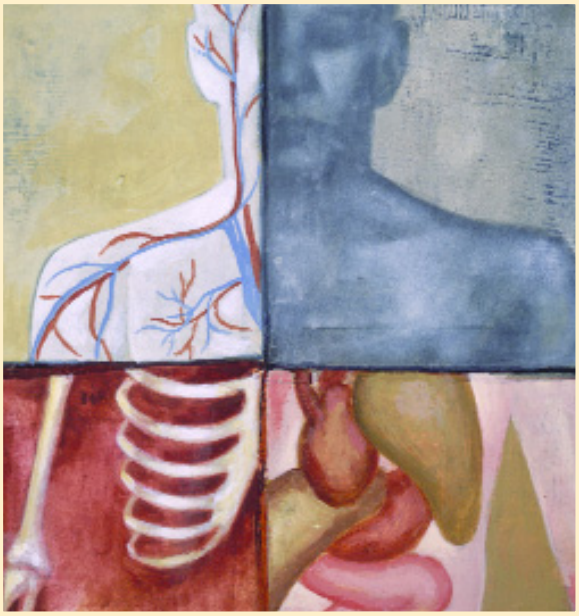
Current PSYCHIATRY

UPDATE ON ATYPICALS

Practical tips to manage common side effects

Using these agents to their greatest advantage requires careful clinical monitoring to prevent their potential disadvantages.



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Atypical antipsychotics are powerful medications for acute and chronic psychotic disorders, with a similarly powerful potential for adverse systemic effects. To use these agents to their greatest advantage, we must balance the benefits against the risks.

We often see patients with weight gain, diabetes, dyslipidemia, cardiac toxicity, hyperprolactinemia, and sexual dysfunction—all possible effects of atypical antipsychotics. Based on the latest evidence and our experience, we offer tips for using clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, and preliminary impressions about the newly approved agent, aripiprazole.

Weight gain

Clinical trials have shown convincingly that atypical antipsychotics pose a greater risk of weight gain and central adiposity than do most older antipsychotics.[1] Overweight

Table 1

POTENTIAL FOR ADVERSE EFFECTS WITH ATYPICAL ANTIPSYCHOTICS

	Metabolic changes	Weight gain	Increased prolactin	QT interval	EPS	Sedation	Orthostasis
Risperidone	+	+	+++	+	++	+	++
Ziprasidone	+	+	–	++	+	+	+
Clozapine	+++	+++	–	++	+/-	+++	+++
Olanzapine	+++	+++	–	+	+	++	+
Quetiapine	++	++	–	++	+	++	++
Aripiprazole	+	+	–	+	+	+/-	+/-

and obesity are associated with increased risks of hypertension, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, and some forms of cancer. Moreover, obesity's socially stigmatizing effect can discourage patients with schizophrenia—particularly adolescents—from taking their medication.

Comparative effects. Olanzapine and clozapine are associated with greater weight gain (*Table 1*)[1-3] than risperidone and ziprasidone.[4] Data regarding quetiapine are inconsistent—some studies show weight gain similar to that caused by olanzapine, and others find much less.[5] Weight gain associated with quetiapine, ziprasidone, and risperidone tends to plateau within the first few months, whereas patients taking olanzapine and clozapine may continue to gain weight for 9 months or more.[6]

Adolescents and young adults may be particularly susceptible to antipsychotic-induced weight gain.[7] No studies have directly compared weight gain in adults versus adolescents, but adolescents are exceedingly susceptible to the atypicals' metabolic dysregulation. For example:

- A higher prevalence of extreme weight gain (>7% of baseline body mass) with olanzapine and risperidone has been reported in adolescent inpatients than among adults.[7]
- Extreme weight gain was seen in 78% of a group of risperidone-treated children; for 6 months, their weight gain averaged 1.2 kg/month without leveling off.[8]

These findings suggest that risperidone's apparent metabolic advantage in adults disappears in children and adolescents. Risperidone's effect on prolactin may account for a higher risk of weight gain in younger patients. These populations have exquisite end-organ sensitivity to changes in prolactin levels and may be more susceptible to the weight gain—and perhaps diabetes—believed related to hyperprolactinemia.[9]

Mechanisms. The mechanism(s) of weight gain may be related to the receptor systems upon which the atypicals act. These agents block noradrenergic, dopamine, serotonin, and histamine receptors, all of which are thought to affect metabolism or appetite control. Stimulation of alpha and D2 receptors by sympathomimetic amines causes weight loss, as does stimulation of certain 5HT receptors by weight-loss drugs such as fenfluramine.[10] With respect to appetite, it has been suggested that peripheral antagonism of H1 receptors interferes with normal satiety signals.[11] This may explain why affinity to histamine H1 receptors is among the best of correlates with potential for weight gain.[12]

