Effects of Atypical Antipsychotics on Weight and Serum Lipid Levels

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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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PHENOMENOLOGY OF OBESITY DURING ATYPICAL ANTIPSYCHOTIC THERAPY

Overweight and obesity have quickly become one of America's paramount health concerns because of the rapid rise in the prevalence of these conditions over the past 20 years. Overweight is defined by the World Health Organization as a body mass index (BMI) of 25.0 to 29.9 kg/m^2, and obesity is defined as BMI ≥ 30 kg/m^2. Accumulated results of the 1999 National Health and Nutrition Examination Survey (NHANES), released in December 2000 by the National Center for Health Statistics, document this alarming trend in the United States (Figure 1). The proportion of obese individuals in 1999 was 80% greater than when measured by NHANES II (1976 to 1980) and 17% greater than measured by NHANES III in 1997. The public health implications are enormous, and the resulting economic impact is equally staggering. An estimated $70 billion, or 7% of the total U.S. health care budget, is spent annually on the cost of medical conditions related to obesity, 60% of which is relegated to the treatment of diabetes mellitus.[1]

Psychiatrists have become particularly concerned about health issues related to weight gain because of emerging data linking the use of certain newer antipsychotics with weight increases in excess of that seen with typical antipsychotics and the subsequent effects of weight gain on health and compliance. In general, patients with schizophrenia suffer increased mortality compared with the general population, with greater prevalence and severity of medical conditions.[2–5] Prior to the first release of atypical antipsychotics in the United States, the 1989 National Health Interview Survey data revealed that a significantly greater proportion of female patients with schizophrenia had BMI distributions in the overweight and obese spectrum compared with their counterparts in the general medical population; a trend toward greater BMI was also seen among male schizophrenic patients.[6] Thus, the development of significant weight gain during atypical antipsychotic treatment may further compromise patient health by contributing to comorbid conditions associated with obesity such as hypertension, coronary artery disease (CAD), and type 2 diabetes mellitus.[7] Importantly, excessive weight gain has adverse implications for psychiatric health through its effect on medication compliance.[8–10] Investigators at the Columbia-St. Luke's Obesity Research Center released survey data[11] that examined the link between obesity and antipsychotic medication compliance. Obese patients were 13 times more likely to request discontinuation of their current antipsychotic agent because of concerns about weight gain and 3 times as likely to be noncompliant with treatment compared with nonobese individuals.[11]

In the past 2 years alone, a number of articles have been published reviewing the relative weight gain from antipsychotic therapy and imploring action on behalf of the mental health community in the management of this important side effect.[12–17] A gradient of weight increases is seen during extended treatment with atypical agents, with published studies showing relatively less gain with ziprasidone and risperidone and more substantial gains with the

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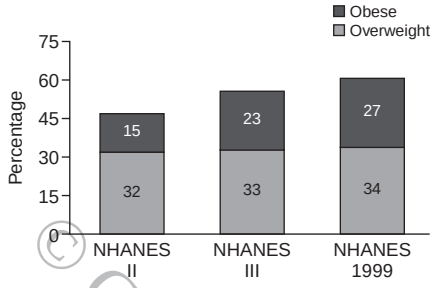
Figure 1. U.S. Prevalence of Overweight and Obesity, 1976–1999[a]



[a]Data from the National Center for Health Statistics.[102] Abbreviation: NHANES = National Health and Nutrition Examination Survey.

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.[18–21] 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.[14,15,17,22–25] 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.[15,17,26] 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.[20,21] In patients receiving ziprasidone, risperidone, or quetiapine, the plateau occurs much earlier, typically during the first few months of treatment.[14,15,17,22–26] The pharmacologic mechanisms underlying antipsychotic-induced weight gain are discussed below, but the synergistic effects of histamine H_1 and serotonin 5-HT_{2C} antagonism have been postulated as underlying the generally greater weight gain experienced with atypical antipsychotics; effects on leptin possibly play a role as well.[14,27,28]

Multiple variables have been examined attempting to elicit risk factors that may predict excessive weight gain independent of the particular atypical antipsychotic. Initial

Table 1. Effect of Lithium or Valproate Use on Weight Gain at 1 Year During Treatment With Risperidone or Olanzapine[a]

