Effects of Atypical Antipsychotics on Weight and Serum Lipid Levels

Jonathan M. Meyer, M.D.

Psychiatrists have become particularly concerned about health issues in patients with schizophrenia because of emerging data that link some of the newer atypical antipsychotics with both significant weight gain and increases in serum triglyceride levels. Excessive weight gain during antipsychotic therapy has an adverse effect on health and medication compliance, while hyperlipidemia presents an additional cardiovascular risk factor in patients with schizophrenia who typically smoke, are inactive, and possess poor dietary habits. An understanding of appropriate monitoring for metabolic adverse effects is important for those who prescribe atypical antipsychotics, as is a working knowledge of behavioral and pharmacologic treatments for weight gain and hyperlipidemia.

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dibenzodiazepine-derived agents, quetiapine, clozapine, and olanzapine. Long-term data with clozapine- and olanzapine-treated patients document weight gain far in excess of that seen with the low-potency typical antipsychotics such as chlorpromazine or thioridazine. Mean increases during the first year of therapy are 5.3 to 6.3 kg (11.8 to 14.0 lb) for clozapine and 6.8 to 11.8 kg (15.1 to 26.2 lb) for olanzapine, with substantial portions of each group gaining more than 20% of their initial body weight in this time frame. While risperidone and quetiapine have more weight gain than that associated with a high-potency agent such as haloperidol, their reported mean gains of 2.0 to 2.3 kg (4.4 to 5.1 lb) and 2.77 to 5.60 kg (6.2 to 12.4 lb), respectively, over 12 months compare favorably with those of clozapine, olanzapine, and low-potency typical antipsychotics. Ziprasidone has recently been released in the United States, and long-term studies show a mean gain of 0.23 kg (0.5 lb) at 6 months, with 14.0% gaining ≥ 7% of their baseline weight at 10.5 months. The time course in the progression of weight increase varies with the potential of each individual agent to cause weight gain. For those atypicals associated with greater weight gain, namely olanzapine and clozapine, a plateau appears between 39 and 52 weeks of therapy, although patients on clozapine treatment may continue to gain approximately 4 lb (1.8 kg) per year through the fourth year of treatment. In patients receiving risperidone, ziprasidone, or quetiapine, the plateau occurs much earlier, typically during the first few months of treatment. The pharmacologic mechanisms underlying antipsychotic-induced weight gain are discussed below, but the synergistic effects of histamine H1 and serotonin 5-HT2C antagonism have been postulated as underlying the generally greater weight gain experienced with atypical antipsychotics; effects on leptin possibly play a role as well.

Multiple variables have been examined attempting to elicit risk factors that may predict excessive weight gain independent of the particular atypical antipsychotic. Initial low BMI (< 23 kg/m²) was thought to be associated with greater weight gain in some studies, but subsequent investigations have not corroborated these findings. Correlation with antipsychotic dosage has been examined for a few long-term studies, and there appears not to be a strong association when examined at 1 year or greater; however, it should be noted that weight gain often plateaus by 52 weeks, thus muting an association that appears more significant in short-term studies. Lithium and valproate are mood stabilizers with significant potential for weight gain and were examined retrospectively to determine the effect of their concurrent use with risperidone or olanzapine among state hospital patients (Table 1). The data are cause for concern, since patients receiving lithium or valproate plus risperidone experienced twice the amount of weight gain as those who were not taking one of these mood stabilizers, while olanzapine-treated patients taking concurrent lithium or valproate sustained a mean weight gain of 27.35 lb (12.3 kg), almost 3 times that without these mood stabilizers. Older age does mitigate the extent of weight gain during atypical antipsychotic therapy, with several studies documenting weight increases in those ≥ 60 years old lower than that experienced by younger adults.

