Weight Loss Interventions for Patients with Schizophrenia

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Abstract

Introduction: Obesity, metabolic syndrome, diabetes, hypertension, and other risk factors for cardiovascular disease occur in persons with schizophrenia at rates twice those in the general population. Epidemiologic studies also reveal that persons with schizophrenia are likely to have their lives shortened by as much as twenty percent. Since obesity is an independent risk factor for heart disease, dyslipidemia, and diabetes, interventions that decrease the rates and severity of obesity have the potential for reducing both morbidity and mortality in persons with schizophrenia. **Methods:** A selective electronic MEDLINE search of published articles to review tested pharmacological and nonpharmacological interventions to address obesity in patients with schizophrenia was conducted. **Results:** Antiobesity drugs, behavioural approaches, and in select cases, bariatric surgery, may all lead to clinically significant weight loss in obese individuals with schizophrenia. We found no published long-term, randomized, controlled clinical trials to determine whether weight loss achieved in short-term studies is maintained. There were also few studies of combinations of the best behavioural and pharmacologic approaches. **Conclusion:** Weight loss is difficult to achieve, but attainable for individuals suffering from schizophrenia. Even small amounts of weight loss may provide significant long-term health benefits, if sustained. Rigorous controlled trials of combined pharmacologic and behavioural approaches, and maintenance studies with long-term follow up, are urgently needed.

Keywords: Schizophrenia, Obesity, Weight Loss, Treatment, Behavioural Therapy, Lifestyle

Introduction

Obesity rates have increased dramatically in the United States, and it is estimated that more than 66% of Americans are overweight, and among them, 32% are obese (1). Similarly, between 1999-2000, the combined unadjusted prevalence of total diabetes and impaired fasting glucose in adults aged ≥20 years was 14.4%. The prevalence further increases with age, reaching 33.6% by age ≥60 years (2). Physical health risks of excess body weight are numerous and include insulin resistance, diabetes mellitus, blood lipid abnormalities, hypertension, and coronary heart disease (3). The degree of obesity predicts associated health risks (Table 1).

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Submitted: Jan 24, 2007; Revised: Mar 1, 2007; Accepted: Mar 5, 2007

Endocrine and cardiovascular disease (CVD) often coexist and may share common risk factors. The metabolic syndrome, a clustering of atherogenic dyslipidemia, insulin resistance, impaired fibrinolysis, and increased susceptibility to thrombosis, hypertension, and inflammation, is an important predictor of mortality in the population (5) (Table 2). CVD and diabetes risk are significantly increased in the presence of the metabolic syndrome, particularly in men aged >45 years and women aged >55 years. The metabolic syndrome predicts diabetes onset beyond glucose intolerance alone (6).

Patients suffering from schizophrenia appear to be at equal or greater risk for obesity than the general population (7-9). A survey by Dickerson et al (10) found high rates of obesity (50% in females, 42% in males) in a random sample of outpatients with schizophrenia when compared to the United States population data. The sample also had higher rates of severe obesity. We, too, have observed an alarmingly high prevalence of obesity in a recently concluded survey of body weight, body mass index (BMI), and nutritional habits in patients with schizophrenia (11). In our survey,

Table 1 Classification of Overweight and Obesity by BMI, Waist Circumference and Associated Disease Risks (4)

			Disease Risk* Relative to Normal Weight and Waist Circumference	
	BMI (kg/m^2)	Obesity Class	Men ≤102 cm (≤40 in) Women ≤88 cm (≤35 in)	> 102 cm (40 in) > 88 cm (35 in)
Underweight	<18.5		—	—
Normal†	18.5–24.9		—	—
Overweight	25–29.9		Increased	High
Obesity	30–34.9 35–39.9	I II	High Very High	Very High Very High
Extreme Obesity	>40	III	Extremely High	Extremely High

*Disease risk for type 2 diabetes, hypertension, and CVD
†Increased waist circumference can also be a marker for increased risk even in persons of normal weight

Table 2 National Cholesterol Education Program (NCEP ATP III) Criteria for the Metabolic Syndrome (5)