Treatment	Lithium or Valproate	No Mood Stabilizer
Risperidone	N = 15	N = 32
Weight gain, lb (kg)	+16.10 (+7.2)	+8.14 (+3.7)
BMI increases, kg/m^2	+2.27	+1.21
Olanzapine	N = 20	N = 27
Weight gain, lb (kg)	+27.35 (+12.3)	+10.14 (+4.6)
BMI increases, kg/m^2	+4.06	+1.43

[a]Data from Meyer.[31]

low BMI (< 23 kg/m^2) was thought to be associated with greater weight gain in some studies, but subsequent investigations have not corroborated these findings.[14,29–31] 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.[20,21] Lithium and valproate are 2 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).[31] 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.[31] 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.[25,31–35]

PHARMACOLOGY OF ATYPICAL ANTIPSYCHOTIC–INDUCED OBESITY

The pharmacology of obesity is a rapidly growing field, but the accrued data implicate histamine H_1 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 H_1 antagonism are associated with significant weight gain, including antidepressants, antipsychotics, and centrally acting antihistamines such as cyproheptadine.[36] The primary role of histaminic blockade in atypical antipsychotic–induced weight gain relative to 5-HT_{2C} 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-HT_{2C} antagonist, and ziprasidone

Table 2. Binding Affinities (K_i, nM)[a]

Drug	D_2	H_1	5-HT_{2C}	5-HT_{2A}
Haloperidol	1.4	440	4700	120
Clozapine	130	1.8	17	8.9
Olanzapine	20	2.8	10	3.3
Quetiapine	180	8.7	1400	220
Risperidone	2.2	19	10	0.29
Ziprasidone	3.1	47	0.72	0.39

[a]Data from Simansky et al.[103] Abbreviations: 5-HT = serotonin, D = dopamine, H = histamine.

the most potent 5-HT_{2C} blocker among the atypicals, yet olanzapine possesses significantly greater histamine H_1 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_1 antagonism contributes to weight gain.[37]

For atypical antipsychotics, 5-HT_{2C} antagonism most likely plays a synergistic role in causing more weight gain than would be seen with a potent H_1 antagonist such as chlorpromazine that lacks serotonergic activity. The atypicals are designed to be antagonists at 5-HT_{2A} receptors, yet they also possess activity at 5-HT_{2C} 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_{2C} receptor that develop marked obesity and insulin resistance as adults.[40] In addition, drugs such as dexfenfluramine that act as agonists at 5-HT_{2C} 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.[27,28,43,44] Leptin is a cytokine product of the *ob* 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]

TREATMENT OF ATYPICAL ANTIPSYCHOTIC–RELATED OBESITY

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. 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.[57,58]

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-

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 β_3 adrenergic agonism.[42] These receptors are present in brown and white adipose tissue and respond to agonists by increasing lipolysis and thermogenesis in adipocytes.[59] 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.[60–62] 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.[63]

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 show sustained weight loss of 9.7% at 2 years on a dose of 120 mg thrice daily with meals.[64,65] 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[66] 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.[67] 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.[68] 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.[67]

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.[69,70] Shortly after their introduction, phenothiazines were found to elevate serum triglyceride and total cholesterol levels, but with greater effects on triglyceride concentrations.[71–73] 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.[74–78] There was scant subsequent data on the issue of lipid levels and antipsychotics for a decade until the publication of Sasaki and colleagues'[79,80] 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 28 patients in one study,[81] and in a subsequent study[82] 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[83] described 4 clozapine-treated patients with hypertriglyceridemia whose lipid levels returned to normal upon switching to risperidone and later published a chart review[84] 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[85] 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

(mean ± SD = 202.9 ± 131.1 mg/dL) but not the typical group (134.4 ± 51.9 mg/dL), without significant differences in total cholesterol levels (clozapine, 197.1 ± 46.4 mg/dL vs. typical, 194.9 ± 51.5 mg/dL. The first published cases of olanzapine-associated hypertriglyceridemia were Sheitman and others'[86] 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. Osser 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[87] 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[21] 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 clozapine and olanzapine that demonstrate triglyceride elevations not associated with weight gain. Meyer[88] 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[31] 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[89] 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/m^2; risperidone mean ± SD = 26.7 ± 4.7 kg/m^2). 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).[90,91]

