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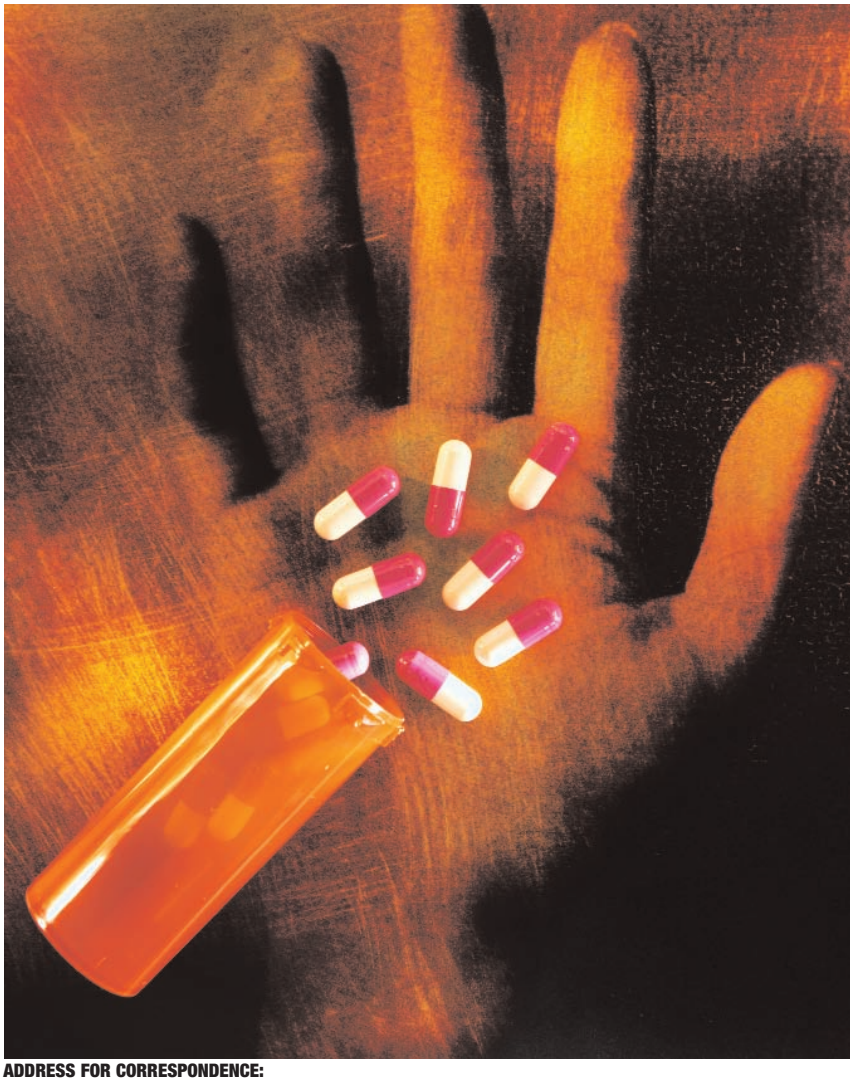
Psychotropic-Induced Weight Gain and Potential Pharmacologic Treatment Strategies

Weight gain has been associated with a variety of psychotropic medications, including atypical antipsychotics, lithium, divalproex sodium, and certain antidepressants. One acceptable method of quantifying weight and weight change is by using categories of the body mass index, or BMI. The BMI is determined by dividing weight in kilograms by height in meters squared. Categories of BMI in adults are presented in Table 1. In children and adolescents, BMI is interpreted by the percentile value for age and gender; a person with a BMI less than 85 percent is considered within the normal range; a person with a BMI of 85 to 95 percent is considered at risk for overweight; and a person with a BMI greater than 95 percent is considered overweight. The Centers for Disease Control has charts available for determining these percentiles at www.cdc.gov.

