

Prevention and Reversal of Weight Gain Associated with Antipsychotic Treatment

Case Study and Commentary, *Christopher O'Keefe, MA, and Douglas Noordsy, MD*


There is growing concern about weight gain and related health problems associated with treatment with antipsychotic medications [1]. These medications are first-line treatments for psychotic disorders, including schizophrenia and schizoaffective disorder. Such disorders affect 1% to 2% of the general population and can be quite disabling [2]. Antipsychotic agents are also a key element in the treatment of bipolar disorders and to a lesser extent other psychiatric disorders.

Psychotic disorders typically present with symptoms grouped into 5 clusters: positive symptoms (hallucinations, delusions), disorganized speech and/or behavior, negative symptoms (flat affect, alogia, avolition, social indifference), cognitive symptoms, and mood symptoms [3]. These symptoms can often interfere with work, interpersonal relationships, and self-care. All antipsychotic medications can be effective in reducing positive symptoms and disorganization; however, newer agents may uniquely improve symptoms in the other 3 clusters. In order for a medication to be maximally effective, however, it must be well accepted by the patient. Weight gain may adversely affect patients' adherence to their medication regimens, undermining the success of pharmacologic treatment for schizophrenia [4,5]. Potential health problems related to weight gain include obesity, diabetes mellitus, hyperlipidemia, hypertension, osteoarthritis, and sleep apnea [6].

Providers must educate patients about weight gain as a potential side effect at the outset of treatment with antipsychotics, assess for changes in appetite and weight throughout treatment, teach patients the skills necessary to manage the process, and if needed, consider pharmacologic interventions. All of these interventions must take place in the larger context of treating the primary presenting psychiatric disorder. Taking modest steps to prevent and, if necessary, reverse weight gain can lead to better adherence to treatment regimens and fewer health problems, ultimately enhancing patients' quality of life.

CASE STUDY

Initial Presentation

 A 32-year-old man with a diagnosis of schizophrenia presents for a routine office visit as part of his ongoing care.

History

The patient is the third of 5 children. His parents were strict disciplinarians who emphasized the value of work and achievement. The patient states that he is the only one of his siblings who is not a successful achiever. He obtained a high school diploma and took some college courses. He has worked mostly as a prep cook or busboy. In his late twenties, he began experiencing auditory hallucinations and paranoid delusions. He was admitted to an inpatient psychiatric unit at that time and diagnosed with schizophrenia, paranoid type. At discharge, he was referred to a local community mental health center. There, the patient was seen at least quarterly by a psychiatrist and twice a month by a nurse for case management and supportive counseling. With the assistance of a vocational counselor, he has maintained a part-time job delivering pizza.

He is single and lives with his parents and relies on them for some financial support. He enjoys playing video games, watching sports, listening to music, and going out with his family.

A progress note reports that 6 weeks ago his antipsychotic medication regimen was changed to olanzapine, one of the second-generation antipsychotic agents. The note describes a long history of psychotic symptoms, including auditory hallucinations, paranoid delusions, and disorganized behavior. Attempts to control these symptoms began with thiothixene in the 1980s. His symptoms remained poorly controlled despite augmentation with chlorpromazine and gradual dose escalation of both agents. These symptoms prevented him from working and caused stress between the patient and his family. The olanzapine was prescribed to assist the patient in obtaining better symptom control. When asked, the patient reports that his symptoms are less bothersome now, and he has returned to work.

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ANTIPSYCHOTICS AND WEIGHT GAIN

Table 1. Estimated Mean Weight Change After 10 Weeks of Treatment with Antipsychotic Agents

Antipsychotic Drug or Study Condition	Mean Weight Change (kg)	95% Confidence Interval
Conventional antipsychotics		
Chlorpromazine	2.58	0.91 to 4.25
Fluphenazine	0.43	-0.65 to 1.51
Haloperidol	1.08	0.35 to 1.81
Molindone	-0.39	-2.43 to 1.65
Thioridazine/ mesoridazine	3.19	1.39 to 4.99
Second-generation antipsychotics		
Clozapine	4.45	0.91 to 4.25
Olanzapine	4.15	3.82 to 4.48
Risperidone	2.10	1.69 to 2.51
Sertindole	2.92	1.76 to 4.08
Ziprasidone	0.04	-0.49 to 0.57
Other conditions		
Nonpharmacologic control	1.33	0.84 to 2.80
Placebo	-0.74	-1.60 to 0.12
Polypharmacy	1.82	0.84 to 2.80

Data are from reference 8.