Screening tools	
Hypertriglyceridaemic waist phenotype	
Simultaneous presence of:	
Fasting triglycerides ≥2.0 mmol/L	
Waist circumference ≥90 cm	
NCEP-ATP III criteria	
Presence of at least 3 of 5 parameters:	
Blood pressure ≥130/85	
Fasting glucose ≥6.1 mmol/L	
Fasting triglycerides ≥1.7 mmol/L	
HDL cholesterol	Men <1.0 mmol/L Women <1.3 mmol/L
Waist circumference	Men >102 cm Women >88 cm

60% of patients in the study sample (n=146) were obese, 22% were overweight, and only 18% were of normal body weight. Patients with schizophrenia appear to be predisposed for increases in abdominal fat accumulation regardless of drug treatment (12, 13), which is highly correlated with insulin resistance and diabetes (14). Recent data from the CATIE study shows that the metabolic syndrome is almost twice as prevalent in schizophrenia patients as in healthy controls (15). Thirty-six percent of males and 51.7% of females with schizophrenia (vs. 19.7% [m] and 25.1% [f] in the United States population) fulfilled criteria for the metabolic syndrome.

Patients with schizophrenia die earlier than people in the United States population; their life expectancy is 20% shorter, largely due to an increased risk for CVD (16). Numerous factors contribute including poor diet (11) and lack of exercise (17), high smoking rates (18), fewer health-promoting behaviours (19), underlying neurobiological abnormalities (20), and possible genetic determinants (21). Importantly, it is now known that a variety of antipsychotics cause weight gain (22), new-onset diabetes (23), and lipid abnormalities (24). Clinicians may find themselves in a double-bind situation; some of the most effective newer antipsychotics may also cause the greatest untoward effects on metabolic parameters. Fontaine and co-workers (25), for example, have estimated that the therapeutic benefits of clozapine, although considered a "life saving" drug for many, may be offset by associated premature death secondary to weight gain and cardiovascular complications.

Methods

An electronic MEDLINE (1951–February 2007) search of articles published pertinent to the use of pharmacological and nonpharmacological interventions to address obesity in patients with schizophrenia was conducted. The following keywords were used to gather relevant data: "schizophrenia," "weight loss," "weight gain prevention," "weight management," "diet," "exercise," "obesity," "antipsychotics," "lifestyle modification," "behavioural/behavioural intervention," and "behavioural/behavioural treatment." Resulting reports and randomized controlled trials were manually screened for relevance; only peer-reviewed reports and reports encompassing at least 75% of patients with schizophrenia and schizoaffective disorder were included. References were reviewed for pertinence as well. Several areas of interest were identified, and will be reviewed, that may benefit the obese patient with schizophrenia: medication choice and monitoring of metabolic risk factors, adjunct pharmacological and behavioural interventions, and bariatric surgery.

Table 3 ADA/APA Guidelines (28)

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	5 years
Personal/family history	x					x	
Weight (BMI)	x	x	x	x	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x			x

Initial Medication Choice

It seems self-evident that prevention of weight gain, in the first place, might be a desirable goal. Accordingly, considering the risk of weight gain might guide the initial choice of antipsychotic medication, especially in subjects with high risk of complications from obesity. Since certain mood stabilizers and antidepressants independently contribute to weight gain (26), and since there is some data to indicate that patients receiving two or more antipsychotics have higher rates of the metabolic syndrome and lipid markers of insulin resistance (27), close attention should be employed to avoid polypharmacy.

Monitoring of Metabolic Risk Factors in Patients on Antipsychotics

After initiation of antipsychotic therapy, periodic monitoring of a variety of metabolic parameters has been recommended by the American Psychiatric Association (Table 3). Should abnormalities arise, switching to less metabolically active drugs may be helpful (29). For example, Meyer et al (30), in a post hoc analysis, reported a significantly decreased prevalence of the metabolic syndrome (53.5% to 36.6%) in n=71 overweight schizophrenia patients twenty weeks after being switched from olanzapine to risperidone. Similarly, Weiden et al (31) found significant improvements in health status in outpatients with schizophrenia only six weeks after being switched to ziprasidone. Patients switched from olanzapine had a mean weight loss of 1.76 kg, and significant reductions in total cholesterol and triglycerides; those switched from risperidone had a lesser reduction in weight (–0.86 kg), but equally significant reductions in cholesterol and triglycerides. A switch can be particularly effective when new-onset diabetes occurs early in treatment, often resulting in remission of the diabetes (32). However, some patients gain weight on any antipsychotic medication, even those medications with a low propensity such as ziprasidone and aripiprazole, and other patients may respond only to a medication with a high propensity for weight gain like olanzapine or clozapine. In these situations it is fortunate that there are both pharmacologic and nonpharmacologic options for weight management.