Excessive weight gain represents a significant risk to general health and well-being. Common complications are listed in Table 2. This risk becomes additive to the already increased baseline risk for medical comorbidity in patients



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with schizophrenia and bipolar disorders. The percentage of disease burden due to obesity is outlined in Table 3 and has special implications for women, including an increased risk of uterine cancer.[1]

THE METABOLIC SYNDROME

The metabolic syndrome, also known as the insulin resistance syndrome, is directly attributable to obesity and occurs in 47 million Americans, of which approximately 1 million are adolescents. The metabolic syndrome is a precursor state to type II diabetes mellitus (DM) and cardiovascular disease (CVD). The highest incidence of this syndrome is found in African-American and Mexican-American women. Children with the highest insulin resistance have been documented as well to be at the greatest risk of developing CVD.[2,3]

In 2001, the Adult Treatment Panel III (ATP-III) defined the metabolic syndrome; diagnostic criteria are listed in Table 3. Three of 5 criteria for the following must be met: increased waist circumference, increased serum triglycerides, decreased high density lipoprotein (HDL) cholesterol, increased blood pressure, or elevated fasting glucose.[4] Adolescent criteria for the syndrome have recently been defined[5] and are included in Table 4 as well.

SELECTIVE REVIEW OF WEIGHT GAIN CLASSIFIED BY PSYCHOTROPIC MEDICATION

Atypical antipsychotics.

The European Federation of Associations of Families of Mentally Ill People, (EUFAMI) conducted a study on the effects of atypical antipsychotics.[6] Of 441 patients surveyed, 91 percent reported side effects; 60 percent experienced significant weight gain. Fifty-four percent reported weight gain as the most difficult side effect, which may well affect patients' compliance with treatment.

An average weight increase of 10kg in patients treated with clozapine has been found.[7] An extra 416 deaths per 100,000 were estimated to be associated with this weight gain over 10 years, with 492 suicides per 100,000 estimated to be prevented. Due to medical complications, the magnitude of weight gain affects the risk of mortality and is, therefore, a crucial component of the potential risks versus potential benefits that determine overall outcome and success of a drug. In a five-year naturalistic study, 82 percent of patients who did not have DM Type II or an elevated fasting glucose at baseline, continued to gain weight while taking clozapine over 42 of the 60 months.[8] Patients with lower initial BMI gained more weight.

A mean weight gain of 8.3kg in 37 out of 39 adults treated with risperidone over a two-year period was found in a retrospective review.[9] Twenty of the 37 were then calorie-restricted; only three lost a negligible amount of weight (0.1kg/month), while 17 actually gained 0.4 kg/month over the next two years. The amount of weight gain was not considered dose-related.

Another retrospective controlled review, adjusted for age and gender, found a weight increase of 1.2kg/month in 37 child and adolescent inpatients taking risperidone for six months.[10] Unlike in adults, weight gain did not reach a plateau. Seventy-eight percent of those taking risperidone vs. 24 percent of an inpatient control group had clinically significant weight gain ($p<0.001$). Dose and concomitant medication was unrelated to the increase in weight.

A retrospective review[11] demonstrated mean weight change as 6.26kg for over 500 patients taking olanzapine versus 0.69kg in 103 patients taking haloperidol for 60 weeks. Weight increase tended to plateau after 39 weeks. A higher baseline BMI was predictive of lower long-term weight gain. Dose was not related to increase in weight gain.

An open-label, 18-month study of 427 adults with schizophrenia treated with clozapine resulted in an overall favorable effect on glycemic control and weight when a mean dose of 473mg/day of quetiapine was added.[12]

TABLE 1. Body mass index*

- **Underweight <18.5kg/m^2**
- **Normal weight = 18.5–25kg/m^2**
- **Overweight ≥25kg/m^2**
- **Obesity ≥30kg/m^2**
- **Severe obesity ≥35kg/m^2**

***Not as accurate in those with short stature, edema, and high muscle volume. Significance of BMI varies by age, gender, and ethnicity.**

TABLE 2. Complications of weight gain

- **Cardiovascular**
  -increased trigylcerides and cholesterol
  -hypertension/cor pulmonale
  -atherosclerosis
- **Endocrine**
  -new onset of Type II diabetes in children and adults
  -early menses/polycystic ovarian syndrome
  -hormonal changes
  -infertility and increased pregnancy risks
- **Gallbladder disease**
- **Pulmonary**
  -sleep apnea
  -pulmonary hypertension
- **Orthopedic**
  -musculoskeletal disorders
  -decreased mobility
- **Psychological**
  -Low self-esteem
  -demotivation