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 $5\text{-}HT_{2C}$ receptors, chronic $5\text{-}HT_{2C}$ blockade does not appear to directly induce hyperlipidemia.[38,39] Knockout mice lacking the $5\text{-}HT_{2C}$ receptor develop obesity and insulin resistance, but do not have significant elevations in serum triglyceride levels when fed either a standard or high fat diet.[40] It is worthwhile noting that those atypicals exerting 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[a]

Time	Triglyceride	Cholesterol	HDL	LDL	VLDL
Normal values	< 200	< 200	≥ 35	< 130	< 40
Baseline	168	174	...	...	...
4 mo	258	216	...	...	...
8 mo	280	241	31	154	56
11 mo	408	258	28	...[b]	...[b]
16 mo	339	238	35	135	68
19 mo[c]	194	192	37	116	39

[a]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.
[b]Invalid when triglyceride levels are above 400 mg/dL.
[c]Gemfibrozil started between 16 and 19 months.

MONITORING AND TREATMENT OF HYPERTRIGLYCERIDEMIA DURING ATYPICAL ANTIPSYCHOTIC THERAPY

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.[92,93] 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.[88] Treatment of sustained hypertriglyceridemia should be initiated since elevated triglyceride levels are now rec-

ognized as an independent risk factor for coronary artery disease.[94,95] Moreover, patients with schizophrenia typically possess multiple risk factors for coronary artery disease, including very high prevalence rates of smoking.[4,96,97] 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.[98,99] 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.[100] 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.[100] 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.[101] Many patients find this natural alternative preferable as an initial therapy for hypertriglyceridemia, with an occasional complaint of fishy aftertaste noted despite coadministration with meals. For outpatient clinics, it is important to establish a liaison with a group of internists or endocrinologists who feel comfortable seeing patients with mental illness so that appropriate follow-up and treatment of hyperlipidemia or other medical conditions is not unnecessarily delayed.

CONCLUSIONS

Each new generation of psychopharmacologic advances brings with it the promise of improved outcomes, but the development of untoward side effects often mitigates the therapeutic benefits. Concerns about the overall health care of patients with schizophrenia fit neatly into the broadening scope of treatment during the past decade for patients with this disorder. For the chronically mentally ill, mental health professionals are often the sole contact with the health care system, so an undeniable burden falls upon those who prescribe antipsychotic agents to individualize and monitor treatment, taking into account the relative risk of adverse metabolic events among the atypical antipsychotics and the long-term health impact of weight gain or hyperlipidemia. 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 those 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.

REFERENCES

1. Colditz GA. Economic costs of obesity and inactivity. Med Sci Sports Exerc 1999;31:S663–S667
2. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239–245
3. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53
4. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187:496–502
5. Osby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000;45:21–28
6. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
7. Must A, Spadano J, Coakley EH, et al. The disease burden associated with overweight and obesity. JAMA 1999;282:1523–1529
8. Fleischhacker WW, Meise U, Gunther V, et al. Compliance with antipsychotic drug treatment: influence of side effects. Acta Psychiatr Scand Suppl 1994;382:11–15
9. Kawachi I. Physical and psychological consequences of weight gain. J Clin Psychiatry 1999;60(suppl 21):5–9
10. Perkins DO. Adherence to antipsychotic medications. J Clin Psychiatry 1999;60(suppl 21):25–30
11. Weiden PJ, Allison DB, Mackell JA, et al. Obesity as a risk factor for antipsychotic noncompliance. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 15, 2000;