Official Weight Loss Recommendations

It has been shown that even a small amount of weight loss is beneficial to the overweight individual (33). For example, a weight loss of five percent of initial body weight may reduce, eliminate, or prevent disorders such as coronary heart disease, hypertension, type 2 diabetes, hyperlipidemia, cardio-respiratory failure and other chronic degenerative diseases (34). A weight loss as little as one kilogram has been associated with a three-to-four month prolonged survival (35).

NHLBI guidelines (available online at http://www.nhlbi.nih.gov/guidelines/obesity) set forth official recommendations for weight management (36). A body mass index of ≥25 is associated with detrimental health outcomes and warrants treatment. Emphasis has been placed on energy expenditure as opposed to intake. There are three components to the official clinical guidelines (Table 4). An ideal combination of these measures should lead to a weight loss of about ten percent from baseline over a six-month treatment period, and translates into a suggested weekly weight reduction of approximately one to two pounds. For obese patients (BMI ≥30), and those with a BMI over 27 with associated medical comorbidities who do not lose weight despite efforts over a sustained period of approximately six months, adjunct pharmacotherapy may be considered as an additional step. However, there are several common behavioural strategies for achieving the above weight loss recommendation, and the application of these behavioural strategies in persons with schizophrenia will be reviewed below.

Table 4 NHLBI (National Heart, Lung and Blood Institute) Antiobesity Recommendations (36)

Low-calorie diet	- should be part of weight loss strategies in overweight and obese persons - fat intake <30% of caloric intake, but fat reduction alone is not sufficient - daily dietary intake reduced by 500 – 1000 kcal from baseline
Physical exercise	- should be part of a comprehensive weight loss therapy - ↓ abdominal fat, ↑ cardiovascular fitness - may help with maintenance of weight loss - moderate levels of physical activity for 30 to 45 min, 3 to 5 days/week
Behavioural strategies	- set attainable goals - regular self-monitoring of body weight and eating habits - stimulus control (eat in one place only, eat slowly)

Pharmacological Management

Despite increasing knowledge about centrally mediating pathways of appetite regulation and energy preservation, few medications thus far have shown significant sustained weight reduction properties. None of the currently available antiobesity drugs produces greater than a five-to six-pound weight loss over a year of treatment, and long-term efficacy remains to be established (37). For schizophrenia patients, choices of adjunct weight loss agents are limited (38). Adjunctive medications always increase the propensity for unpredictable side effects; some, for example, through centrally mediated actions, may exacerbate psychosis. Evidence for the effectiveness and safety of currently available adjunct medication interventions is limited. Long-term prospective trials are needed to better understand the risk-benefit profile of some of the suggested medication interventions.

Table 5 gives an overview of pharmacological management options that have been tested in the schizophrenia population.

***Anorexiants*—**fenfluramine and d-fenfluramine produced clinically meaningful weight loss in patients with schizophrenia (39, 40). However, significant adverse effects have lead to market withdrawal of these agents. Other anorexic agents, such as phenmetrazine or phenylpropanolamine, were unsuccessful in halting weight gain in patients treated with chlorpromazine (41) and clozapine (42), respectively.

***Orlistat*—**a gastric and pancreatic lipase inhibitor that blocks approximately 30% of the intestinal absorption of ingested dietary fat. It has been used for obesity treatment (BMI ≥30) and works best in conjunction with a hypocaloric diet containing less than 30% fat. Few case reports on the use of orlistat in the mentally ill population are available. Two patients treated with olanzapine were given orlistat 120 mg three times/day, resulting in a weight loss of nine pounds over four weeks in the first patient; and twenty-nine pounds over fourteen weeks in the second patient (43). Similarly, two antipsychotic-treated patients experienced a BMI decrease from 36 to 31 after one year of orlistat-addition; the second lost three kilograms over three months when treated with orlistat 120 mg three times/day (44). Orlistat is not absorbed systemically, and thus does not interfere with centrally acting psychotropic drugs. Its use, however, is limited through rather unpleasant gastrointestinal side effects including faecal urgency, oily spotting, and diarrhoea.

