Behavioral Therapy for Weight Loss in Patients With Schizophrenia

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Compared with the general population, individuals with schizophrenia demonstrate an increased prevalence of obesity. While most antipsychotics are associated with weight gain, certain second-generation antipsychotics (SGAs) appear to be especially problematic. Weight gain and obesity are highly distressing to these patients, can reduce treatment adherence, and may increase the relative risk of serious medical conditions and all-cause premature mortality. The selection of an antipsychotic on the basis of its effectiveness and relative side effect profile is recognized as an important initial consideration in the treatment of schizophrenia. However, less is known regarding the efficacy of dietary, pharmacologic, and behavioral therapy in reducing antipsychotic-related weight gain and obesity. Behavioral therapy, in particular, is understudied, and there are relatively few controlled trials of its effectiveness in reducing SGA-induced weight gain. Although weight loss resulting from behavioral therapy has been observed mostly as a result of effective short-term interventions, controlled behavioral studies do exist to suggest that weight can be controlled long term. In addition, a small pilot study in patients with schizophrenia or schizoaffective disorder recently demonstrated that behavioral therapy that utilizes stepped interventions, involving body weight self-monitoring, diet, and exercise, can prevent weight gain in patients initiating treatment with SGAs. Additional studies of behavioral therapy for long-term weight control in patients with schizophrenia and other forms of severe mental illness are warranted.

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Antipsychotic medications are considered the mainstay of medical treatment for schizophrenia and other psychotic disorders. Since their introduction in the 1990s, second-generation antipsychotics (SGAs) have displaced first-generation antipsychotics (FGAs) as first-line agents due to their reduced risk of causing extrapyramidal symptoms and tardive dyskinesia. Despite these advantages, several SGAs have been reported to cause or exacerbate a number of metabolic disorders, such as hyperglycemia, dyslipidemia, and obesity.[1–4]

Among these metabolic disturbances, obesity has emerged as a common and serious problem in individuals with schizophrenia, with estimates of overweight and obesity ranging from 40% in those treated with FGAs to 50% in those treated with SGAs.[5] While the etiology of obesity in patients with schizophrenia remains a topic of debate, its physical and psychological complications are well documented.[6] It has been argued that the management of obesity is especially challenging in schizophrenia, as the disorder is frequently accompanied by deficits in attention, motivation, and memory, all of which may directly affect patients' ability to benefit from weight loss programs.[7] However, a number of studies[8–10] have shown that patients with schizophrenia are aware of their overweight or obese status, want to lose weight, and derive benefit from weight loss interventions and weight gain prevention strategies.

This report examines the problem of weight gain and obesity in people diagnosed with schizophrenia. After a review of the epidemiology, risk factors, physical and psychological complications, and management issues associated with overweight and obesity in patients with schizophrenia, the effectiveness of behavioral approaches for weight loss is discussed. Given how difficult it is for these patients to lose weight, the use of behavioral therapy techniques for the prevention of weight gain in patients being treated with SGAs is also considered.

OVERWEIGHT AND OBESITY IN SCHIZOPHRENIA

Incidence

Body mass index (BMI) is the most frequently used measure of excess weight in clinical and epidemiologic studies.[11,12] As defined by the National Institutes of Health and the National Heart, Lung, and Blood Institute, BMI is equal to a person's weight in kilograms divided by his or her height in meters squared (kg/m^2). Another method for approximating BMI is to multiply a person's weight in pounds by 703, and then divide the product by the height in inches squared ($[lb \times 703]/in^2$).[11] The classification of overweight and obesity according to BMI is shown in Table 1.[11]

As determined by BMI, compelling evidence exists indicating a high incidence of overweight and obesity in patients with schizophrenia.[8,12–14] A large retrospective analysis by Allison et al.[13] used age-adjusted data from the U.S. National Health Interview Survey (NHIS) to compare the distribution of BMI among individuals with and without schizophrenia. Men with schizophrenia had a mean BMI similar to that of men without schizophrenia (26.14 vs. 25.63, respectively), whereas women with schizophrenia were found to have a significantly higher BMI on average than women without schizophrenia (27.36 vs. 24.50, respectively; $p < .001$). In another publication, the same group of investigators[15] examined NHIS data obtained from 1987 to 1996