### PHARMACOLOGY OF ATYPICAL ANTIPSYCHOTIC-INDUCED OBESITY

The pharmacology of obesity is a rapidly growing field, but the accrued data implicate histamine H1 antagonism as the primary mechanism underlying antipsychotic-induced weight gain through direct effects on appetite. This inference is based on evidence that drugs of various classes with potent central histamine H1 antagonism are associated with significant weight gain, including antidepressants, antipsychotics, and centrally acting antihistamines such as cyproheptadine. The primary role of histaminic blockade in atypical antipsychotic–induced weight gain relative to 5-HT2C antagonism can be seen more clearly upon an examination of the binding affinities for these agents. The data in Table 2 were obtained from radioligand binding in human cortex, caudate, and choroid plexus. A look at the comparative affinities shows risperidone to be equipotent with olanzapine as a 5-HT2C antagonist, and ziprasidone...
the most potent 5-HT<sub>2C</sub> blocker among the atypicals, yet olanzapine possesses significantly higher histamine H<sub>1</sub> antagonism and is associated with greater weight gain than either of these 2 agents. Quetiapine is a weak antagonist at serotonergic receptors, but possesses a level of histamine blockade intermediate between risperidone and olanzapine and is clinically associated with weight gain that is also intermediate between these 2 drugs. Increased appetite, and possibly decreased activity from sedation, are the mechanisms by which H<sub>1</sub> antagonism contributes to weight gain.37

For atypical antipsychotics, 5-HT<sub>2C</sub> antagonism most likely plays a synergistic role in causing more weight gain than would be seen with a potent H<sub>1</sub> antagonist such as chlorpromazine that lacks serotonergic activity. The atypicals are designed to be antagonists at 5-HT<sub>2A</sub> receptors, yet they also possess activity at 5-HT<sub>2C</sub> receptors, which is implicated in hyperphagia and the subsequent development of obesity and adult-onset diabetes.38,39 Evidence for this activity and its effects comes from studies of mutant mice lacking the 5-HT<sub>2C</sub> receptor that develop marked obesity and insulin resistance as adults.40 In addition, drugs such as dexfenfluramine that act as agonists at 5-HT<sub>2C</sub> receptors decrease appetite and are effective weight loss agents.41,42

Limited data exist in the form of several small studies that have shown that treatment with clozapine and olanzapine is also associated with effects on leptin physiology not seen in patients treated with haloperidol.37,38,41,42 Leptin is a cytokine product of the <i>ob</i> gene related to interleukin-6, secreted by white adipose cells to regulate insulin secretion and energy metabolism via receptors in the hypothalamus, adipocytes, and skeletal muscle.45–47 Disorders of leptin regulation include the rare congenital leptin deficiency, which results in early-onset obesity, and the phenomenon of leptin resistance observed in chronically obese individuals who manifest elevated serum leptin levels.48 Whether agents such as clozapine and olanzapine have direct effects on leptin homeostasis or simply induce elevated leptin levels as a consequence of weight gain and increased adipose mass is an interesting issue that may have future ramifications for obesity treatment. Currently, leptin injections have been employed experimentally to induce weight loss in a dose-dependent manner, but commercial leptin agonists have yet to be realized.49

### Behavioral Treatment of Obesity

The treatment of obesity is challenging in individuals without a major mental illness; nevertheless, a body of data documents success in the behavioral management of obesity in the chronically mentally ill.50–52 Many of these studies are methodologically weak and utilize rewards that do not readily translate into an outpatient setting, but the outcomes show evidence that patients with schizophrenia can acquire skills related to eating behavior in the same manner that other psychosocial skills are taught through training programs.53,54 The essential aspects of any behavioral intervention for overweight or obese individuals generally comprise the following:

1. Frequent monitoring
2. Nutritional and lifestyle counseling geared toward the population
3. Skills training focusing on exercise, nutrition, health education, and behavioral techniques

Although implementing this type of program seems a daunting task, simply restricting intake by 500 calories per day and exercising for 30 minutes may produce sustained weight loss.55 Nutritional counseling is ideally provided by a dietitian, but motivated providers in a clinic setting are capable of organizing groups focused on diet, exercise, and coping strategies that serve to reinforce these recommendations. Strategies such as food diaries are useful tools for engaging patients in their treatment and for eliciting specific behaviors (e.g., pizza as a nighttime snack) that can be modified. Monitoring weight on every clinic visit also helps reinforce the importance of weight gain to the physician and patient alike.56 Realistic goals should be set to prevent frustration on the part of the patient, since most will experience no more than 10% to 15% weight loss in 1 year.56 While this amount of loss seems minimal, sustained decreases in body mass of 8.5% to 10.0% are sufficient to improve glucose tolerance and decrease lipid levels.37,58