***Sibutramine*—**originally developed as an SNRI antidepressant, sibutramine was found to suppress appetite and cause weight loss and is approved by the FDA for this purpose (45). Sibutramine may centrally increase satiety through both serotonergic and noradrenergic actions and may prevent decline in energy expenditure that may accompany weight loss (46). Despite some controversy regarding its long-term risks, sibutramine is still approved for obesity treatment in most countries. In schizophrenia patients taking olanzapine, Henderson et al (47) administered 15 mg of sibutramine or placebo, along with dietary counselling. After twelve weeks of treatment, the sibutramine group had significantly greater mean weight loss than the placebo group (–8.3±2.4 vs. –1.8±1.6 lbs). Palpitations, sleep disturbance, constipation, increased blood pressure, and blurred vision occurred in a larger proportion of sibutramine patients as compared to placebo patients. In a subsequent investigation, Henderson et al (48) used sibutramine in a similar fashion for patients taking clozapine, but failed to show a statistically significant benefit for the drug over placebo.

***Fluoxetine*—**early clinical trials pointed to modest weight loss properties of fluoxetine. Goldstein et al (49) reported a mean body weight reduction of 5.1±6.9 kg in 458 obese and mentally healthy adults after twenty-eight weeks of treatment with fluoxetine. At study endpoint at week fifty-three, a small but no longer significant weight loss remained (–1.7±8.7 kg). In a similar study, obese diabetics receiving a hypocaloric diet (50) achieved a mean weight loss of 5.8 kg after receiving 60 mg fluoxetine for one year.

Concomitant fluoxetine and olanzapine treatment, however, has not been shown to significantly ameliorate weight gain introduced by olanzapine. Poyurovsky et al (51) studied thirty inpatients with schizophrenia in an eight-week, double-blind, placebo-controlled trial of treatment with olanzapine plus 20 mg fluoxetine or placebo. Patients gained an average of 9.14% (6.1±5.5 kg) and 9.49% (5.9±4.6 kg) over baseline body weight in the placebo and fluoxetine groups, respectively, and the difference in weight gain between the two groups was not significant.

Table 5 Studies of Pharmacological Interventions for Weight Reduction in Schizophrenia (only studies with at least 75% schizophrenia/schizoaffective patients)*