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Table 1. Classification of Overweight and Obesity by BMI[a]

Classification	BMI (kg/m^2)	Obesity Class
Underweight	< 18.5	
Normal	18.5–24.9	
Overweight	25.0–29.9	
Obesity	30.0–34.9	I
	35.0–39.9	II
Extreme obesity	≥ 40	III

[a]Based on reference 11.
Abbreviation: BMI = body mass index.

for trends in changes of BMI in the population. Of note, SGAs were introduced in 1990, in the middle of this period. Overall, there were no significant trends for increasing BMI in most persons with schizophrenia as compared to the general population, with the exception of young women. Starting in 1990, which happened to coincide with the year in which clozapine was introduced, women 18 to 30 years of age showed a significant increase in the prevalence of obesity.

In a Canadian study by Coodin,[12] the prevalence of obesity (BMI ≥ 30) was 42% (3.5 times higher) in persons with schizophrenia compared to 12% in the general population. The average BMI among male schizophrenics compared to males without schizophrenia in the general population was 28.49 and 26.3, respectively. Among females, the corresponding average BMI measurements were 30.02 and 24.3, respectively. Although this study did not examine the causal role of medications, the findings are in agreement with those of Allison et al.,[13] indicating that persons with schizophrenia are, in general, much heavier than the general population.

Causes

Numerous publications[5,6,16] have linked the use of virtually all FGAs and SGAs to weight gain. In comparing weight gain associated with the use of FGAs and SGAs, a meta-analysis[6] of 81 studies of at least 10 weeks' duration demonstrated that weight gain was higher in patients receiving the low-potency FGAs thioridazine or mesoridazine (both 3.49 kg [7.7 lb]) than in those receiving the high-potency FGA haloperidol (0.48 kg [1.1 lb]). Among the SGAs, weight gain was greatest for clozapine (3.99 kg [8.8 lb]) and olanzapine (3.51 kg [7.7 lb]), moderate with risperidone (2 kg [4.4 lb]), and minimal for ziprasidone (0.04 kg [0 lb]). During the period when the meta-analysis was performed, there were insufficient data available to determine the effects of quetiapine or aripiprazole on weight gain.

In patients with schizophrenia, certain SGAs can cause a rapid increase in body weight during the first few months of therapy that may not reach a plateau even after 1 year of treatment.[16] The majority of research on SGA-induced weight gain has shown that among the SGAs, clozapine and olanzapine are associated with the greatest increases in mean weight gain, and ziprasidone and aripiprazole are associated with the least. Risperidone and quetiapine have been linked to intermediate levels of weight gain.

Illness-related factors may predispose people suffering from schizophrenia to develop obesity. Long before the introduction of antipsychotics, Kraepelin,[17] for example, described rapid weight gain in some of his patients with schizophrenia. Jaspers also noted that in schizophrenia there is often "a great gain in weight during convalescence."[18(p247)] Thus, increased risk of obesity may be associated with schizophrenia per se, and this risk is further increased by some antipsychotics. This hypothesis is consistent with the results from studies[13] that have shown that schizophrenic patients treated with or without antipsychotics exhibited equal amounts of weight gain.

In addition, some researchers[19,20] have theorized that schizophrenia may be genetically linked to weight gain. Furthermore, because an association between schizophrenia and type 2 diabetes was made long before the advent of current lifestyles and pharmacologic interventions, a shared genetic basis between these diseases is being actively investigated.[21]

Environmental factors also may play a role in overweight and obesity in patients with schizophrenia. Weight gain has been observed in schizophrenics who have been homeless for many years and have not had access to supervised or supportive environments.[22] When this particular group of patients receives treatment, weight gain is thought to occur as a result of the stability and routine of having 3 meals provided on a daily basis. Such treatment-emergent weight gain may be a marker of clinical improvement, rather than an attribute of the pharmacologic properties of antipsychotic medication.

In the end, weight gain pathophysiology is a highly complex, multifactorial phenomenon. It is mediated by many central and peripheral factors involved in energy homeostasis.[23] The interaction of these factors with schizophrenia requires continued research.