Physical Examination

The patient is 5'11" tall and weighs 225 lb with a body mass index (BMI) of 31. His heart rate is 100 bpm, blood pressure is 150/90 mm Hg, and respiratory rate is 20 respirations/min. Skin is warm and dry, without rash. Neurologic examination is nonfocal, with mild, diffuse hyporeflexia. HEENT, cardiac, and pulmonary examinations are unremarkable. His abdomen is mildly obese, soft, nontender, and without masses, with normal bowel sounds.

On mental status examination, the patient's affect appears somewhat blunted. He denies suicidal or homicidal ideation. Speech is slightly tangential. He is oriented to person, place, and time.

- What are the risks for weight gain in patients treated with antipsychotic agents?

Risks for Weight Gain

In general, persons with schizophrenia have a greater tendency to be overweight and obese than do persons not diagnosed with schizophrenia [7]. Physicians in the 1950s noted that patients taking first-generation antipsychotic agents developed problems with obesity [8]. Weight gain remained

a modest yet persistent concern over the first 4 decades of treatment with the first generation of antipsychotics, but has become a growing concern in the past decade due to the introduction of a new generation of medications. Conventional or first-generation antipsychotics are potent blockers of dopamine-2 receptors. While they are often effective for controlling the positive psychotic symptoms of schizophrenia and related disorders, they can worsen negative and depressive symptoms [2]. Additionally, they are known to cause prolactin elevation and parkinsonian symptoms and can markedly increase the risk for movement disorders.

The second generation of antipsychotics, known as "atypical" or "novel" antipsychotics, are dopamine-2 and serotonin-2A receptor antagonists. This dual receptor blockade improves the agents' specificity in addressing the pathophysiology of schizophrenia by concentrating maximal dopamine blockade in the mesolimbic pathways while facilitating dopamine release in other dopaminergic tracts [9]. Second-generation antipsychotics are characterized by minimal neurologic and hormonal side effects (except risperidone) and by improvements in negative symptoms, mood, and cognition. However, weight gain has emerged as one of the most problematic side effects remaining with second-generation antipsychotic agents.

A review of existing studies of atypical antipsychotics suggested that the prevalence of weight gain is as high as 50%, depending on the medication [10]. There was, however, great variability in the prevalence for each medication between studies. Table 1 shows the results of a meta-analysis of 81 studies involving patients treated with antipsychotics in which weight change was reported [8]. A regression analysis was used to estimate weight change after 10 weeks of treatment with each antipsychotic. Consistent with other literature, clozapine and olanzapine were associated with the greatest average weight gain [11,12]. This association may be related to their similar receptor binding-profiles. The next greatest weight change was associated with first-generation agents thioridazine and mesoridazine. Only molindone was associated with a loss in weight, although ziprasidone appeared to be weight neutral. Data on quetiapine were not presented in this analysis, but in a systematic review of weight gain related to novel antipsychotics, that agent was associated with a weight gain similar to olanzapine and with more substantial weight gain than chlorpromazine, haloperidol, and placebo [10].

- What is the biological mechanism by which patients gain weight?

The mechanism by which antipsychotic agents may induce weight gain is not entirely clear. It is believed that blockade of

5HT_{2C}, α_1 -adrenergic, and/or histaminic receptors by second-generation antipsychotic agents distorts signals from the gut to the brain, leading to excessive appetite and an impaired or delayed satiety response [13]. Excessive caloric consumption presumably then leads to weight gain. However, ziprasidone has a relatively high affinity for 5HT_{2C} receptors, and it is the most weight-neutral agent among the group. The mechanism of action of weight gain associated with conventional antipsychotic agents is believed to be related to blockade of cholinergic, serotonergic, and histaminergic sites, all of which are related to appetite stimulation [14].

- Are there clinical and patient-related factors that indicate which patients are likely to gain weight?

Factors That Predict Weight Gain

Understanding factors that affect weight gain could guide treatment providers in the selection and dosing of antipsychotics so that patients' dual needs of symptom management and minimizing/avoiding side effects may be met. Unfortunately, the evidence tends to be limited and, at times, even contradictory due to differences in methods and assessment between studies.