TABLE 3. Prevalence of obesity-related diseases

NIDDM	61%
Uterine Cancer	34%
Gallbladder disease	30%
Osteoarthritis	
inflammation related	24%
HTN	17%
CAD	17%
Breast Cancer	11%
Colon Cancer	11%
Dyslipidemia	(F>M) 21%
Sleep apnea	(M>F) 33–50%
Cancer-related death	(F>M) 33–55%

Wirshing, et al.,[13] compared weight gain between novel antipsychotics, including clozapine, olanzapine, risperidone, haloperidol, and sertindole among 92 male patients with schizophrenia who were participating in eight 20-week randomized clinical trials (RCTs). A stepwise weight intervention was put into place. The first step had each patient weighing himself/herself and reporting the weight during follow-up visits. If the subject gained more than 10 pounds, the second step of intervention began, which was to keep a food diary of all intake during the study. If the subject continued to gain weight even after keeping track of all food intakes, they were referred to a dietitian, exercise group, and weight loss support group. At the conclusion of the study, clozapine and olanzapine were reported as having the highest maximal weight gain as compared to risperidone, haloperidol, and sertindole. Weight gain reached a plateau at 10 weeks for subjects taking risperidone and sertindole. No relationship between initial and final weight and 5-HT2C receptor affinity was found. An exponential relationship between H1 receptor affinities and maximum weight gain was present when adjusted maximum weight gain was plotted against 1/H1 receptor affinity.

Lithium. A review of six previous studies on weight gain associated with lithium reflects an increase in obesity in up to 25 percent of patients. A small eight-week, prospective, uncontrolled study in inpatients diagnosed with bipolar I disorder who began lithium treatment found a mean weight gain of 5.9kg.[14] BMI increased from 23.8 to 26.8kg/m^2. Leptin levels rose from 6.9 to 10.3ng/mL, a significant difference (p<0.01), suggesting an association between leptin and lithium-induced weight gain.

Two older studies[15,16] demonstrated a mean weight gain of 4 to 10kg across 7 to 10 years, respectively. Risks for lithium-related weight gain included female gender, diabetes insipidus, prior overweight status, and exposure to other weight-increasing medications. Weight gain with lithium may plateau after two years. The mechanisms of action responsible for lithium-induced weight gain include an increased glucose uptake into the cells through stimulation of hexokinase and pyruvate kinase and inhibition of muscle protein kinase. An insulin-like effect has also been observed, resulting in glucose tolerance and an increase in insulin and insulin sensitivity. In rats, lithium also increases glucagon secretion.[17]

Valproic acid (VPA). Fifty-seven percent of adults with epilepsy treated with VPA gained more than 4kg (median gain 7.5kg; range 4.0–17.0).[18] The remaining 43 percent maintained a stable weight. No predictive factors, including family history of obesity, Type II DM, or weight gain during pregnancy, were determined.

In a group of children and adolescents treated with VPA for epilepsy, height and weight were recorded for up to three years after the start of treatment. A significant increase in weight gain was documented according to Z-score (which allows a comparison to same-age children) and BMI.[19] A significant decrease in the rate of growth was found in girls and was also associated with duration of treatment.

In adolescents and adults divided between treatment with VPA or lamotrigine, significant weight gain in the VPA group occurred by the end of Week 10, and continued.[20] Overall mean VPA-weight gain was 12.8±9.3 pounds, while mean LTG-weight gain was 1.3±11.9 pounds. Dose was not related to weight gain.

A cross-sectional study[21] examining valproate, weight gain, and reproductive hormone changes measured the increase in weight and BMI in 38 women being treated for bipolar I or bipolar II disorder with VPA or lithium over a mean of 26 months. The mean BMI of those taking VPA was 31.1kg/m^2, slightly greater than those taking lithium.

Antidepressants. Antidepressants commonly contributing to weight gain include the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), resulting in potential weight gain of 1.3 to 2.9 pounds per month.[22] Fifteen percent of those taking TCAs gain 10 percent of their initial body weight over the course of treatment.