Chicago, Ill. Abstract NR218:114
12. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? J Clin Psychopharmacol 1999;19:316–321
13. Ganguli R. Weight gain associated with antipsychotic drugs. J Clin Psychiatry 1999;60:20–24
14. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
15. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
16. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. Gen Hosp Psychiatry 2000;22:224–235
17. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Psychiatr Scand 2000;101:416–432
18. Bustillo JR, Buchanan RW, Irish D, et al. Differential effect of clozapine on weight: a controlled study. Am J Psychiatry 1996;153:817–819
19. Nemeroff CB. Dosing the antipsychotic medication olanzapine. J Clin Psychiatry 1997;58(suppl 10):45–49
20. Kinon BJ, Basson BR, Gilmore JA, et al. Effect of long-term olanzapine treatment on weight change in schizophrenia [poster]. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1999; Acapulco, Mexico
21. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
22. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–546. Corrections 1998;59:200
23. Song F. Risperidone in the treatment of schizophrenia: a meta-analysis of randomized controlled trials. J Psychopharmacol 1997;11:65–71
24. Csernansky J, Okamoto A. Risperidone versus haloperidol for prevention of relapse in schizophrenia [poster]. Presented at the 10th Biennial Winter Workshop on Schizophrenia; Feb 5–11, 2000; Davos, Switzerland
25. Jones AM, Rak IW, Raniwalla J, et al. Weight changes in patients treated with quetiapine. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 18, 2000; Chicago, Ill. Abstract NR712:250
26. Food and Drug Administration, Psychopharmacological Drugs Advisory Committee. July 19, 2000. Zeldox (ziprasidone hydrochloride capsules) NDA 20-825, Pfizer Inc. Available at: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1.htm. Accessed June 19, 2001
27. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156: 312–314
28. Melkersson KI, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000;61:742–749
29. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
30. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. J Clin Psychiatry 1997;58(suppl 10):13–17
31. Meyer JM. A retrospective comparison of lipid, glucose and weight changes at one year between olanzapine and risperidone treated inpatients [poster]. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
32. Howanitz E, Pardo M, Smelson DA, et al. The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. J Clin Psychiatry 1999;60:41–44. Correction 1999;60:341
33. Madhusoodanan S, Brecher M, Brenner R, et al. Risperidone in the treatment of elderly patients with psychotic disorders. Am J Geriatr Psychiatry 1999;7:132–138. Correction 1999;7:268
34. Maixner SM, Mellow AM, Tandon R. The efficacy, safety, and tolerability of antipsychotics in the elderly. J Clin Psychiatry 1999;60(suppl 8):29–41
35. Juncos JL, Evatt ML, Jewart RD, et al. Long-term quetiapine treatment for psychosis in patients with Parkinson's disease who failed treatment with other atypical antipsychotics [poster]. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12–15, 1999; Acapulco, Mexico
36. Devlin MJ, Yanovski SZ, Wilson GT. Obesity: what mental health professionals need to know [see comments]. Am J Psychiatry 2000;157:854–866
37. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiatry 1997;58(suppl 10):55–62
38. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors [see comments]. Nature 1995;374: 542–546
39. Curzon G, Gibson EL, Oluyomi AO. Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability [see comments]. Trends Pharmacol Sci 1997;18:21–25