Evidence suggests that weight gain will emerge and progress most rapidly during the first 3 to 20 weeks of treatment with the various second-generation antipsychotic agents [15]. For some agents, such as clozapine, the gain may be rapid at first (in the first 6 to 12 months) but continue at a slower rate beyond that point (over the next 36 months) [16]. This underscores the importance of recording patients' weight throughout treatment to be able to address both early and ongoing weight changes. There is little evidence that dose impacts weight gain; therefore, dosing should be titrated as needed for symptom control [15]. Some studies have indicated that patients who gain weight have a better clinical response, though other evidence is contradictory [15].

There are no gender differences in terms of which patients will gain weight, but there is a positive correlation between weight gain and age [17,18]. Patients treated with antipsychotics who smoke may gain less weight than those who do not smoke [15]. Patients in hospital settings are more likely to gain weight than community patients, perhaps due to unrestricted diet and limited physical activity [15,18]. Finally, some evidence suggests that patients with a lower baseline BMI are likely to gain more weight than patients with a higher baseline BMI [15].

Brief Physician Intervention



The physician notes that the patient weighs 10 lb more than he did at an office visit 6 months prior.

Concerned that this may be related to antipsychotic treatment, the physician reviews with the patient that weight gain is a common side effect of his antipsychotic medication, affecting about half of those treated. The mechanism of weight gain discussed earlier is explained to the patient in lay terms. The patient is urged to ignore his appetite as a guide and to "eat with his head, not his stomach." Since the patient lives with family, they are provided with information about weight gain and strategies to help the patient to focus on maintaining portion sizes rather than just eating when hungry. Arrangements are made to have the nurse case manager obtain the patient's weight monthly.

- What interventions can be used to try to prevent weight gain when antipsychotic agents are initially prescribed?

Preventing and Managing Weight Gain

Schizophrenia can produce substantial disability and is potentially life-threatening. Treatment responses to antipsychotic medication are typically partial at best, with a limited number of patients responding to any given agent. Some of the most effective antipsychotics are associated with the most weight gain [19]. Therefore, effective strategies for preventing and managing weight gain will ensure that treatment decisions can focus on maximizing efficacy and do not compromise functional outcomes due to concern over side effects.

Education

Patients and families must be educated about appetite stimulation and weight gain as a potential side effect and about strategies for their management. Because weight gain rarely occurs without appetite stimulation or impaired satiety, these factors are excellent markers for patients at risk. When patients report appetite stimulation or impaired satiety, they should be taught to plan their dietary consumption, as signals from the gut are no longer accurate guides to consumption.

Practitioners should also educate patients that they may develop particular cravings for calories at specific times. Common examples are eating foods rich in fats and eating carbohydrates in the middle of the night or while watching television. A related problem is increased eating at social events or other situations in which large quantities of food are readily available. Patients can use cognitive-behavioral techniques to avoid eating in response to these situations (Table 2). Additionally, they should be encouraged to avoid food high in calories, restrict the consumption of fat, and limit intake of high-caloric drinks [20]. It is important to explain this material in concrete terms using examples and to be sure that patients understand the concepts.

If family, professional staff, or other support people are

Table 2. Cognitive-Behavioral Skills for Managing Cravings

Technique	Examples
Put off consumption	When tempted to eat, wait 30 minutes before eating
Plan consumption	Plan portions in advance for both home and social gatherings (eg, limit self to one serving)
Self-talk	Use self-statements created with physician or independently to cope with hunger: <ul style="list-style-type: none"> • I've had the amount of food I planned, I'll stop eating now. • I'll feel better later if I don't eat this now.
Offer refusal	Behaviorally rehearse statements to decline offers of food
Restricting cues	Eat in one place, with a full place setting
Distraction	Participate in some activity incompatible with eating <ul style="list-style-type: none"> • Craft or other activity that occupies hands • Active exercise • Call a friend to do something not related to food

involved in the patient's treatment, they can be educated and involved in efforts to prevent weight gain [12]. A support person's objective observations may be especially important, as patients may not realize how much more they are eating. Patients being treated on an inpatient unit may be prescribed a restricted calorie diet in an attempt to prevent weight gain and to help them adjust to taking the medication while consuming the same number of calories.