### Pharmacologic Treatment of Obesity

In general, pharmacotherapy is reserved for obese patients who fail to lose weight with several months of behavioral interventions, particularly those with comorbid disorders such as diabetes mellitus.41 It is inappropriate to utilize anorectic agents for short periods of time; rather, these drugs should be considered part of a comprehensive long-term treatment strategy, since cessation of the agent typically results in regaining lost weight. Complicating their use in patients with chronic mental illness is the fact that appetite suppressants are sympathomimetic amines or stimulating serotonergic agonists with potential for exacerbating underlying psychosis.55 Fenfluramine and dexfenfluramine have been withdrawn from the market, al-

<table>
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<tr>
<th>Drug</th>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>H&lt;sub&gt;1&lt;/sub&gt;</th>
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<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
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<td>4700</td>
<td>120</td>
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<tr>
<td>Clozapine</td>
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<td>17</td>
<td>8.9</td>
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<tr>
<td>Olanzapine</td>
<td>20</td>
<td>2.8</td>
<td>10</td>
<td>3.3</td>
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<tr>
<td>Quetiapine</td>
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<td>1400</td>
<td>220</td>
</tr>
<tr>
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<td>19</td>
<td>10</td>
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<td>Ziprasidone</td>
<td>3.1</td>
<td>47</td>
<td>0.72</td>
<td>0.39</td>
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</table>

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though amphetamines and phentermine are still available but should be eschewed both for the abuse liability of amphetamines and the overall risk of psychotic exacerbation. Phenylpropanolamine has been removed from the nonprescription market because of a risk of hemorrhagic stroke. Two newer agents available since the mid-1990s are considered the treatments of choice: sibutramine and orlistat.

Sibutramine was initially developed as an antidepressant with both serotonin and norepinephrine reuptake blockade, but its short central nervous system half-life rendered it impractical for this use. However, dose-dependent weight loss was noted during clinical trials, and subsequent investigation ascribed its weight loss potential primarily to β₁ adrenergic agonism. These receptors are present in brown and white adipose tissue and respond to agonists by increasing lipolysis and thermogenesis in adipocytes. Sibutramine has a low potential for abuse, and long-term studies show weight loss of 8.8% on a daily dose of 20 mg at 24 weeks with improvements noted in serum triglyceride, total cholesterol, and low-density lipoprotein (LDL) levels. Increases in both blood pressure and pulse necessitate monitoring, but the most common side effects are dry mouth and insomnia. A recent case report documenting new-onset psychosis in a 19-year-old woman receiving sibutramine means that care must be exercised in the use of this agent for patients with underlying psychosis or a history of mania.

Orlistat represents a superior choice for the treatment of obesity in the chronically mentally ill since it lacks central nervous system activity, exerting its weight loss effects solely through the inhibition of gastric and pancreatic lipase. Long-term studies showed sustained weight loss of 9.7% at 2 years on a dose of 120 mg thrice daily with meals. Improvements in fasting lipid profiles and glucose tolerance were noted, and only 6% withdrew due to intolerable gastrointestinal side effects (e.g., steatorrhea, increased stool frequency). Orlistat may interfere with the absorption of fat-soluble vitamins to the extent that vitamin A and E replacement may be necessary. As of this writing, there are case reports of its safe and effective use in 2 psychiatric patients with no interference noted in the bioavailability of psychotropic medications.

Topiramate has received recent attention as an anticonvulsant that may have mood-stabilizing properties and has been associated with weight loss in short-term trials. The limitations of topiramate as a weight loss agent are due primarily to difficulties patients experience with sedation and cognitive slowing. In one 12-week study, patients in 3 groups were titrated up to a daily dose of 100 mg: 25 healthy subjects, 25 treatment-responsive bipolar patients, and 25 partially responsive bipolars. Weight loss was 16.4 lb (7.4 kg), 16.7 lb (7.5 kg), and 13.5 lb (6.1 kg), respectively, for the groups, but the number of dropouts in each group was quite high: 3, 9, and 14 respectively. In longer studies, weight loss usually peaked within 3 to 12 months of the initiation of topiramate, with the majority of loss seen among obese patients. The weight loss may be sustained during prolonged therapy, but some patients do return to pretopiramate weight levels.