40. Nonogaki K, Strack AM, Dallman MF, et al. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene [see comments]. Nat Med 1998;4:1152–1156
41. Rissanen A. Pharmacological intervention: the antiobesity approach. Eur J Clin Invest 1998;28:27–30
42. Heal DJ, Aspley S, Prow MR, et al. Sibutramine: a novel anti-obesity drug: a review of the pharmacological evidence to differentiate it from d-amphetamine and d-fenfluramine. Int J Obes Related Metab Disord 1998;22:S18–S28; discussion S29
43. Bromel T, Blum WF, Ziegler A, et al. Serum leptin levels increase rapidly after initiation of clozapine therapy. Mol Psychiatry 1998;3:76–80
44. Baptista T, Lacruz A, de Mendoza S, et al. Body weight gain after administration of antipsychotic drugs: correlation with leptin, insulin and reproductive hormones. Pharmacopsychiatry 2000;33:81–88
45. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice [see comments]. Science 1995;269:540–543
46. Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene [see comments]. Science 1995;269:543–546
47. Stahl SM. Neuropharmacology of obesity: my receptors made me eat it [BRAINSTORMS]. J Clin Psychiatry 1998;59:447–448
48. Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. Ann Intern Med 1999;130:671–680
49. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial [see comments]. JAMA 1999;282:1568–1575
50. Klein B, Simon WE, Steele RL, et al. Reinforcement and weight loss in schizophrenics. Psychol Rep 1972;30:581–582
51. Rotatori AF, Fox R, Wicks A. Weight loss with psychiatric residents in a behavioral self control program. Psychol Rep 1980;46:483–486
52. Knox JM. A study of weight reducing diets in psychiatric in-patients. Br J Psychiatry 1980;136:287–289
53. Liberman RP, Wallace CJ, Blackwell G, et al. Skills training versus psychosocial occupational therapy for persons with persistent schizophrenia. Am J Psychiatry 1998;155:1087–1091
54. Kopelowicz A, Liberman R, Mintz J, et al. Comparison of efficacy of social skills training for deficit and nondeficit negative symptoms in schizophrenia. Am J Psychiatry 1997;154:424–425
55. Greenberg I, Chan S, Blackburn GL. Nonpharmacologic and pharmacologic management of weight gain. J Clin Psychiatry 1999;60(suppl 21): 31–36
56. Foster GD, Wadden TA, Vogt RA, et al. What is a reasonable weight loss? patients' expectations and evaluations of obesity treatment outcomes. J Consult Clin Psychol 1997;65:79–85
57. Granberry MC, Fonseca VA. Insulin resistance syndrome: options for treatment. South Med J 1999;92:2–15
58. Rossner S, Sjostrom L, Noack R, et al, for the European Orlistat Obesity Study Group. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. Obes Res 2000;8:49–61
59. Lipworth BJ. Clinical pharmacology of beta 3-adrenoceptors. Br J Clin Pharmacol 1996;42:291–300
60. Hanotin C, Thomas F, Jones SP, et al. Efficacy and tolerability of sibutramine in obese patients: a dose-ranging study. Int J Obes Related Metab Disord 1998;22:32–38
61. Bray GA, Blackburn GL, Ferguson JM, et al. Sibutramine produces dose-related weight loss. Obes Res 1999;7:189–198
62. Schuh LM, Schuster CR, Hopper JA, et al. Abuse liability assessment of sibutramine, a novel weight control agent. Psychopharmacology (Berl) 2000;147:339–346
63. Taflinski T, Chojnacka J. Sibutramine-associated psychotic episode. Am J Psychiatry 2000;157:2056–2057
64. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes: a 1-year randomized double-blind study. Diabetes Care 1998;21:1288–1294
65. Hill JO, Hauptman J, Anderson JW, et al. Orlistat, a lipase inhibitor, for