Assessment of Weight, Appetite, and Satiety

Monitoring of body weight is especially important. Patients should be weighed at baseline, every 1 to 3 months in the first year of treatment, and at least annually thereafter. To ensure accuracy, it is preferable for the patient to be weighed at the physician's office rather than relying on self-report. BMI can be easily calculated by multiplying weight in pounds by 703, then dividing this number by height in inches squared [21]. **Table 3** presents classification of obesity by BMI. In addition to monitoring body weight, laboratory testing including measurement of fasting glucose and hemoglobin A_{1c} levels and a fasting lipid panel is indicated at baseline, every 3 months for the first 6 months, and every 6 to 12 months thereafter. As patients treated for schizophrenia are at increased risk for developing diabetes mellitus and hyperlipidemia, early detection and treatment may prevent these issues from disrupting treatment. Detection of increased blood sugar or lipids may also assist in motivating patients to manage their weight.


Table 3. Classification of Obesity by Body Mass Index (BMI)

BMI (kg/m ²)	Classification
18.5–24.9	Normal
25.0–29.9	Overweight
30.0–34.9	Obese
35.0–39.9	Medically significant obesity
40.0–44.9	Severe obesity
45.0–49.9	Super obesity
> 50	Supermorbid obesity

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It is also necessary to assess appetite and satiety. Patients should be asked about appetite. Do they find themselves eating more frequently or feeling hungry more often than before the medication was initiated? Similarly, practitioners need to assess satiety by inquiring whether patients find themselves eating more at meals or not feeling as full. By knowing whether one or both mechanisms is leading to increased caloric consumption, interventions can be chosen to manage the process.

1 Year Later

 The patient gains 37 lb in the first year he is treated with olanzapine at a dose of 20 mg/day, resulting in a BMI of 37. Auditory and visual hallucinations persist during the year, although they are less severe than they had been prior to initiation of treatment with olanzapine.

At the outset of the second year, the patient complains to his psychiatrist of increased paranoid ideation at work and says he is considering quitting his job. After discussing treatment options, both patient and psychiatrist are pleased with the improvement on olanzapine and choose to augment treatment with risperidone. The dose is titrated to 4 mg/day. The patient's symptoms decrease and he is able to maintain his job.

16 Months Later

Sixteen months after risperidone was added to his treatment regimen, the patient again presents for evaluation. At this point, he weighs 302 lb, a 77-lb increase from baseline. His BMI is 42, in the range for severe obesity. He complains that while the hallucinations are much better, he is embarrassed by his weight gain, feels stigmatized, and finds movement more difficult. Laboratory testing indicates that his triglycerides are 350 mg/dL and his fasting blood glucose is elevated at 120 mg/dL. In addition, the patient is experiencing an increase in symptoms. He acknowledges that he started taking his medications every other day for a period of

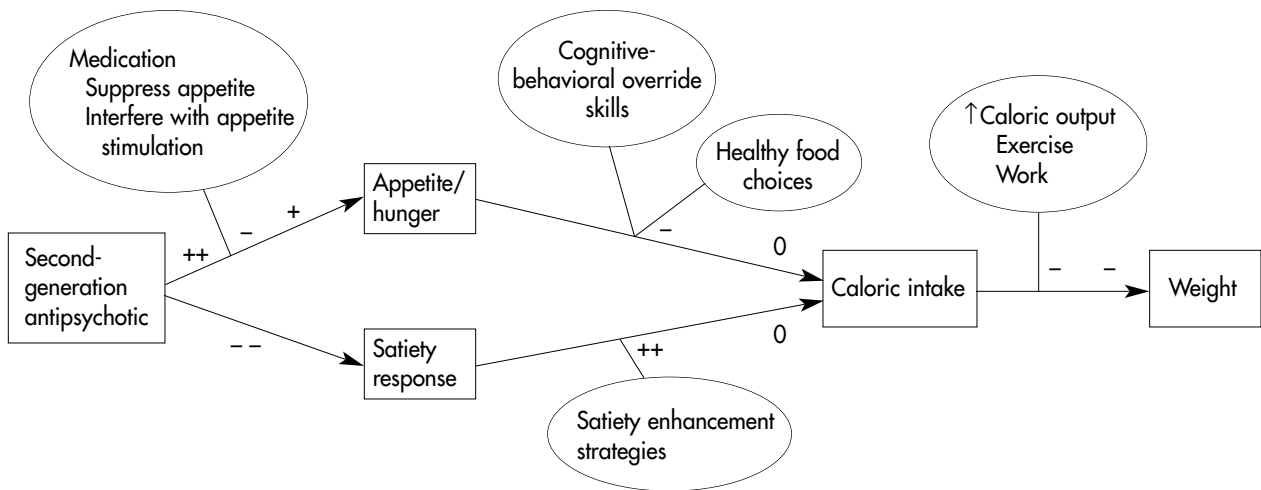


Figure. Interventions to prevent or reverse weight gain associated with second-generation antipsychotic medications.