Effects

A recent systematic review[24] of studies reporting total and all-cause mortality in pooled cohorts, including identified patients with schizophrenia, showed that life expectancy was 20% shorter among those with schizophrenia than in the general population. Suicides accounted for less than half of the excess mortality in the patients with schizophrenia, and cardiovascular disease was the most frequent "natural" cause of death. These data are in close accord with those from numerous large epidemiologic investigations,[25–29] which consistently found higher standardized mortality ratios and higher rates of cardiovascular disease among persons with schizophrenia as compared to contemporary cohorts in the general population. The major risk factors for cardiovascular disease include obesity, hyperlipidemia, diabetes, hypertension, and smoking, all of which have been shown to have a higher prevalence in individuals with schizophrenia.[30–36] Obesity is itself a major risk factor for the development of dyslipidemia, diabetes, hypertension, and heart disease.[37,38]

A number of factors that contribute to the high rate of medical comorbidities in patients with schizophrenia have been identified. These include insufficient access to primary and preventive health care, poverty, and an unhealthy lifestyle, characterized by lack of self-care, poor nutrition, smoking, lack of exercise, and engagement in high-risk sexual behaviors.[39–41] The effects of psychiatric illness and the medications used in its treatment on the endocrine and immune systems also contribute to the poor health of these individuals.[41,42]

Barriers to accessing proper medical care in patients with schizophrenia are well known (Table 2).[43] Furthermore, when these patients do seek physical care, the treatment they receive is frequently substandard.[41,42] A U.K. survey[44,45] of 2222 individuals receiving either FGAs or SGAs for severe mental illness

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Table 2. Barriers to Accessing Health Care in Patients With Schizophrenia and Those With Chronic Mental Illness[a]

Reluctance of psychiatrists and other mental health care providers to take comprehensive care of individuals with schizophrenia
Lack of continuity of care and follow-up by patients
Screening for physical problems is not routinely performed
Time and resource constraints in mental health care service settings
Difficulties for patients in navigating the health system
Cognitive and psychosocial deficits reduce accurate self-assessment
Lack of cooperation with providers
Fragmentation of the health care system
Lack of access to care
Lack of support in re-medication compliance
Difficulties in making lifestyle changes (eg, cessation of smoking and reducing alcohol intake)
Failure to receive primary health information and available primary health information inappropriate for needs

[a]Adapted with permission from Muir-Cochrane.[43]

clearly showed that ignoring weight gain and other patient concerns can worsen patients' poor physical health and further complicate the issue of how best to help them.

When surveyed, patients regarded weight gain as one of the most undesirable side effects of medication.[44] Patients' subjective experiences have been linked to medication compliance.[46] Both clinicians and patients often cite weight gain as a reason for switching to a different SGA. In a more recent survey,[47] as many as one third of all patients taking SGAs reported weight gain as one of the most significant side effects of their medication. Apart from the effect of weight gain on compliance, an inverse correlation between weight gain and quality of life measures has been reported.[48]

WEIGHT MANAGEMENT

The combination of reduced caloric intake and increased physical activity is the general goal of almost all weight loss programs. In addition to producing weight loss, this combination may result in a decrease in abdominal fat and an increase in cardiorespiratory fitness.[11] Most investigations of weight loss interventions can be broadly classified into pharmacologic or behavioral approaches or a combination of both approaches.

No pharmacologic agent has received U.S. Food and Drug Administration approval specifically for the treatment of antipsychotic-associated weight gain.[5] Although orlistat, a locally acting pancreatic and gastric lipase inhibitor, and sibutramine, a norepinephrine and serotonin reuptake blocker, have been approved for the long-term treatment of obesity, at best, these medications result in modest weight loss that is sustained only as long as patients continue to take the medication.[49] Uncontrolled studies[5] have reported potential benefit from amantadine, nizatidine, and topiramate. In randomized controlled trials, sibutramine combined with behavioral therapy has demonstrated efficacy in schizophrenic patients with olanzapine-associated[50] but not clozapine-associated[51] weight gain. There is limited evidence of weight loss in patients with schizophrenia who have received reboxetine[52] or amantadine.[53]

In patients who are already being treated with an SGA, the risks (e.g., drug interactions, adverse events, and adherence problems) of adding an anti-obesity agent to the treatment regimen probably outweigh the benefits. Therefore, nonpharmacologic approaches, such as behavioral therapy for weight management, may be a more favorable alternative to complement antipsychotic therapy in improving the health and well-being of patients with schizophrenia.