Authors	Sample Characteristics	Agent	Behavioural Augmentation	N	Duration weeks	Results
Correa et al, 1987 (56)	Inpatients; cross-over design	200–300 mg amantadine	NO	10	7	–1.82 kg; all lost weight
Floris et al, 2001 (57)	Outpatients receiving olanzapine; pre-post design	100–300 mg amantadine	NO	12	21	–3.5±2 kg weight loss
Breier et al, 2001 (62)	Schizophrenia and schizoaffective patients treated with olanzapine	Nizatadine 300 mg po twice daily	NO	132	16	H2 blocker –2.8 kg vs. placebo –5.5 kg
Cavazzoni et al, 2003 (63)	In- and outpatients on olanzapine	Nizatadine 150 mg bid vs. 300 mg bid vs. placebo	NO	175	16	No in-between group differences (+3.56±4.95 vs. 3.29±5.33 vs. 4.18 ±4.33 kg)
Poyurovsky et al, 2002 (51)	Inpatients receiving olanzapine	Fluoxetine 20 mg/d vs. placebo	NO	30	8	No difference (+5.9±4.6 kg for intervention vs. 6.1 ±5.5 kg placebo)
Poyurovsky et al, 2003 (59)	First episode schizophrenics on olanzapine 10 mg/day	Reboxetine 4 mg/day vs. placebo	NO	26	6	Significantly lower wt. gain in reboxetine group (+2.5±2.7 kg vs. placebo 5.5 ±3.1 kg)
Ko et al, 2005 (54)	Inpatients with schizophrenia; atypical antipsychotics	Topiramate 200 mg vs. 100 mg vs. placebo	NO	66	12	–5.35, –1.68, –0.35 kg with 200 mg, 100 mg, and placebo, respectively. Significant only in 200 mg group
Kim et al, 2006 (55)	Outpatients with schizophrenia; newly treated with olanzapine	Topiramate 50 mg bid vs. placebo	NO	48	12	Less weight gain with concomitant topiramate vs. placebo (2.66±1.79 vs. 4.02±2.52 kg)
Baptista et al, 2006 (66)	Inpatients with schizophrenia or schizoaffective disorder; switched to olanzapine	Metformin 850–1700 mg daily vs. placebo	NO	40	14	5.5 kg vs. 6.3 kg weight gain with metformin vs. placebo, not significant
Henderson et al, 2005 (47)	Patients with schizophrenia or schizoaffective disorder on olanzapine; BMI ≥30	Sibutramine (up to 15 mg/day) vs. placebo	YES	37	12	Significantly lower weight gain in sibutramine group (–8.3±2.4 lbs vs. +1.8 ±1.6 lbs for placebo)
Henderson et al, 2007 (48)	Patients with schizophrenia or schizoaffective disorder on clozapine	Sibutramine (up to 15 mg/day) vs. placebo	YES	21	12	No significant difference in weight loss between sibutramine and placebo groups

*Weight change in units reported in respective studies

***Topiramate*—** is an anticonvulsant that exerts its effect through central kainate/AMPA antagonism. Moderate dose-dependent weight loss properties have been observed. Early case series in psychiatric patients show at least modest weight loss properties when added to antipsychotic agents (52, 53). Ko et al (54), for example, investigated the effects of topiramate or placebo on body weight in sixty-six Korean inpatients suffering from schizophrenia who were treated

with novel antipsychotics. After a twelve-week period, significantly greater weight loss occurred in the 200 mg/day topiramate group compared with the placebo group and the 100 mg/day topiramate group; weight loss was 0.4% (0.3 kg), 2.2% (1.68 kg), and 6.8% (5.35 kg) for the placebo group, the 100 mg/day topiramate group, and the 200 mg/day topiramate group, respectively. The body mass index decreased significantly in the 200 mg/day topiramate group only. Similarly, waist and hip measurements also decreased more in the 200 mg/day topiramate group than in the 100 mg/day topiramate group or the placebo group. Another twelve-week, randomized, open-label, parallel group trial of outpatient subjects with schizophrenia started on olanzapine versus olanzapine plus topiramate (55) reported less weight gain in patients receiving concomitant topiramate (2.66±1.79 vs. 4.02±2.52 kg). Topiramate is burdened by dose-dependent side-effects such as paresthesias, cognitive slowing, and drowsiness which may preclude its use at higher doses in susceptible patients, thereby limiting its potential as a treatment for obesity.

***Amantadine*—**this agent has been primarily used to treat antipsychotic-induced motor side effects and Parkinson's disease, but there are reports that it may protect from excess weight gain or lead to modest weight loss when administered in conjunction with antipsychotics. Correa (56), in a sample of ten inpatients with schizophrenia receiving various neuroleptics, reported a mean weight loss of 1.82 kg after seven weeks of adjunct treatment with 200-300 mg amantadine, which was not sustained after withdrawal of amantadine. Floris et al (57) observed that in twelve patients with schizophrenia who had experienced a mean weight gain of 7.3 kg during olanzapine treatment, the addition of 100-300 mg amantadine led to an initial weight stabilization, and over the subsequent three to six months, led to an average weight loss of 3.5 kg. Similarly, a study conducted by Graham et al, (58), randomly assigned twenty-one adults who had gained at least five pounds with olanzapine to receive concomitant amantadine (N=12) or placebo (N=9) for twelve weeks. The authors observed that significantly fewer subjects taking amantadine gained weight, with a mean change in body mass index of –0.07 kg/m^2 for the amantadine group and 1.24 kg/m^2 for the placebo group. The effect remained significant when the authors controlled for the baseline body mass index and the length of olanzapine treatment. No changes in fasting glucose, insulin, leptin, prolactin, and lipid levels were seen. Although the exact mechanism of amantadine-induced weight loss remains unclear, it appears that amantadine may exert its effect through enhancement of central dopamine transmission, thereby raising the possibility for psychotic exacerbations.