2 weeks to see if his weight would decrease, without benefit. He asks for assistance in losing weight. On assessment, the patient reports both frequent eating throughout the day (increased appetite) and that he usually has 2 to 3 helpings at meals (impaired satiety response).

After discussing reasonable goals, the physician and patient agree on a goal of losing 27 lb over 12 months. The goal is entered in his treatment plan. He is referred to a consulting dietitian for weekly nutritional counseling. He begins walking daily, which the family encourages and the case manager reinforces.

- What are appropriate goals for weight loss?

Appropriate Goals for Weight Loss

Ideally, weight gain should be addressed early in its course, when the patient has gained as little as 5 lb. Initial treatment for persons who gain weight may consist of counseling by the physician, who assesses appetite and satiety responses and reiterates and/or supplements information about nutrition and exercise presented prior to initiating treatment with the antipsychotic agent [21]. As weight gain associated with second-generation antipsychotics nearly always involves overeating, this should be the focus of initial assessment and educational efforts.

Goal setting in collaboration with the patient is an important initial step. For patients who have gained little weight but for whom there is a concern about the potential for additional gain, an initial goal may simply be to arrest the weight gain. Patients who gain 10 lb or more should be encouraged to set a weight loss goal. The Institute of Medicine recom-

mends an initial goal of losing 5% to 15% of total body weight per year [22]. Anderson et al argue against setting larger goals, as a 5% to 15% loss represents the weight most individuals are able to lose and maintain over a year with state-of-the-art weight loss programs [21]. Smaller losses do improve health, including improvements in hypertension, hyperlipidemia, and diabetes mellitus [23]. Such goals can be formally entered in the treatment plan with the patient as a means of firming their commitment.

- What interventions are recommended for assisting patients with schizophrenia to cope with excessive hunger and impaired satiety?

The Figure presents a model for addressing the various factors that lead to and maintain weight gain for patients treated with second-generation antipsychotics. Having assessed the patient’s appetite and satiety responses, interventions can be selected to address the cause of the weight gain and may be supplemented by an increase in activity that can boost caloric output.

Dietary Counseling

Teaching patients to make healthy food choices can assist them in coping with excessive hunger by offering them alternative foods to eat. The consulting dietitian on our staff asks patients to record the foods and amounts they eat. This provides information for making dietary recommendations and giving feedback to patients about the amount of food they consume. The dietitian then focuses on changing 1 or 2 items in the patient’s diet at a time to a low-fat, low-calorie substitute. We have

found that almost a quarter of patients who gained weight as a result of treatment with an antipsychotic reversed the process. Most used some form of diet and some engaged in exercise, but a few used solely nonbehavioral interventions, such as medication or surgery [24].

An important factor in changing eating habits is to be very specific about amounts and even brands of food that are lower in fat and calories. Some patients need assistance with grocery shopping to help them to learn both the foods they should purchase and to control impulses to purchase high-fat foods. Given the amount of time and the familiarity with appropriate alternatives required, physicians may find a referral to a dietitian or trained staff member to be an appropriate alternative to performing this counseling themselves. Families may be able to help reinforce behavioral changes. Some patients may opt for a self-directed diet or participation in some form of commercial or self-help program.

Teaching Cognitive-Behavioral Skills

Cognitive-behavioral skills can be combined with dietary interventions so that patients with excessive appetite not only eat the right foods but also eat reasonable amounts (Table 2). Patients can be taught that cravings for food do pass, and that they can delay eating by self-talk or distraction. Patients lacking the skills to turn away food may need to behaviorally rehearse statements for declining offers of food or suggesting healthy alternatives to offers for unhealthy eating. Another strategy is to help patients develop plans for themselves around eating, such as restricting the amount of food at a meal or always leaving something on their plate. Alternatively, patients who have developed unhealthy routines, such as eating while watching television or in bed, may choose to create a plan whereby they only eat in a specific place with a full table setting. This strategy delays food intake, increases the response cost in order to eat, and helps patients to stop eating out of habit.