BEHAVIORAL THERAPY FOR WEIGHT LOSS

Most approaches to the treatment of obesity are described as "behavioral" and are based on learning theory[54] and the principles of classical conditioning.[55] In the last 20 years or so, cognitive approaches have been added to behavioral therapy programs to restructure and correct distorted and irrational thoughts that undermine motivation and progress in treatment.[55] Common components of most behavioral weight reduction programs include (1) goal-setting, especially on realistic short-term goals[56]; (2) self-monitoring of nutritional intake and physical activity[57]; (3) a nutritional focus, teaching and demonstrating healthy eating habits[58,59]; and (4) strategies to increase exercise and decrease sedentary behavior.[60–62] By changing the environment to alter cues, so as to increase appropriate (and decrease inappropriate) eating behavior, stimulus control was an early component of behavioral weight loss programs.[63,64] More recently, problem-solving has been included to help patients develop strategies individualized to their own unique situations.[54,65] Once weight loss is achieved, most behavioral programs move participants to relapse prevention or weight maintenance regimens.[66–70]

One of the most impressive demonstrations of the efficacy of lifestyle modification using behavioral strategies for weight reduction was observed in the Diabetes Prevention Program (DPP).[71,72] The DPP study randomly assigned > 3000 overweight or obese individuals with impaired glucose tolerance to a lifestyle intervention, a pharmacologic intervention (metformin), or placebo. Not only was significant weight reduction achieved in the lifestyle intervention group, but progression to diabetes also was reduced.[72] In addition, lifestyle intervention was approximately twice as effective as metformin in helping study participants lose weight. A second randomized trial[73] of lifestyle modification to prevent diabetes by means of weight reduction showed efficacy similar to that seen in the DPP study.[72]

Several reviews[58,70] of early behavioral weight loss programs as compared to current programs have suggested that results, especially in terms of mean weight loss, have improved over time. Additionally, it has been reported that the rate of weight loss has not changed much from the 1970s to the present, with a greater length of treatment as the potential reason for most of the increased efficacy achieved by contemporary weight loss programs.[74] It is difficult to extrapolate from the wealth of data on behavioral treatments for weight loss or prevention of weight gain to individuals with schizophrenia because they have been almost always excluded from such studies. For example, the DPP study[72] and its successor, the "Look AHEAD" study,[75] both list "serious mental disorder" among the exclusion criteria.

Fortunately, there are a number of studies[18,76–82] that have evaluated behavioral interventions for weight loss in patients with schizophrenia. The earliest study[76] was published in 1968, by which time obesity had already been identified as a problem in patients with schizophrenia. As such, the authors suspected that medications might play some role in weight gain. In this randomized controlled clinical trial, negative reinforcement was employed for failure to lose weight. Yet, despite the small sample size, there were significant treatment effects of behavior modification. However, the relevance of these results for patients today is tempered by the fact that the participants were long-term resi-

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dents in a State mental health hospital, their diet was strictly controlled, and the negative reinforcement strategy involved withholding money for each week that patients failed to lose weight.

Rotatori and colleagues[77] developed a behavioral treatment for use with children and mentally retarded adults with Down syndrome. Among the 14 study participants with schizophrenia, 7 were randomly assigned to receive behavioral treatment, and the remaining 7 were assigned to a waiting-list control group. After 14 weeks, patients in the behavioral treatment group had a mean weight loss of 3.30 kg (7.28 lb), with a weekly average weight loss of 0.23 kg (0.52 lb) per patient. In contrast, the control group had an average weight gain of 0.18 kg (0.40 lb) per patient.

Ball and colleagues[78] used the Weight Watchers program in 21 patients with olanzapine-related weight gain. Eleven patients completed the 10-week program. Weight loss was significant only for male patients (mean –3.32 kg [–7.31 lb], $p < .05$). No randomization was employed.