***Reboxetin*—**this norepinephrine reuptake inhibitor has been used successfully in the attenuation of olanzapine-induced weight gain over a six-week period in first-episode schizophrenia patients (59). Twenty patients were allocated to treatment with 10 mg/day of olanzapine and either reboxetine 4 mg/day or placebo in double-blind design. Patients receiving reboxetine demonstrated a significantly lower increase in body weight (2.5±2.7 kg) than those given placebo (5.5±3.1 kg). The effect may derive from potent inhibitor action at central presynaptic norepinephrine transporters.

***Histamine H2-receptor blockers*—**agents such as nizatadine and cimetidine have been reported to aid in weight loss (60), probably through central reduction in appetite or suppression of gastric acid secretion (61). Breier et al (62), in a sixteen-week randomized, controlled trial, estimated the effects of 300 mg nizatadine twice daily versus placebo when added to olanzapine treatment for schizophrenia or schizoaffective disorder. The authors found no significant differences in weight loss after the sixteen-week treatment period, but noted improvements in glycaemic control and lipid levels in the nizatadine group. Cavazzoni et al (63) reported no significant group differences in weight loss over a fifteen-week treatment in 175 outpatients with schizophrenia, allocated to either olanzapine or placebo and 150 mg or 300 mg of nizatadine three times daily. Compared to baseline body weight, subjects gained 5.41% in the placebo group, 4.44% in the low-dose nizatadine group, and 4.34% in the high-dose nizatadine group, respectively.

***Rimonabant*—**endocannabinoids play a role in the regulation of appetitive behaviour. The cannabinoid-1 (CB1) receptor blocker rimonabant has been shown to inhibit both acute and long-term food intake in rodents. Chronic treatment with CB1 antagonists results in a sustained reduction in body weight in rodents (five weeks) and weight loss in humans (sixteen weeks) (64). Rimonabant has been examined in four Phase III clinical trials (20 mg vs. 5 mg vs. placebo), and modest weight loss properties were observed for the 20 mg dose. Pi-Sunyer et al (65) have reported (placebo-subtracted) a mean weight loss of –4.7 kg (CI 4.1–5.4), and improvements in triglyceride levels and HDL cholesterol after one year of rimonabant treatment of obese patients. Patients who were switched to a placebo after one year regained their weight, whereas patients who continued on 20 mg rimonabant sustained their weight loss and improvements in blood lipids. There were high dropout rates, and a small number of patients developed depressive symptoms while receiving rimonabant. No data is as yet available to estimate its effectiveness as a weight loss agent in psychiatric patients receiving antipsychotic medication.

***Metformin*—**Baptista et al (66) studied the potential prevention of weight gain through metformin addition in antipsychotic-treated inpatients with schizophrenia or schizoaffective disorder. Forty patients previously receiving conventional antipsychotics were switched to receive olanzapine (10 mg) and were randomly allocated to either metformin (800-1700 mg daily) or placebo addition; after a fourteen-week follow-up period, there were no significant differences in weight gain between the metformin group (5.5 kg) and the placebo group (6.3 kg). Similarly, no differences in changes of glucose, insulin, insulin resistance, and plasma

lipid levels were noted. Results of this study are in contrast with those of another recently published study of metformin addition-to treatment with novel antipsychotics in children and adolescents (67). This sixteen-week randomized double-blind placebo-controlled trial found a mean weekly weight gain of –0.03±0.33 kg in the antipsychotic-metformin group, which amounted to a significant difference when compared to the mean weekly weight gain of 0.31±0.44 kg in the antipsychotic-only group.