For those patients who have impaired or delayed satiety responses, additional interventions may be needed. Patients can be encouraged to drink a large glass of water or eat a salad or other vegetables prior to eating their meal so that they may feel satiated faster. Also, patients may need to plan the consumption of a certain amount of food, thereby basing consumption on portion size not their subjective feeling. Because there is a potential delay in satiety, patients can be instructed to consume food slowly so that they eat less by the time they are satiated.

Increasing Caloric Output

Two means of reducing weight through increasing caloric output are work and exercise. Unemployed patients with schizophrenia can increase their activity level through work. Even if the work is not vigorous, the movement associated with com-

muting and even minor tasks can be of benefit. Ideally, work should be incompatible with additional food consumption, such as working as a receptionist rather than as a cook at a fast-food restaurant. Introducing patients with schizophrenia to exercise programs may be more of a challenge due to negative and mood symptoms (avolition and depression). If patients can recognize that exercise does not have to be painful or hard and that any exercise is better than none, then they are more likely to engage [21]. Simple lifestyle modifications can also be recommended, such as taking stairs instead of the elevator. Residential and inpatient staff can encourage walking by accompanying residents on short walks. Some mental health centers offer an exercise group or referral to a consulting dietitian. We have found that an exercise induction group can successfully assist patients with severe and persistent mental illness to engage in regular exercise [25].

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- What pharmacologic interventions can be tried?
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Pharmacotherapy


There is growing evidence that some pharmacologic interventions may be helpful in preventing or managing weight gain associated with antipsychotic treatment. Such medication trials are particularly appropriate when there is a primary medical indication for their use. For example, high-dose histamine₂ (H₂) blockers have been proposed as an antidote to the antihistaminic properties of antipsychotics that may stimulate appetite. The best evidence for such treatment comes from a placebo-controlled trial of nizatidine in patients initiating olanzapine treatment [26]. Patients randomized to olanzapine plus nizatidine 300 mg twice daily demonstrated half the weight gain seen in the olanzapine plus placebo group. Nizatidine 150 mg twice daily did not differ from placebo. In our clinical experience, high-dose H₂ blockers may also help patients who have been on antipsychotics for years to experience less appetite stimulation and to successfully lose weight again. Many patients with schizophrenia are treated for gastrointestinal distress and may already be taking an H₂ blocker. Adjusting the dose to the higher range can be a simple, low-risk way to assist patients who are experiencing appetite stimulation related to antipsychotic treatment.

Small open trials of amantadine and metformin have indicated that these agents may also be helpful in managing weight gain associated with antipsychotic treatment [27,28]. Appetite suppression or weight loss are also known side effects of topiramate, amphetamines, bupropion, and lamotrigine. Many of these agents may be appropriate for treating comorbid medical or psychiatric conditions, and may even be able to be substituted for another agent in the same class that contributes to weight gain (ie, lithium, valproate, or

tricyclic antidepressants). There are no agents specifically approved by the Food and Drug Administration for prevention or management of weight gain associated with antipsychotic treatment. Several agents are approved for the treatment of obesity, such as orlistat and sibutramine.

Some physicians routinely prescribe an agent for prevention of weight gain when prescribing a high-risk antipsychotic. However, given the fact that weight gain is not universal and that appetite stimulation is a specific marker for those at risk for weight gain, we recommend a more conservative approach. We start with education and careful assessment of patients prescribed agents frequently associated with weight gain. In those patients who report appetite stimulation, we then proceed to behavioral interventions. When behavioral interventions prove inadequate or cognitive limitations limit successful implementation, we add pharmacologic interventions. The pharmacologic interventions described here are rarely adequate by themselves to prevent or manage weight gain. In our experience, combinations of behavioral (predominantly dietary) and pharmacologic interventions are associated with the greatest success.

Additional Follow-Up

 Over 5 weeks, the patient loses 6 lb but stops meeting with the dietitian. While his motivation to meet with the dietitian is low, he reliably meets with his case manager every other week. She assumes the role of weighing him, encouraging him to eat low-fat, low-calorie foods, and assisting him in applying cognitive-behavioral skills to lose weight. After 24 months, he weighs 275 lb, with a BMI of 38. A year later, his weight is 282 lb. (BMI of 39). In an effort to further assist the patient in losing weight, nizatidine 300 mg twice daily is prescribed. In addition, he begins to eat a banana at night to quell evening hunger and increases the distance he walks per day. A year later his weight is 210 lb, and his BMI is 29. Although still overweight, he is no longer obese. Both his triglycerides and fasting blood glucose levels are within normal limits. The case manager continues to reinforce healthy lifestyle choices, but it becomes less of a focus of treatment.