Littrell et al.[80] randomized individuals with schizophrenia to a 16-week behavioral treatment program focused on nutrition, wellness, fitness, and exercise, or to usual care (controls). A statistically significant difference in weight change between the 2 groups was observed posttreatment and at endpoint ($p < .05$). At endpoint, the mean weight change in the intervention group was –0.02 kg (–0.06 lb), while the mean weight change in the standard care group was 4.35 kg (9.57 lb). In both groups, men gained significantly more weight than did women ($p < .05$). On the basis of these outcomes, this could be classified as a preventive (weight gain minimization) study.

Two reports from the same group[7,81] demonstrated that patients with schizophrenia are capable of adhering to a program of modifying their lifestyle, losing weight, and participating in lifestyle interventions for up to 1 year. The study subjects were not, unfortunately, randomly assigned to treatment and control conditions.

Most recently, Brar et al.[82] conducted a 14-week, multicenter, open-label, rater-blinded, randomized study to evaluate the effects of group-based behavioral therapy for weight loss in 71 overweight and obese stable patients with schizophrenia or schizoaffective disorder who had been switched from olanzapine to risperidone. The subjects were recruited from 19 sites, and all were on treatment with risperidone as their only antipsychotic. A total of 72 consenting subjects were randomly assigned to a behavioral intervention program or usual care. Approximately 70% of the total sample ($N = 50$) completed the study. The intervention was delivered in 7 steps and included goal-setting, self-monitoring, stimulus control, incorporating lifestyle changes to increase physical activity, and changing snacking habits. The mean weight loss at study endpoint was significant in both groups ($p < .05$) and numerically greater in patients receiving behavioral therapy than in those receiving usual clinical care (–2.0 kg [4.4 lb] and –1.1 kg [–2.4 lb], respectively). In addition, more patients in the behavioral therapy group (26.5% [9/34]) than in the usual clinical care group (10.8% [4/37]) lost ≥ 5% of their body weight at study endpoint ($p = .082$). A post hoc analysis of 50 patients attending at least 1 behavioral therapy session showed that significantly more patients in the behavioral therapy than the usual clinical care group lost ≥ 5% of their body weight at study endpoint (32.1% [9/28] vs. 10.8% [4/37], respectively, $p = .038$) and at week 14 (subjects who completed the study: 40.9% [9/22] and 14.3% [4/28], respectively, $p = .027$).

Overall, this study[82] demonstrated the feasibility and effectiveness of a specific behavioral therapy program for weight reduction in patients with schizophrenia. More specifically, it showed that successful behavioral strategies for weight management should contain 3 key elements: (1) behavioral modification through self-monitoring and stimulus control, (2) diet, and (3) exercise. It is suggested that the behavioral therapy program utilized in this study could emerge as an option for use in any community setting that treats people with chronic mental illness. In contrast to other programs, it does not require special training to implement, has a very simple content, emphasizes a reduction in the quantity of food intake rather than extensive changes in food choice, and does not require the purchase of special food supplements. Its general applicability was confirmed by the ease with which it was implemented across the 19 study sites.

PREVENTION OF WEIGHT GAIN

Since attention to antipsychotic-induced weight gain is recent, it is not surprising that there are few studies of interventions to prevent it. One recently published study[83] evaluated the efficacy of a dietician-delivered nutritional counseling program to prevent weight gain in patients initiating treatment with olanzapine. Fifty-one individuals were randomly assigned either to 6 one-on-one nutrition education sessions, provided by a registered dietician, or to usual care. The primary outcomes were changes in weight and BMI at 3 and 6 months following baseline assessments. Subjects in the intervention group had gained significantly less weight than the controls at both 3 months (2.0 kg [4.4 lb] vs. 6.0 kg [13.2 lb], $p < .002$) and 6 months (9.9 kg [21.8 lb] vs. 2.0 kg [4.4 lb], $p < .013$). At 6 months, the BMI of the intervention group increased by 0.8 kg/m^2 compared to an increase of 3.2 kg/m^2 in the control group ($p < .017$). The proportion of patients in whom weight gain could be completely prevented was not, however, reported.