Behavioural Management

When compared to pharmacologic interventions, behavioural approaches (68) have thus far yielded more consistent and sustained weight loss results (38). Behavioural management may span from simple psychoeducation, counselling about food choices, or dietary restriction advice to more structured programs such as Weight Watchers or behavioural treatments proper that may include individual and group therapy. Surprisingly, there are still only a handful of studies that have examined behavioural weight reduction strategies in patients with schizophrenia using a randomized controlled clinical trial design (Table 6).

The earliest study published in 1968 (69), only a few years after introduction of antipsychotics, indicated that weight gain was already identified as a problem in institutionalized schizophrenia patients. The design was a randomized controlled clinical trial and the behaviour modification technique employed was negative reinforcement of withholding money from the participants for failure to lose weight. The number of subjects was small, but there were significant treatment effects for the behavioural intervention.

Table 6 Controlled Studies of Behavioural Weight Reduction in Schizophrenia*

Authors	Intervention	N	Randomization	Duration	Mean Weight Change
Harmatz and Lapuc, 1968 (69)	Diet only Diet + group therapy Diet + negative reinforcement	21	YES	10 weeks	Diet = 0 % Diet + group = –2% Diet + neg. reinforcement = –7%
Rotatori et al, 1980 (70)	Behaviour therapy adapted from Down's syndrome intervention	14	YES	14 weeks	Intervention = –7.3 lbs Controls = +0.4 lbs
Aquila and Emanuel, 2000 (72)	Low cal monitored diet; dietary education; group therapy; "supportive care"	31	NO Comparison to wt gained in past	1.5 years	NONE
Ball et al, 2000 (73)	Weight Watchers "exercise sessions" 3 walks per week/25 mins each	21	NO "Comparators" from same clinic	10 weeks	Significant weight loss only in men –7.3±5.9 lbs
†Vreeland et al, 2003 (74)	Nutrition counselling, exercise, behaviour treatment, motivational counselling	31	NO 14 controls retrospectively assembled	12 weeks	Intervention = –6.0 lbs Controls = +6.4 lbs
†Menza et al, 2004 (75)	"Multimodal weight control program" incorporating nutrition, exercise, and behavioural interventions	31	NO	52 weeks	Intervention = –6.6 lbs Controls = +7.0 lbs
Evans et al, 2005 (77)	Six 1-hour nutrition education sessions over 3 months in patients started on olanzapine	51	YES	6 months	Intervention = +2 kg Controls = +9.9 kg
Brar et al, 2005 (76)	Behaviour therapy; nutrition, exercise and behavioural interventions	72	YES	14 weeks	Intervention = –2 kg Controls = –1.1 kg (5% weight loss in 32.1% of intervention subjects vs. 10.8% in control subjects)
Weber and Wyne, 2006 (14)	Cognitive/behavioural (CB) group intervention in schizophrenia outpatients on novel antipsychotics	17	YES	16 weeks	CB group = –5.4 lbs Controls = –1.3 lbs

*Weight change in units reported in respective studies
†May represent the same patient sample

In the study by Rotatori and colleagues (70), a behavioural treatment originally developed for use with children and mentally retarded adults with Down's syndrome (71) was employed to facilitate weight loss in a small sample of fourteen residents living in a semi-independent residential facility. Subjects were randomly assigned to a behavioural therapy (BT) group (n=7) or to a waiting-list control group (n=7). After fourteen weeks, patients in the BT group had achieved a mean weight loss of 7.28 pounds, with a weekly average weight loss of 0.52 pounds per patient. In contrast, the controls gained 0.4 pounds on average.

In a study of previously homeless schizophrenia subjects with erratic eating habits conducted by Aquila and Emanuel (72), patients were provided with a 2,000 calories/day diet, with increased fresh produce and smaller portion sizes. All meals were limited to only one serving. Participants also attended support groups for weight reduction, as well as educational groups with a nutritionist. No weight reduction was observed at the conclusion of the study.

Ball and colleagues (73) used the Weight Watchers weight loss program in twenty-one patients who had gained significant amounts of weight while receiving olanzapine. Eleven patients completed the program. Weight loss was significant for male patients only, who lost a mean of 7.31 pounds (SD = 5.87 pounds, range 1 to 18 pounds) during the ten-week period. No randomization was employed, but a "comparison" group was constructed utilizing patients who "matched" the patients referred to Weight Watchers.