Patients taking selective serotonin reuptake inhibitors (SSRIs) alone may also experience weight gain. In one retrospective study,[23] 17.9 percent of remitted depressed patients experienced more than a seven-percent weight gain while taking an SSRI. Another study found no difference in weight gain between patients taking fluoxetine compared to placebo for a 26-week period.[24] A six-month RCT found that 25 percent of patients taking paroxetine experienced a seven-percent weight gain,[25] as compared to 4.2 percent of those taking sertraline and 6.8 percent of those on fluoxetine.

Of the novel antidepressants, nefazodone and venlafaxine are considered to be weight-neutral whereas bupropion may actually result in weight loss and mirtazapine weight gain. There are no data on effects on weight for the use of combinations of antidepressants.

POTENTIAL PHARMACOLOGIC STRATEGIES FOR THE MANAGEMENT OF PSYCHOTROPIC-INDUCED WEIGHT GAIN

General pharmacologic strategies for weight reduction in patients with psychotropic-related weight gain potentially include the following medications: the psychostimulants, xenical, sibutramine, metformin hydrochloride, topiramate, nizatidine, naltrexone, and amantadine.

Stimulants, xenical, and sibutramine. No specific data has been published on actual use of stimulants for psychotropic-related weight gain. Potential reasons to avoid stimulant treatment include concerns of dependence in a patient with a substance abuse history or exacerbation of mania or psychosis in patients with underlying bipolar disorder or schizophrenia. Nonetheless, there is a large amount of data concerning stimulant use in the bipolar population in the child and adolescent age group, in which stimulants may be tolerated fairly well in some individuals who also have a history of comorbid attention deficit hyperactivity disorder (ADHD). Stimulant-related weight loss is usually in the range of five percent. This degree of benefit may be insufficient for the potential risks incurred of a stimulant trial; thus patients must be considered individually in deciding whether stimulant use is a reasonable option for them.

Xenical (Orlistat) is one of only two compounds approved by the Food and Drug Administration (FDA) for long-term treatment of obesity. Xenical works by inhibiting intestinal lipase, which also lowers cholesterol as well as absorption of beta-carotene and Vitamin E. Decreased absorption of dietary fat leads to a 5- to 10-percent decrease in weight. The indication for a patient to be prescribed xenical is a BMI of >28kg/m^2 with medical complications of obesity or a BMI of 30kg/m^2 without complications, as well as a previously failed trial of dieting. A multivitamin and low-fat diet are necessary. Twenty percent of those taking xenical develop fecal spotting, abdominal pain, flatus with discharge, and/or oily stools. In addition, the amount of weight loss may be again insufficient for the potential adherence difficulties in some patients with keeping a low-fat diet. A one-year treatment study, which included a diet of 600kcal/day energy deficit in addition to xenical, demonstrated only an 8.5-percent weight loss versus five percent in the placebo group. However, one potential benefit is that xenical does have a cholesterol lowering effect.[26]

Sibutramine HCL monohydrate (Meridia) is the other FDA-approved medication for long-term obesity treatment. Sibutramine inhibits the reuptake of norepinephrine, dopamine, and serotonin. The active ingredient is a racemic mixture of cyclobutanemethanamine. Sibutramine is contraindicated for use with SSRIs as their concomitant use can precipitate serotonin syndrome. Sibutramine also can inhibit beta-carotene and vitamin E absorption, making the addition of a multivitamin necessary. A 5- to 10-percent decrease in weight has been reported.[27] There are no longitudinal studies beyond two years for either compound.

Metformin hydrochloride. Morrison, et al.,[28] conducted a 12-week open-label study of metformin (Glucophage), an oral hypoglycemic agent. Nineteen pediatric patients, aged 10 to 18, who experienced a weight gain of more than 10 percent of baseline weight were included in the study. Weight gain ranged from 6.0 to 59kg with the children taking olanzapine, risperidone, quetiapine, or valproate for 1 to 36 months. Subjects were given metformin 500mg t.i.d. Subjects were instructed not to change their diet or level of physical activity during the study, yet fifteen of the 19 lost weight (mean ±2.93kg). Subjects also experienced a decrease in BMI (mean —2.2kg/m^2). Elevated liver functions, lactic acidosis, and