In a pilot study to prevent weight gain in subjects starting therapy from a variety of SGAs, Ganguli and Brar[10] adapted a standard behavioral intervention for weight loss to attempt to prevent weight gain. The intervention involved body weight self-monitoring, diet, and exercise. Since only some of the patients were expected to gain weight, the intervention was provided in steps of increasing complexity and intensity, triggered by actual weight gain (if any). A total of 51 subjects consented and were randomized; 46 completed at least 1 assessment after randomization (26 in the intervention group and 20 in the control group) and were included in the intent-to-treat analysis. Of those in the intervention group, 63% succeeded in not gaining weight. In the control group, the proportion of subjects who did not gain weight was only 22% ($p = .009$). There is a suggestion that the behavioral intervention was more effective in preventing weight gain associated with risperidone and quetiapine than the weight gain associated with olanzapine and clozapine. However, the sample was too small to test these differences statistically. This small study[10] and the study by Evans et al.[83] provide encouragement for further, more definitive studies to explore behavioral strategies to prevent weight gain in patients who are at risk for antipsychotic-induced weight gain. The suggestion in the study by Ganguli and Brar[10] that olanzapine-associated

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weight gain may not be as effectively prevented by behavioral strategies needs to be investigated in a more definitive manner.

There also have been attempts to explore the potential for preventing antipsychotic-induced weight gain by pharmacologic means. On a theoretical basis, it was proposed that histamine H_2 blockers might interfere with antipsychotic-induced weight gain. However, a study by Cavazzoni et al.[84] found that nizatidine had only a transient effect on ameliorating olanzapine-induced weight gain. Poyurovsky et al.[85] investigated another H_2 blocker, famotidine, in a double-blind, placebo-controlled trial in patients starting treatment with olanzapine. They found no difference in weight gain between subjects who were randomly assigned to receive famotidine and the control subjects.

Metformin, an insulin-sensitizing biguanide, is indicated for lowering blood sugar in type 2 diabetics and is often associated with weight loss. The possibility that it might prevent weight gain associated with olanzapine has been investigated. Early small pilot studies[86,87] suggested some benefit in terms of weight loss. However, a randomized, double-blind, placebo-controlled trial[88] failed to show any evidence that metformin attenuated olanzapine-induced weight gain.

The results of these studies provide support for further investigations of lifestyle interventions to prevent antipsychotic-induced weight gain. Since weight gain is associated with many classes of psychotropic medications besides antipsychotics, the behavioral interventions described should be investigated to prevent weight gain with those medications as well.

CONCLUSION

Obesity is a common condition in patients with schizophrenia and is frequently associated with the antipsychotic medications used to treat the disease. Weight gain that can lead to obesity has been negatively associated with the metabolic side effects of antipsychotic medications and poor lifestyle habits, with serious implications for the physical and psychological health of this patient population. Because these individuals often see psychiatrists more frequently than primary care physicians, mental health care professionals should assume a greater role in monitoring the physical health of their patients. The extra effort will help reduce the risk of obesity-associated medical comorbidities and their potentially life-threatening complications.

When selecting an SGA, clinicians should consider the side effect profile carefully to avoid the problem of weight gain in patients who are obese or already have existing weight problems. Overweight and obesity are strongly linked to the development of type 2 diabetes, which further complicates decision-making. Once a patient begins an antipsychotic regimen, the clinician needs to be vigilant and persistent in monitoring and intervening if weight gain occurs.

Behavioral therapy for weight reduction has been employed with variable success in patients with schizophrenia and schizoaffective disorder. Based on the results of the studies presented in this review, mental health care professionals treating people who are taking SGAs should educate and encourage them to follow dietary advice and engage in regular exercise and behavioral modification programs. All weight maintenance programs should include dietary therapy, exercise, and behavioral interventions. When persons taking SGAs cease to attend these programs, experience has shown that lost weight will almost always be regained.

Long-term weight control continues to be a challenge in patients with schizophrenia and other forms of severe mental illness who are treated with antipsychotic agents. Evidence that behavioral therapy is an effective approach for preventing weight gain and its potentially serious consequences in many of these patients continues to accrue.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), famotidine (Pepcid and others), haloperidol (Haldol and others), nizatidine (Axid and others), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), sibutramine (Meridia), topiramate (Topamax and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amantadine, famotidine, nizatidine, topiramate, and reboxetine are not approved by the U.S. Food and Drug Administration for weight loss.

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