It is not entirely clear if the two reports from the same group (74, 75) involve the same subjects or whether they are derived from two cohorts. Unfortunately the subjects were not randomized to treatment and control conditions. However, they do demonstrate that schizophrenia patients are capable of adhering to a program of lifestyle modification for up to a year, and that patients both achieve and maintain significant weight loss throughout the course of the program.

A study of behavioural intervention to facilitate weight loss in outpatients with schizophrenia and schizoaffective disorder, by Brar et al (76), controlled for antipsychotic exposure. A group of sixty-five overweight or obese patients who had been maintained on stable doses of antipsychotic monotherapy with risperidone was included. Fifty subjects completed the entire program (28 controls and 22 experimental subjects.) Among the completers, a significant in-between group weight loss difference was found (–2.84±3.5 kg for the BT group vs. –0.8±2.8 kg for controls.) The BT subjects experienced greater mean loss of weight and BMI as compared to the control subjects.

Evans et al (77) investigated the effects of six nutrition counselling sessions spread over three months versus no such intervention in fifty-one patients newly started on olanzapine, and then followed both groups for an additional three months. After three months, individuals in the control group had gained significantly more weight than those in the treatment group (+6.0 vs. 2.0 kg), and at six months, the control group continued to show significantly more weight gain since baseline than the treatment group (9.9 vs. 2.0 kg). Weber and Wyne (14) conducted a cognitive/behavioural group intervention for weight loss in seventeen patients with schizophrenia or schizoaffective disorder patients treated with only one newer antipsychotic. The cognitive/behavioural intervention consisted of once weekly one-hour group sessions for sixteen weeks. Patients in the treatment group lost 5.4 pounds on average, whereas patients in the control group lost 1.3 pounds, a difference that did not achieve statistical significance.

It has now been demonstrated that combining behaviour therapy and pharmacotherapy for weight loss is more effective than either treatment administered by itself (78). There is a need for rigorous clinical trials in persons with schizophrenia in which the best evidence-based behavioural treatments are combined with pharmacologic weight loss medications.

Bariatric Surgery

Severe and treatment-resistant obesity, with comorbidities, is a potential indication for weight loss surgery. Patients selected usually have a BMI of at least 40; or a BMI ≥35 and associated medical comorbidities (79). Despite the risks, weight loss surgery can produce clinically significant and durable weight loss in appropriately selected individuals (80). Persons with severe mental illnesses such as schizophrenia are often not considered good candidates for bariatric surgery, but this assumption is not based on any solid evidence. In a small study of morbidly obese patients with schizophrenia (n=5), three received a duodenal switch operation, one underwent a sleeve gastrectomy, and one underwent a biliopancreatic diversion. Probands not suffering from schizophrenia undergoing similar bariatric surgery were used as a control group. The schizophrenia group experienced a similar percent of excess weight loss as control patients, with approximately 11% body weight lost by one month post surgery and increased weight loss over time (81). We would not recommend ruling out bariatric surgery for persons with schizophrenia, but careful selection and preparation of subjects, and attentive long-term follow up and support should be available before considering this option.

Conclusions

Weight loss can be consistently achieved by caloric restriction, but it generally requires behaviour modification to ensure adherence to weight reducing dietary regimens (82). Even though overweight and obese persons suffering from schizophrenia may be at a greater disadvantage due to their need to take medications that can induce or exacerbate weight gain, studies show behavioural treatments produce results similar to those obtained in the general population. Thus, evidence-based weight loss strategies should be readily available in the treatment settings in which persons with

schizophrenia are served. If sufficient weight loss is not attained with behavioural techniques, pharmacotherapy and, if necessary, surgical options should also be considered. Given the well-established risks of weight gain and the difficulties inherent in achieving weight loss, attentive monitoring of weight and early intervention to prevent and reverse weight gain would be desirable. Early indications are that behavioural approaches can be used to prevent weight gain in schizophrenia (83), but more research is urgently needed. As pointed out in a recent systematic Cochrane review, the data from pharmacologic approaches to weight loss are even less robust than that for behavioural interventions (84), and thus more research, especially studies which explore combinations of pharmacologic and behavioural strategies, are needed.

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