endocrinologists, and the North American Association for the Study of Obesity emphasized the association between antipsychotics and diabetes, weight gain, and dyslipidemia (Table 2).[36] The consensus panel determined that the atypical antipsychotics olanzapine and clozapine were the most likely to be associated with weight gain, diabetes, and dyslipidemia compared with risperidone, quetiapine, aripiprazole, and ziprasidone. Even though the findings of the consensus statement are a few years old, most of the conclusions are accurate, although the risk of dyslipidemia and the need for monitoring may be slightly higher than it appeared then.[43]

The ADA consensus statement guidelines recommend that, at the start of treatment, baseline measurements of BMI, waist circumference, blood pressure, fasting glucose, and fasting lipid profiles be taken in addition to a detailed patient and family history to determine the patient's potential risk for developing cardiovascular disease, metabolic syndrome, or diabetes (Table 3).[36] Clinicians should then periodically recheck these measurements during treatment to make certain that the patient is not experiencing adverse effects from the treatment. If serious problems arise, a switch or aggressive medical interventions may be necessary.[31,39]

METABOLOMICS AND LIPIDOMICS

Metabolomics is a new field of study that is emerging as part of the *-omics* technology, which includes *genomics*, the study of genetics, and *proteomics*, the study of proteins. Metabolomics is the study of the small molecule metabolites that are broken down from the proteins that are produced by the gene. The development of metabolomics will be important for monitoring diseases because a substantially wider range of tests will be available for patients. Currently, clinicians perform a Chem-20 examination of the blood serum (which is a group of 20 chemical tests) using a finger prick as part of a physical examination. With metabolomics, clinicians may in the future be able to perform a Chem-3000 examination; with a single drop of blood, 3000 metabolites could be measured, which represents the global biochemistry of an individual at any given time.

Lipidomics is a subset of metabolomics in which approximately 300 different lipid fractions can be measured using fasting blood. Currently, clinicians might measure HDL, LDL, total cholesterol, and triglycerides, which give an incomplete picture of what is happening in an individual's body. With lipidomics, the entire lipid map of a person can be measured. Kaddurah-Daouk et al.[55] used metabolomics to study how the atypical antipsychotics olanzapine, risperidone, and aripiprazole affect lipid metabolism in patients with schizophrenia. Blood samples were taken from the patients before and after acute treatment over 2 to 3 weeks, and their lipid profiles were mapped. Heat maps generated from the tests showed differences in the individual lipid metabolites and which metabolites were modified by pharmacologic treatment. The study showed that olanzapine and risperidone affected nearly 50 different lipid fractions compared with aripiprazole, which showed relatively little effect on lipids.[55]

Table 3. ADA Monitoring Protocol for Patients Given Atypical Antipsychotics[a,b]

Clinical Parameter	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

[a]Reprinted with permission from American Diabetes Association.[36]
[b]More frequent assessments may be warranted based on clinical status.
Abbreviations: ADA = American Diabetes Association, BMI = body mass index.

CONCLUSION

Clinicians must routinely consider, work to prevent, and detect the health consequences of antipsychotic treatment. Patients should be counseled on nutrition, exercise, and potential adverse effects related to prolactin increases. Interventions to address serious side effects should be proactive, including referring patients to specialists if necessary or switching medication.

REVIEW QUESTIONS

If a patient who has been stabilized on antipsychotic treatment has a breast examination and galactorrhea is discovered, what step(s) should the clinician take?

If a patient who is taking an atypical antipsychotic with good efficacy presents with a 10-lb weight gain over a 4-week period, what step(s) should the clinician take?

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), metformin (Riomet, Fortamet, and others), olanzapine (Zyprexa), orlistat (Xenical), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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Questions and Answers

Question: Prolactin levels can become elevated with risperidone. What does this mean for clinical practice, and does this apply to paliperidone extended release (ER) as well?

Dr. Doraiswamy: It does apply to paliperidone ER and will potentially apply to long-acting versions of both drugs; anything that the short-acting version can do, the long-acting version will also do. When starting risperidone treatment, make sure to screen patients for pituitary tumors by history or examination. If a pituitary tumor is suspected, then risperidone is probably not a good drug to start treatment with. Always educate patients. If a patient on risperidone treatment experiences prolactin-related side effects, check the patient's prolactin level. If the prolactin level is quite high, reassess risk-benefit.