Increases in serum levels of leptin—a peptide hormone produced in direct proportion to adiposity and thought to be anorexigenic, possibly through effects on satiety[13]—parallel weight gain during treatment with atypicals. However, there is no indication that leptin imbalance causes weight gain; it may instead be the result. Altered sensitivity to leptin may be a contributing factor, perhaps at the hypothalamus.[14]

Diabetes

The risk of type 2 diabetes increases with weight gain,[15] so it is no surprise that diabetes is more prevalent among patients taking atypicals. In a study of 38,000 schizophrenic patients,

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those taking atypicals were 9% more likely to have diabetes than those receiving typical antipsychotics,[16] and all atypicals were associated with a significant increase in diabetes risk in patients younger than 40. The pervasiveness of diabetes[17] and reports of new-onset diabetes in non-overweight patients[18] suggest that—in addition to their effect on weight—atypicals may alter insulin and glucose metabolism.[19]

Atypical antipsychotics probably increase diabetes risk in a number of ways:

- An increase in adipose tissue can lead to insulin resistance, glucose intolerance, and ultimately diabetes.[20]
- Serotonin receptor antagonism may lead to hyperglycemia by decreasing pancreatic beta cell response to signals that advance insulin production.[21]
- Atypicals may contribute to hyperglycemia by impeding cellular uptake of glucose.[22]
- The increase in free fatty acids associated with atypicals can alter glucose metabolism. This may explain why clozapine and olanzapine—the atypicals with the greatest potential for severe hyperlipidemia—have the strongest association with new-onset diabetes.

Table 2

RECOMMENDED METABOLIC MONITORING OF PATIENTS TAKING ATYPICAL ANTIPSYCHOTICS

Every visit	Check weight Check blood pressure
Every 3 months	Fasting blood glucose Fasting triglycerides Fasting cholesterol

Hyperlipidemia

Case reports and controlled studies have linked atypical antipsychotics with hyperlipidemia. Whether the hyperlipidemia is a consequence of weight gain or some other metabolic disturbance is unknown. Even without conclusive data, however, the link is of concern because elevated triglyceride levels represent an independent risk factor for heart disease.[23]

Although all atypicals increase serum triglycerides to some degree, severe hypertriglyceridemia occurs predominantly with clozapine and olanzapine.[24] Both drugs have favorable efficacy profiles, and the mechanism of their antipsychotic activity may include altering the various lipid pools.

For example, studies have found that decreased triglyceride levels correlate with hostility and psychological distress.[25] Increased triglycerides have been theorized to enhance membrane fluidity, which in turn may augment presynaptic reuptake of serotonin and diminish postsynaptic serotonin activity.[26] In other words, elevated triglyceride levels could play a role in atypical antipsychotic-mediated inhibition of serotonin transmission. It is not yet known whether lipid-lowering drugs might alter atypicals' efficacy.

> Never sacrifice antipsychotic efficacy in pursuit of a regimen with more benign side effects

Metabolic monitoring

Managing mental illness concurrently with weight gain, diabetes, and hypertriglyceridemia is a challenge. In our clinic, we try to diminish the atypicals' adverse metabolic effects by monitoring a few basic parameters and taking preventive measures (*Table 2*).

We routinely screen patients for diabetes symptoms by asking questions about changes in belt size (a sign of weight change), urinary frequency, and thirst (*Table 3*). We also document baseline weight, blood glucose (*Table 4*), blood chemistry, and lipid levels, with routine follow-up throughout therapy and greatest scrutiny during the first months of a new treatment.

Patients who cannot control their weight with lifestyle modifications (*Table 5*) may require a lipid-lowering medication—a "statin" and/or fibrate (such as gemfibrozil)—or, if those measures are ineffective, a switch to another antipsychotic. Hyperlipidemia and hyperglycemia may be reduced substantially when patients discontinue the aggravating medication.[27]

Although discontinuing or switching medications may reduce metabolic side effects, the hazard of psychotic

Table 3

5 SCREENING QUESTIONS TO MONITOR FOR METABOLIC AND SEXUAL SIDE EFFECTS

1. Has your weight changed?
2. Has your belt or pants size changed?
3. Are you constantly thirsty?
4. Do you urinate frequently?
5. Are you having problems with sexual interest or function?

Table 4

DIAGNOSTIC CRITERIA FOR DIABETES

- Symptoms of diabetes (such as polyuria, polydipsia, or unexplained weight loss) plus nonfasting plasma glucose (PG) >200 mg/dL (11.1 mmol/L)

OR

- Fasting plasma glucose >126 mg/dL (7.0 mmol/L)

OR

- 2-hour PG >200 mg/dL during an oral glucose tolerance test

Source: American Diabetes Association

decompensation is substantial. Achieving an antipsychotic effect is extremely difficult for most patients, and one should not discontinue an effective treatment without seriously considering the consequences. Antipsychotic efficacy should never be sacrificed in the pursuit of a regimen with more benign side effects. Consider switching to an atypical with a more moderate effect on weight, however, if weight gain would likely lead to noncompliance. Even the most effective treatment will not work if a patient never takes it.