**HYPERTRIGLYCERIDEMIA DURING ANTIPSYCHOTIC THERAPY**

Hypertriglyceridemia is associated with various forms of drug therapy and occurs among compounds with unrelated modes of action such as protease inhibitors and interferon alpha-2b. Shortly after their introduction, phenothiazines were found to elevate serum triglyceride and total cholesterol levels, but with greater effects on triglyceride concentrations. On the other hand, early studies with butyrophenones in the mid-1960s noted that these compounds exerted a minimal or slightly favorable effect on serum lipid levels in schizophrenic patients. There was scant subsequent data on the issue of lipid levels and antipsychotics for a decade until the publication of Sasaki and colleagues in the mid-1980s examining serum lipid levels in Japanese schizophrenics. These studies corroborated earlier findings by demonstrating significant elevations in serum triglyceride levels for phenothiazine treated patients (mean ± SD = 163 ± 65 mg/dL) compared with the butyrophenone group (104 ± 52 mg/dL) and the control group (127 ± 71 mg/dL). No significant differences were reported in total cholesterol values between the 3 groups, but the phenothiazine-treated patients had significant elevations in LDL and decreased high-density lipoprotein (HDL) concentrations. Trials in the mid-1980s of fluperlapine, a dibenzazepine structurally related to clozapine but not commercially released, revealed problems with hypertriglyceridemia in 16 of 25 patients in one study, and in a subsequent study, 1 patient on fluperlapine treatment developed a serum triglyceride level greater than 900 mg/dL by day 7, with a subsequent decline over the next 3 weeks.

Nearly a decade elapsed before the publication of hyperlipidemia cases with the currently available atypical antipsychotics. Ghaeli and Dufresne described 4 clozapine-treated patients with hypertriglyceridemia whose lipid levels returned to normal upon switching to risperidone and later published a chart review comparing serum lipid levels in patients receiving clozapine or typical antipsychotics for at least 1 year who had no prior history of hyperlipidemia or use of lipid-lowering agents. This retrospective study found that serum triglyceride levels were significantly elevated (p < .001) in the clozapine group (mean ± SD = 264.0 ± 160.5 mg/dL) compared with the typical group (149.8 ± 78.3 mg/dL), but not so for total cholesterol levels (clozapine, 217.0 ± 52.9 mg/dL vs. typical, 215.0 ± 43.2 mg/dL). A 1998 study comparing Israeli patients taking clozapine (N = 30) or typical antipsychotics (N = 30) for at least 1 year confirmed those findings of significant hypertriglyceridemia in the clozapine group.
This study was the first to report a significant association from a mean weeks. Fasting triglyceride levels in that group increased olanzapine therapy who were tracked prospectively for 12 months who experienced an increase in mean serum triglyceride levels from 170 mg/dL (range, 135–369 mg/dL) to 240 mg/dL (range, 135–369 mg/dL), without significant changes in cholesterol levels. Osser et al.87 subsequently reported on 25 inpatients (21 men, 4 women) commencing olanzapine-associated hypertriglyceridemia were Sheitman typical, 194.9 ± 51.5 mg/dL. The first published cases of olanzapine-associated hypertriglyceridemia were Sheitman and others group of 9 patients followed for an average of 16 months who experienced an increase in mean serum triglyceride levels from 170 mg/dL (range, 25–200 mg/dL) to 240 mg/dL (range, 135–369 mg/dL), without significant changes in cholesterol levels. Osse et al.87 subsequently reported on 25 inpatients (21 men, 4 women) commencing olanzapine therapy who were tracked prospectively for 12 weeks. Fasting triglyceride levels in that group increased from a mean ± SD of 162 ± 121 mg/dL to 222 ± 135 mg/dL. This study was the first to report a significant association between weight gain and triglyceride change for patients receiving atypical antipsychotic therapy. Subsequent analysis of 5-year outcome data for a group of clozapine-treated patients (N = 81) by Henderson and coworkers also showed a significant correlation between weight gain and increases in fasting cholesterol and triglyceride levels when controlled for time of exposure.