Question: Would you suggest getting a baseline prolactin level before starting treatment? Also, how do you screen for pituitary adenoma?

Dr. Doraiswamy: Getting a baseline prolactin level would be great for patients going to a research clinic, but many patients visiting mental health centers probably cannot afford it. I would counsel those patients about potential sexual side effects. You can give patients a list of various prolactin-related side effects that they can refer to at each return visit to the clinic. If they have new-onset or worsening symptoms, then check the patient's prolactin level. The definitive way to check for a pituitary adenoma is with a contrast-enhanced MRI. A functional adenoma can also be detected with a positron emission tomographic (PET) scan. Patients should talk to an endocrinologist if an adenoma is suspected.

Question: Some patients gain weight and some do not, and some patients develop metabolic syndrome independent of weight gain. How do I detect these problems in clinical practice?

Dr. Henderson: Metabolic changes in the patient may not be readily apparent, which is why clinicians need to monitor for medical conditions. Patients who experience obvious weight gain are more likely to receive blood tests than patients whose weight might look good on a scale but who are gathering fat in their abdomen. In these patients, a waist measurement is needed using a measuring tape. These patients may be skinny but have a belly, which may indicate insulin resistance, an elevation in the lipids, and eventually an increased risk for diabetes and cardiovascular disease. They may currently have ß-cell function and seemingly normal glucose levels, but eventually, ß-cell functioning may decline and glucose levels increase.

Question: How can clinicians manage metabolic issues and sedation with atypical antipsychotic use, and how should clinicians select the most appropriate treatment for long-term maintenance therapy?

Dr. Doraiswamy: Dealing with issues like these is a risk-benefit judgment call. Use treatments that have worked for patients in the past. If the drug that has benefited the patient is olanzapine, use it but carefully monitor the patient for potential metabolic problems. Otherwise, use an agent with a lower risk for metabolic problems.

Question: Why are some atypical antipsychotics associated with prolactinemic effects while others are not? Is it because risperidone is lipophilic or in the case of aripiprazole, does it have to do with the partial dopamine agonism? Perhaps the differences are related to the relative blockade of serotonin transporter versus dopamine transporter?

Dr. Doraiswamy: Pharmacologic differences play a big role, although there could be other differences as well. Risperidone is a potent D_2 blocker and aripiprazole is a partial agonist. There may be differences in the blood-brain penetrability, but these differences are not yet fully established.

Question: Do selective serotonin reuptake inhibitor agents elevate prolactin levels and increase the risk for breast cancer, particularly among individuals with a history of breast cancer?

Dr. Doraiswamy: The simple answer is that we do not know. More research is needed before definitive conclusions can be made. Presently, I would not suggest that anyone avoid certain drugs, but if a patient is concerned about an increased risk for breast cancer, then ask the patient to undergo more self-exams. Also, it is good to get the patient's family history of cancer.

Question: Can the antidiabetic drug metformin be used to prevent weight gain or treat weight gain that has already occurred with atypical antipsychotic use?

Dr. Henderson: This question is based on a couple of small studies[56,57] of adolescents that found that adjunctive metformin with olanzapine reduced weight but did not completely eliminate weight gain. It certainly improves glucose metabolism, but whether or not it will reduce long-term weight gain is not entirely clear. But because metformin is indicated for the treatment of type 2 diabetes, I think adding it is dangerous. Patients may actually have diabetes without knowing it, and, when they are taken off metformin, then they can have problems. So I would not recommend metformin as a clinical treatment. Instead, I recommend diet, exercise, and switching to other agents as the best methods for avoiding and managing weight gain.

Question: What is the nature of insulin resistance? Is it a change in structure or a change at the membrane level? Is it intracellular or immunologic?

Dr. Henderson: Some drugs cause peripheral insulin resistance in the muscle and or hepatic insulin resistance in the liver. But whether the resistance is caused by blocking something in the periphery (such as glucose transporters) or whether it is a central mechanism from certain receptors in the brain is not known.