Cardiac toxicity

QTc prolongation. Atypical antipsychotics—like their typical counterparts—cause QTc prolongation to varying degrees. On an ECG, the QT interval corresponds to cardiac depolarization and repolarization phases. The QT interval—which changes naturally with the time of day, stressors, and heart rate—is commonly corrected for heart rate to yield QTc.[28] If QTc is prolonged beyond a certain threshold, repolarization can occur simultaneously with early depolarization. The consequence may be ventricular arrhythmias, such as torsades de pointes, which can degenerate into ventricular tachycardia, fibrillation, and even death.

All the atypicals are thought to prolong QT intervals to some degree by reducing the flow of repolarizing K+ currents, ultimately making the myocardium more excitable.[29] Although there is no specific threshold above which torsades de pointes will occur, it appears there is no significant risk of developing arrhythmias below a QT interval of 500 msec.[30] In fact, because the atypicals behave like type IIIa antiarrhythmics, they will overdrive the ventricle and suppress other emergent ventricular arrhythmias. Notwithstanding the FDA's scrutiny of ziprasidone, no data indicate that this agent is disproportionately toxic.

Clinical precautions. Overall, atypicals cause only a modest increase in the QT interval. Ziprasidone and quetiapine appear to have somewhat more pronounced effects, with ziprasidone prolonging the QT interval on average about 20 msec.[31] These mean increases are clinically irrelevant in most patients, but use caution when treating patients who:

- have pre-existing heart disease that is known to be associated with ventricular arrhythmias
- are taking other medications that prolong QT through the same mechanism
- have historically had idiosyncratic sensitivities to prolonged QT.[32]

Bradycardia, electrolyte imbalances, and endocrine disorders—which themselves increase QTc—also might make an individual more susceptible to the consequences of subtle QT prolongation.[29]

Managing patients at risk. In our clinic, we assess patients for risk of QT prolongation by inquiring about a family history of cardiac disease or a personal history of arrhythmia, syncope, or near syncope. In at-risk patients, we:

- monitor clinical progress more frequently, focusing on symptoms that suggest syncope or near syncope (unexplained episodic nausea, drowsiness)
- obtain routine ECGs to identify the rare population at increased risk for arrhythmia with either severely pro-

longed QT (>500 msec) or a serious AV conduction delay at baseline (second-degree or greater).

Laboratory tests should include electrolytes, as hypoleukemia is compellingly associated with development of arrhythmias.

Cardiac toxicity with clozapine. Reports of myocarditis and cardiomyopathy associated with clozapine have raised concern that this agent may be associated with other forms of cardiac toxicity. In January 2002, Novartis Pharmaceuticals Corp. reported 213 cases of myocarditis, 85% of which occurred while patients were taking recommended doses of clozapine within the first 2 months of therapy.[33] Eosinophilia in many of the cases indicates that an IgE-mediated hypersensitivity reaction may be involved.[34]

Novartis also reported 178 cases of clozapine-associated cardiomyopathy, 80% of which occurred in patients younger than 50. Almost 20% of the incidents resulted in death, an alarming figure that may reflect either delay in diagnosis and treatment or simple reporting bias.

Detecting cardiac toxicity is particularly challenging because its manifestations—tachycardia, fatigue, and orthostatic hypotension—are frequently observed in clozapine-treated patients, particularly when dosages are changed.[35] The poor specificity of signs for cardiac toxicity requires that we:

- identify at baseline patients with a personal or family history of heart disease
- set our threshold for suspicion of direct cardiotoxicity particularly low when titrating clozapine.[36]

Table 5

INTERVENTIONS TO CONTROL ANTIPSYCHOTIC-RELATED WEIGHT GAIN

- **Weigh** patient at 1- to 4-week intervals
- **Have patient discuss** lifestyle interventions (such as calorie restriction and increased exercise) with a nurse or physician
- **Have patient start** a food intake diary if weight gain exceeds 10 lbs
- **Refer** patient to a nutritionist
- **Refer** patient to a "wellness clinic" for an exercise and diet program
- **In inpatient settings**, work with dietitian to provide patient with low-fat, reduced-calorie meals

Hyperprolactinemia

Higher elevations with risperidone. Many antipsychotics cause hyperprolactinemia because their antidopaminergic activity prevents dopamine from inhibiting prolactin secretion. Among the atypicals, however, only risperidone significantly elevates prolactin.[37] Caracci et al also demonstrated a two- to four-fold greater prolactin elevation with risperidone than with typical antipsychotics[38] and noted that hyperprolactinemia with risperidone could occur at standard daily doses.