The possibility that some atypical antipsychotics may have direct effects on serum lipid levels has been raised by recent studies involving olanzapine and clozapine that demonstrate triglyceride elevations not associated with weight gain. Meyer did not find a correlation between weight gain and peak serum triglyceride levels in a case series of 14 patients treated with olanzapine or quetiapine who developed severe hyperlipidemia. A subsequent retrospective investigation comparing metabolic outcomes during the first year of treatment with risperidone or olanzapine showed comparable weight gain for the 2 agents (8.14 lb [3.7 kg] and 10.14 lb [4.6 kg], respectively), but the olanzapine group experienced a mean increase in serum triglyceride levels of 84.8 mg/dL, compared with a 20.2 mg/dL increase for the risperidone cohort. Moreover, a study examining cardiovascular risk of olanzapine and risperidone found that 32% of the olanzapine group manifested the atherogenic metabolic triad of hyperinsulinemia, elevated apolipoprotein B, and small dense LDL concentrations, but only 5% of the risperidone group had these results despite similar BMI values for the 2 cohorts (olanzapine mean ± SD = 26.9 ± 5.6 kg/m²; risperidone mean ± SD = 26.7 ± 4.7 kg/m²). Lastly, patients switched from olanzapine to ziprasidone experienced a significant decrease in serum triglyceride and cholesterol levels over 6 weeks, despite average weight loss of only 3.3 lb (1.5 kg).

The exact biochemical locus where atypical antipsychotics exert their influence on triglyceride metabolism remains a source of speculation. Although these agents are potent antagonists at 5-HT₃ receptors, chronic 5-HT₃ blockade does not appear to directly induce hyperlipidemia. Knockout mice lacking the 5-HT₃ receptor develop obesity and insulin resistance, but do not have significant elevations in serum triglyceride levels when fed either a high fat diet. It is worthwhile noting that these atypicals exert significant effects on fasting triglyceride levels are dibenzodiazepine-derived compounds. Clozapine, olanzapine, and quetiapine possess a 3-ring structure that is conformationally similar to the phenothiazine nucleus and also share the phenothiazine propensity to increase serum triglyceride levels with lesser effects on cholesterol.

**Table 3. Lipid Changes in a 26-Year-Old Man During Olanzapine Therapy**

<table>
<thead>
<tr>
<th>Time</th>
<th>Triglyceride</th>
<th>Cholesterol</th>
<th>HDL</th>
<th>LDL</th>
<th>VLDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>&lt; 200</td>
<td>&lt; 200</td>
<td>≥ 35</td>
<td>≤ 130</td>
<td>&lt; 40</td>
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<tr>
<td>Baseline</td>
<td>168</td>
<td>174</td>
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<td>...</td>
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<tr>
<td>4 mo</td>
<td>238</td>
<td>216</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>8 mo</td>
<td>280</td>
<td>241</td>
<td>31</td>
<td>154</td>
<td>56</td>
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<tr>
<td>11 mo</td>
<td>408</td>
<td>258</td>
<td>28</td>
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</tr>
<tr>
<td>16 mo</td>
<td>339</td>
<td>238</td>
<td>35</td>
<td>135</td>
<td>68</td>
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<tr>
<td>19 mo</td>
<td>194</td>
<td>192</td>
<td>37</td>
<td>116</td>
<td>39</td>
</tr>
</tbody>
</table>

*Personal observations, J.M.M.*

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very low-density lipoprotein.

*All values reported as mg/dL.*

*Invalid when triglyceride levels are above 400 mg/dL.

*Gemfibrozil started between 16 and 19 months.