TABLE 4. Criteria for metabolic syndrome

Criteria	Adults	Adolescents
High triglyceride level, mg/dL	≥150	≥110
Low HDL-C level, mg/dL males females	<40 <50	<40 ≤40
Abdominal obesity (waist circumference [cm]) males females	>102 >88	≥90th percentile ≥90th percentile
High fasting glucose level, mg/dL	≥110	≥110
High blood pressure, mmHg	>130/85	> 90th percentile

diarrhea are potential side effects. Metformin's mechanism of action is to improve insulin sensitivity, decrease hepatic glucose production and intestinal absorption of glucose, and increase mitochondrial metabolism, which in turn stimulates aerobic respiration and beta-oxidation.

In an RCT of nondiabetic persons with elevated fasting post-load glucose, placebo was compared to metformin 850mg b.i.d. and lifestyle intervention over an average of 2.8 years. The incidence of type II DM was 11, 7.8, and 4.8 cases per 10 person-years, respectively, in each of the three groups, demonstrating that lifestyle management, including exercise and diet, resulted in the best outcome.[29]

Topiramate. Topiramate (Topamax) works to manage weight gain by activating gamma-amino-butyric (GABA) receptors. Although generally used as adjunctive therapy for partial seizures, studies have also reported it to be useful in the treatment of bipolar depression.[30]

Topiramate may modify weight gain associated with SSRIs, antipsychotic agents, lithium, and valproate; however, most of the data concerning weight loss in this population are from large prospective studies in the neurologic literature. A retrospective analysis of topiramate adjunctive therapy for partial seizures found that of the 1319 subjects, 85 percent of the adult patients reported weight loss. The average weight loss was 3.8kg, or 4.6 percent of baseline weight. The greatest reduction was seen with higher doses and in subjects with higher baseline weight.[31] Doses up to 200mg/day are typically prescribed.

In an open-labeled, prospective trial for seizures, 86 percent of 49 subjects lost weight over up to one year while taking topiramate. The average weight loss was 7.1±5.2kg, peaked at 12 to 18 months use, and was sustained. Mean dose was 128.6mg±54.7mg/day, and weight loss was greater in subjects with baseline BMI of more than 30kg/m^2. Improved glucose homeostasis was observed, as well as a trend toward an improved lipid profile.[32]

Topiramate also helped to manage weight in bipolar patients, reporting an average weight loss of 9.4 pounds in 20 patients over five weeks.[33] Doses ranged from 100 to 300mg/day. A chart review of 14 bipolar patients taking topiramate discovered a mean weight decrease of 29.75 pounds.[34] The mechanism of action causing weight loss appears to be related to reduced calorie deposition and reduced insulin levels.

Weight management strategies are still best met with exercise and proper diet...at the outset of treatment.

Data from three combined RCTs of topiramate for diabetic neuropathy, in which a combined 900 patients were treated with topiramate at doses of 100mg, 200mg, or 400mg/day, also demonstrated that most subjects experienced weight loss. A slight decrease in HbA1C and blood pressure as well as reduced plasma cortisol, leptin, and glucose were also seen. Adverse events can include cognitive dulling, hypoglycemia in one percent of pediatric patients, electrolyte changes, and abnormal vision/pain.[35]

A drug-drug interaction between metformin and topiramate has been reported in healthy volunteers undergoing a study examining the steady-state pharmacokinetics when metformin and topiramate were given together. Metformin mean Cmax and mean AUC0-12h increased by 18 percent. Oral plasma clearance of topiramate may be reduced when administered with metformin. The clinical significance of the effect of topiramate on metformin pharmacokinetics or of metformin on topiramate pharmacokinetics is unclear, but if topiramate is added or withdrawn in patients taking metformin, additional attention should be paid to monitoring glucose control.[30]

Histamine H2 blockers. An RCT undertaken by Eli Lilly & Company examined 175 subjects with psychotic disorders assigned to three groups, which received olanzapine with placebo, nizatidine at 150mg b.i.d., or nizatidine at 300mg b.i.d. for 16 weeks. Significantly less weight was gained at Weeks 3 and 4 for subjects on nizatidine 300mg b.i.d. than those taking the placebo ($p<0.05$). However, by Week 16 there was no statistical difference between the two groups.[36] The postulated mechanism is that H2 blockers may increase cholecystokinin, a peptide associated with the appetite regulation pathway.