CONCLUSION

Second-generation antipsychotic agents represent a major step forward in our capacity to effectively manage the full range of symptoms of schizophrenia with few if any neurologic sequelae. Weight gain has emerged as the major side effect liability of many of these agents. Developing an effective approach to assessment and management of changes in appetite and satiety associated with these agents will maximize the practitioner's capacity to achieve optimal pharmacologic management for patients with schizophrenia and minimize adverse sequelae of treatment.

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References

1. Green AI, Patel JK, Goisman RM, et al. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry* 2000;22:224–35.
2. Shriqui CL, Nasrallah HA, editors. *Contemporary issues in the treatment of schizophrenia*. Washington, DC: American Psychiatric Press Inc; 1995.
3. Bell MD, Lysaker PH, Beam-Goulet JL, et al. Five component model of schizophrenia: assessing the factorial invariance of the Positive and Negative Symptom Scale. *Psychiatry Res* 1994;52:295–303.
4. Gitlin MJ, Cochran SD, Jamison KR. Maintenance lithium treatment: side effects and compliance. *J Clin Psychiatry* 1989; 50:127–31.
5. Kane JM. Management strategies for the treatment of schizophrenia. *J Clin Psychiatry* 1999;60 Suppl 12:13–7.
6. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health [published erratum appears in *Obes Res* 1998;6:464]. *Obes Res* 1998;6 Suppl 2: 51S–209S.
7. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 1999;60:215–20.
8. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001;62 Suppl 7: 22–31.
9. Stahl, SM. *Essential psychopharmacology: neuroscientific basis and practical applications*. 2nd ed. New York: Cambridge University Press; 2000.
10. Taylor DM, McAskill R. Atypical antipsychotics and weight gain—a systematic review. *Acta Psychiatr Scand* 2000;101: 416–32.
11. Ganguli R. Weight gain associated with antipsychotic drugs. *J Clin Psychiatry* 1999;60 Suppl 21:20–4.
12. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60:358–63.
13. Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry* 2001;62 Suppl 7:4–10.
14. Vanina Y, Podolskaya A, Sedky K. Body weight changes associated with psychopharmacology. *Psychiatr Serv* 2002; 53:842–7.
15. Blin O, Micallef J. Antipsychotic-associated weight gain and clinical outcomes parameters. *J Clin Psychiatry* 2001;62 Suppl 7: 11–21.
16. Umbricht DS, Pollack S, Kane JM. Clozapine and weight

- gain. *J Clin Psychiatry* 1994;55 Suppl B:157-60.
17. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. *Eur Neuropsychopharmacol* 1995;5:437-40.
 18. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? *J Clin Psychopharmacol* 1999;19:316-21.
 19. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *Am J Psychiatry* 2002;159:255-62.
 20. Kurzthaler I, Fleischhacker WW. The clinical implications of weight gain in schizophrenia. *J Clin Psychiatry* 2001; 62 Suppl 7:32-7.
 21. Anderson DA, Wadden TA. Treating the obese patient. Suggestions for primary care practice. *Arch Fam Med* 1999;8:156-67.
 22. Thomas PR, Institute of Medicine, editors. Weighing the options: criteria for evaluating weight-management programs. Washington (DC): National Academy Press; 1995.
 23. Wadden TA, Anderson DA, Foster GD. Two-year changes in lipids and lipoproteins associated with the maintenance of a 5% to 10% reduction in initial weight: some findings and some questions. *Obes Res* 1999;7:170-8.
 24. O'Keefe CD, Noordsy DL, Liss TB, Weiss H. Reversal of weight gain associated with antipsychotic treatment. American Psychiatric Association's Annual Meeting; 2001 May 5-10; New Orleans, LA.
 25. Hollow L. FITNESS-finding independence through nutrition, exercise, strength and socialization: Program summary. Final report to sponsor: New Hampshire Celebrates Wellness; 2001 September; Manchester, NH.
 26. Sacchetti E, Guarneri L, Bravi D. H(2) antagonist nizatidine may control olanzapine-associated weight gain in schizophrenic patients. *Biol Psychiatry* 2000;48:167-8.
 27. Floris M, Lejeune J, Deberdt W. Effect of amantadine on weight gain during olanzapine treatment. *Eur Neuropsychopharmacol* 2001;11:181-2.
 28. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry* 2002;159:655-7.

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