A characteristic clinical course is seen when serum lipid levels are serially monitored after the onset of dibenzodiazepine treatment. Peak triglyceride levels typically occur within the first year of therapy during the course of dibenzodiazepine therapy, followed by a decrease and subsequent period of stabilization. Wide interindividual variation exists in both the timing of peak triglyceride levels as well as the magnitude of lipid elevations, necessitating quarterly monitoring of total triglyceride and cholesterol levels for the first year after the initiation of treatment with any dibenzodiazepine-derived atypical antipsychotic. Table 3 depicts this pattern as seen in a patient under my care following the onset of therapy with olanzapine. Although cholesterol, HDL, and LDL levels became abnormal concurrent with the marked triglyceride elevation, treatment with gemfibrozil normalized not only triglyceride levels but other lipid parameters as well. In general, individuals can be observed without treatment until achieving a period of stabilization unless the triglyceride levels exceed 400 to 500 mg/dL, thereby putting patients at risk for acute pancreatitis. Fasting triglyceride levels greater than 7500 mg/dL during olanzapine therapy have been described in the literature, underscoring the need for vigilant monitoring in patients placed on dibenzodiazepine treatment. Treatment of sustained hypertriglyceridemia should be initiated since elevated triglyceride levels are now rec-
ognized as an independent risk factor for coronary artery disease. Moreover, patients with schizophrenia typically possess multiple risk factors for coronary artery disease, including very high prevalence rates of smoking. As the use of ziprasidone and risperidone are associated with lesser effects on serum lipids, measuring fasting and total triglyceride and total cholesterol levels annually should be adequate screening for most patients taking these 2 drugs.

Weight reduction and the use of diets low in saturated fats are considered the mainstays in the treatment of mild triglyceride abnormalities. When these measures fail, or when triglyceride concentrations > 500 mg/dL present a risk for pancreatitis, pharmacotherapy is employed to achieve direct reductions in serum triglyceride levels. The common agents used to treat hypertriglyceridemia include fish oil, nicotinic acid (niacin) and fibric acid derivatives (e.g., fenofibrate, gemfibrozil). Diabetic patients may be more likely to benefit from statin therapy than nondiabetic patients, in part because fish oil and gemfibrozil are less effective in the diabetic population, and nicotinic acid is relatively contraindicated since it causes insulin resistance and can thereby aggravate hyperglycemia. Nicotinic acid is capable of correcting most lipid or lipoprotein abnormalities by decreasing synthesis of very low-density lipoproteins (VLDL) and triglycerides, but is often not the first agent of choice even for nondiabetics with hypertriglyceridemia due to significant side effects such as flushing and hepatotoxicity. Fibric acid derivatives decrease synthesis of VLDL and increase triglyceride hydrolysis sufficient to realize reductions in serum triglyceride concentrations of up to 40%; however, hepatotoxicity and myopathy, when used alone or in conjunction with statin therapy, are important issues in the use of these agents. Fish oils contain omega-3 fatty acids, which have potent effects on lowering serum triglyceride levels, but lesser effects on LDL reduction. In dosages of 1000 to 2000 mg t.i.d. with meals, the decreases in serum triglyceride levels achieved during the long term are associated with reduction in both symptoms of coronary artery disease and cardiac death rates. Many patients find this natural alternative preferable as an initial therapy for hypertriglyceridemia, with an occasional complaint of fishy aftertaste native preferable as an initial therapy for hypertriglyceridemia. The dibenzodiazepine-derived agents clozapine, olanzapine, and quetiapine are an important part of the therapeutic armamentarium, but are associated with a greater propensity for weight gain and triglyceride elevations than risperidone or ziprasidone. When dibenzodiazepines are employed, appropriate metabolic monitoring and referral for treatment should be instituted. A working knowledge of the behavioral and pharmacologic options for the treatment of weight gain and hypertriglyceridemia is thus strongly recommended for all psychiatrists, who must also assume responsibility for the initial monitoring and management of health conditions related to the use of these atypical antipsychotic agents with a higher likelihood for adverse metabolic outcomes.

**Drug names:** chlorpromazine (Thorazine and others), clozapine (Clozaril and others), cyproheptadine (Periactin), fenofibrate (Tricor), gemfibrozil (Lopid and others), haloperidol (Haldol and others), niacin (Niaspan and others), olanzapine (Zyprexa), orlistat (Xenical), phentermine (Adipex and others), phenylpropanolamine (Alumadrine and others), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), ziprasidone (Geodon).

**Disclosure of off-label usage:** The author of this article has determined that, to the best of his knowledge, topiramate has not been approved by the U.S. Food and Drug Administration for weight loss.

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