Naltrexone. Zimmermann, et al.,[37] studied the effects of naltrexone on weight management in eight women who were taking TCAs plus lithium (6), antipsychotics (4), or SSRIs (2). Each patient had gained more than 6kg prior to naltrexone treatment. The patients were then given open naltrexone 50mg/day for eight weeks, with other medication doses kept stable. Weight gain reversed in five, stopped in two,

and attenuated in one patient; all patients reported a dramatic decrease in food craving. Transient adverse events included nausea (2), fatigue (2), and altered taste (1).

Amantadine hydrochloride. Amantadine (AMT) is an interesting choice to examine for the following reasons: there are preliminary data in an animal model, it has a high safety profile, documented use in children and adolescents, wide availability, reasonable cost, low abuse potential, few drug-drug interactions, and a broad range of uses, such as flu prophylaxis, treatment of cerebellar dysfunction, chronic hepatitis C, catatonia, and tardive dyskinesia.[38]

Deberdt, et al.,[39] conducted an RCT of 60 adult subjects with severe chronic mental illnesses who were taking olanzapine 5 to 20mg/day and had gained greater than or equal to five percent of initial body weight. Subjects were titrated to between 100 to 300mg/day of AMT with a mean dose of 235.6mg/day. Primary analysis was taken at 16 weeks with a double-blind extension lasting for eight weeks. In obese subjects, AMT appeared to induce weight loss while in less obese patients amantadine may limit weight gain. AMT was safe, well tolerated, and did not impair the therapeutic effects of the OLZ.

In an open study of amantadine in pediatric psychotropic-related weight gain,[38] eight boys and one girl, ages 9 to 16, were titrated to 100mg bid with AMT. The trial length averaged 14.5 weeks and ranged from 4 to 33 weeks. A significant increase in the group weight and BMI were found from baseline to beginning AMT (p=0.001). Mean weight (p=0.001) and BMI (p= 0.001) at baseline and follow-up on amantadine were approximately equal, lending support to the hypothesis that the rate of weight gain could be slowed. Weight change was strongly correlated with length of amantadine treatment for the entire group (p<0.05), and for the group minus subjects on clozapine (p<0.001). Four of 9 (44%) subjects lost more than 2kg without side effects. Although some subjects lost weight without side effects, amantadine was discontinued in one subject who developed orthostatic changes in blood pressure with dizziness and palpitations while concomitantly taking Adderall. Other subjects reported side effects, such as noticeable decreases in appetite, frequency of eating, and amount of food consumed. The anorectic effect was short, lasting less than 12 hours.

While women, children, and minorities may be at the highest risk of burden, preventing weight gain at the start of treatment may be a crucial step for everyone.

Conclusions

Pharmacologic treatment strategies for managing psychotropic-induced weight gain are emerging, but RCTs are necessary to examine these strategies as well as exercise and diet programs for weight loss in the mentally ill. Weight management strategies are still best met with exercise and proper diet, like avoiding "liquid" calories, at the outset of treatment. While women, children, and minorities may be at the highest risk of burden, preventing weight gain at the start of treatment may be a crucial step for everyone.

Prevention may need to take into account the different mechanisms by which weight gain is occurring depending on the associated psychotropic agent. Mechanisms of weight gain for all psychotropics are poorly understood, with much of the data being old, exploratory, and inconclusive. Resilience and vulnerability studies are still needed to identify patients who do not gain weight and why they react differently. Patients with significant weight gain should be systematically screened for comorbid risks for cardiovascular disease and diabetes, with detection resulting in early treatment to prevent complications.

Two differential effects on weight are suggested for further research: one, of preventing or slowing weight gain, and the other, inducing weight loss. The timing of such a strategy in treatment may be crucial to the outcome. Further studies demonstrating mechanism of action,

safety, effectiveness, and maintenance of response for these potential strategies are needed.

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