We believe that risperidone's tendency to disperse disproportionately within the plasma space accounts for its differential effect on D2 receptors in the tubuloinfundibular system (brain/plasma ratio of about 0.02 versus approximately 20 for most other antipsychotics). Thus, the lactotrophs, which are outside the blood brain barrier, are exposed to much higher levels of risperidone than are the D2 receptors within the CSF space, resulting in seemingly paradoxical co-occurence of EPS-free hyperprolactinemia.

Clinical effects. Elevated prolactin levels do not necessarily lead to clinical symptoms. A large study comparing olanzapine and risperidone found that although more patients receiving risperidone had elevated prolactin levels, few patients in either group reported prolactin-related events such as amenorrhea, galactorrhea, gynecomastia, or sexual side effects.[39] Elevated prolactin levels have not been shown to be intrinsically harmful, although they can cause hypogonadism via negative feedback and inhibition of gonadotropin-releasing hormone, leading to inadequate follicle-stimulating hormone and luteinizing hormone.

Hyperprolactinemia also reduces serum testosterone levels in men, which may lead to decreased libido, impotence, infertility, gynecomastia, and rarely galactorrhea.[40] Premenopausal women may experience infertility, oligomenorrhea or amenorrhea, galactorrhea, and reduced bone mineral density.[41]

Treatment options. When patients develop hyperprolactine-

mia, switching to another antipsychotic is not the only option.[42] Standard therapies for hyperprolactinemia—the prodopaminergic drugs bromocriptine and amantadine—are effective, though they may have a slight tendency to provoke or worsen psychosis.[43] In our experience, most patients can be managed with judicious dosages of bromocriptine (less than 5 mg/d) or even lower dosages of cabergoline (0.25 mg weekly to twice weekly), which causes very few psychiatric side effects.

Birth control pills are a reasonable alternative for women below age 35 who are nonsmokers—a relatively small proportion of those afflicted with schizophrenia but a much higher proportion of those likely to develop endocrine toxicities.

Switching antipsychotics is not the only option for managing hyperprolactinemia

Sexual dysfunction

Sexual dysfunction—including decreased libido, impaired arousal, and erectile orgasmic dysfunction—is common among patients receiving atypical antipsychotics.[44] These effects may be caused by anticholinergic activity, alpha-1 inhibition, and hypogonadism due to hyperprolactinemia.[45] Delineating one specific cause of sexual dysfunction can be difficult because:

- antipsychotics are often administered with other psychotropics that influence sexual function
- schizophrenia itself is associated with sexual dysfunction.

The asociality associated with schizophrenia's negative symptoms may be accompanied by decreased libido, fewer sexual thoughts, and fewer sexual relationships. In surveys, patients treated with atypical antipsychotics tend to report improved sex drive and libido but more erectile dysfunction and anorgasmia.[46] Untreated patients report having fewer sexual thoughts and diminished libido but better erectile function and potency.[47] The atypicals' positive effect on social behavior may facilitate a willingness to engage in sexual activity, making sexual dysfunction more apparent.[48]

Priapism has been reported with all atypicals except ziprasidone.[49] The vascular tone of the penis is in part sympathetically mediated, and alpha-1 blockade can inhibit detumescence via its indirect tendency to increase nitric oxide levels.[50] Although priapism does not appear to be common, it is a urologic emergency with potential long-term consequences, including permanent erectile dysfunction. Patients developing abnormally prolonged and painful erections must be counseled to seek immediate medical attention.

Aripiprazole: Preliminary impressions

The recently approved antipsychotic aripiprazole differs from the now-familiar dopaminergic theme by being a partial agonist at the D2 receptor. Aripiprazole has the greatest affinity for the D2 receptor of any available drug, activates the postsynaptic complex at about 30% of the full endogenous DA affect, and appears to lack the metabolic consequences of the other atypicals.

In our research laboratory, aripiprazole has shown a profound prolactin lowering effect, superior subjective tolerability, and a more salutary impact on sexual function, compared with other antipsychotics. Although not devoid of EPS, aripiprazole appears to alter a patient's subjective distress in a way that alters the risk/benefit ratio. Although aripiprazole's clinical niche has yet to be established, it would be reasonable to use it for overweight patients intolerant of the dysphorogenic effects of other antipsychotics.

Bottom Line

Atypical antipsychotics are indispensable in treating psychosis, but their use requires vigilance for adverse systemic effects. Careful monitoring, with early intervention, can often control or prevent weight gain, diabetes, hyperlipidemia, cardiac toxicity, hyperprolactinemia, and sexual dysfunction.

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Related resources

- Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities *J Clin Psychiatry* 1999;60(6)358-63.
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DRUG BRAND NAMES

Aripiprazole • Abilify
Clozapine • Clozaril
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

DISCLOSURE

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