weight maintenance after conventional dieting: a 1-y study [see comments]. Am J Clin Nutr 1999;69:1108–1116
66. Anghelescu I, Klawe C, Benkert O. Orlistat in the treatment of psychopharmacologically induced weight gain. J Clin Psychopharmacol 2000;20:716–717
67. Privitera MD. Topiramate: a new antiepileptic drug. Ann Pharmacother 1997;31:1164–1173
68. Hussain MZ, Hussain S, Chaudry ZA. Topiramate as an anti-obesity agent. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 18, 2000; Chicago, Ill. Abstract NR709:249
69. Keung YK, Rizk R, Wu XY, et al. Drug-induced hypertriglyceridemia with and without pancreatitis. South Med J 1999;92:912–914
70. Echevarria KL, Hardin TC, Smith JA. Hyperlipidemia associated with protease inhibitor therapy. Ann Pharmacother 1999;33:859–863
71. Mefferd RB, Labrosse EH, Gawienowski AM, et al. Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics. J Nerv Ment Dis 1958;127:167–179
72. Clark ML, Johnson PC. Amenorrhea and elevated serum cholesterol produced by a trifluoro-methylated phenothiazine. J Clin Endocrinol Metab 1960;20:641–646
73. Clark ML, Ray TS, Paredes A, et al. Chlorpromazine in women with chronic schizophrenia: the effect on cholesterol levels and cholesterol-behavior relationships. Psychosom Med 1967;29:634–642
74. Simpson GM, Cooper TB. The effect of three butyrophenones on serum cholesterol levels. Curr Ther Res Clin Exp 1966;8:249–255
75. Braun GA, Paulonis ME. Sterol metabolism: biochemical differences among the butyrophenones. Int J Neuropsychiatry 1967;3:26–27
76. Clark ML, Braun GA, Hewson JR, et al. Trifluperidol and cholesterol in man. Clin Pharmacol Ther 1968;9:333–340
77. Serafetinides EA, Colmore JP, Rahhal DK, et al. Trifluperidol in chronic male psychiatric patients. Behav Neuropsychiatry 1971;3:10–12
78. Simpson GM, Cooper TB, Braun GA. Further studies on the effect of butyrophenones on cholesterol synthesis in humans. Curr Ther Res Clin Exp 1967;9:413–418
79. Sasaki J, Kumagae G, Sata T, et al. Decreased concentration of high density lipoprotein cholesterol in schizophrenic patients treated with phenothiazines. Atherosclerosis 1984;51:163–169
80. Sasaki J, Funakoshi M, Arakawa K. Lipids and apolipoproteins in patients treated with major tranquilizers. Clin Pharmacol Ther 1985;37:684–687
81. Muller-Oerlinghausen B. A short survey on untoward effects of fluperlapine. Arzneimittelforschung 1984;34:131–134
82. Fleischhacker WW, Stuppack C, Moser C, et al. Fluperlapine vs haloperidol: a comparison of their neuroendocrinological profiles and the influence on serum lipids. Pharmacopsychiatry 1986;19:111–114
83. Ghaeli P, Dufresne RL. Elevated serum triglycerides on clozapine resolve with risperidone. Pharmacotherapy 1995;15:382–385
84. Ghaeli P, Dufresne RL. Serum triglyceride levels in patients treated with clozapine. Am J Health System Pharm 1996;53:2079–2081
85. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998;21:245–250
86. Sheitman BB, Bird PM, Binz W, et al. Olanzapine-induced elevation of plasma triglyceride levels [letter]. Am J Psychiatry 1999;156:1471–1472
87. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767–770
88. Meyer JM. Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol 2001;21:369–374
89. Bouchard RH, Demers M-F, Simoneau I, et al. Atypical antipsychotics and cardiovascular risk in schizophrenic patients. J Clin Psychopharmacol 2001;21:110–111
90. Daniel DG, Weiden P, O'Sullivan RL. Improvements in indices of health status in outpatients with schizophrenia following a switch to ziprasidone from conventional antipsychotics, olanzapine or risperidone. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 16, 2000; Chicago, Ill. Abstract NR359:154
91. Kingsbury SJ, Fayek M, Trufasiu D, et al. The effects of ziprasidone on plasma lipids and glucose [poster]. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
92. Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am 1994;78:117–141
93. Gershon T, Olshaker JS. Acute pancreatitis following lisinopril rechallenge. Am J Emerg Med 1998;16:523–524
94. Brewer HB Jr. Hypertriglyceridemia: changes in the plasma lipoproteins associated with an increased risk of cardiovascular disease. Am J Cardiol 1999;83:3F–12F
95. Rywik SL, Manolio TA, Pajak A, et al. Association of lipids and lipoprotein level with total mortality and mortality caused by cardiovascular and cancer diseases (Poland and United States collaborative study on cardiovascular epidemiology). Am J Cardiol 1999;84:540–548
96. Addington J, el-Guebaly N, Campbell W, et al. Smoking cessation treatment for patients with schizophrenia. Am J Psychiatry 1998;155:974–976
97. Goldman LS. Medical illness in patients with schizophrenia. J Clin Psychiatry 1999;60(suppl 21):10–15
98. Kreisberg RA. Diabetic dyslipidemia. Am J Cardiol 1998;82:67U–73U; discussion 85U–86U
99. Patti L, Maffettone A, Iovine C, et al. Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyceridemia. Atherosclerosis 1999;146:361–367
100. Ginsberg HN, Goldberg IJ. Disorders of lipoprotein metabolism. In: Harrison TR, Fauci AS, eds. Harrison's Principles of Internal Medicine. 14th ed. New York, NY: McGraw-Hill; 1998:2138–2149
101. Harris WS. Nonpharmacologic treatment of hypertriglyceridemia: focus on fish oils. Clin Cardiol 1999;22(6 suppl):II40–II43
102. National Center for Health Statistics. E-stats: Prevalence of overweight and obesity among adults: United States, 1999. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm. Accessed July 19, 2001
103. Simansky KJ, Zorn SH, Schmidt AW, et al. The unique human receptor binding profile may be related to lack of weight gain with ziprasidone [poster]. Presented at the 152nd annual meeting of the American Psychiatric Association; May 19, 1999; Washington, DC