Behavioral Interventions for Antipsychotic Medication–Associated Obesity: A Randomized, Controlled Clinical Trial

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ABSTRACT

Objective: To demonstrate the effectiveness of a Diabetes Prevention Program–inspired 12-month behavioral intervention for patients with severe mental illness (SMI) and medication-associated obesity.

Method: This randomized, controlled, parallel, superiority study screened 225 volunteers from November 2005 to August 2008 at the VA Greater Los Angeles Healthcare System. 122 outpatients with *DSM-IV*–diagnosed SMI taking antipsychotic medications who had ≥ 7% weight gain or body mass index (BMI) > 25 were randomized by computer-generated number to Lifestyle Balance treatment intervention (n = 60) or usual care control (n = 62) groups. Clinical raters were masked to randomization. Treatment intervention included weekly classes and individual counseling for 8 weeks, food and exercise diaries, rewards, caregiver consultations, and monthly booster classes and counseling for 1 year. Controls received self-help materials and visited at equivalent intervals without formal classes or counseling. Outcomes were changes in anthropometric measurements, psychiatric symptoms, health knowledge, and glucose, hemoglobin A1c, and lipid levels.

Results: Our intention-to-treat analysis found significant differences in predicted trajectory of mean weight change between the groups over 12 months ($P < .01$), with treatment participants expected to lose an average 4.6 kg, while control participants would gain an average 0.6 kg. BMI and body fat percentage followed the same pattern. Both groups demonstrated statistically significant improvements in health knowledge quiz scores over time ($P = .006$), without significant difference between groups.

Conclusions: Treatment was more effective than usual care control in treating medication-associated obesity, independent of SMI diagnosis, antipsychotic medication, and knowledge gained, suggesting that behavioral interventions are effective in SMI patients.

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Severe mental illnesses (SMIs) are among the most costly medical conditions due to their chronicity and association with vocational impairments, cardiovascular disease, and suicide. Second-generation antipsychotic (SGA) medications offer a treatment option with less extrapyramidal side effect risk compared to first-generation antipsychotic medications. However, many SGAs are associated with weight gain, dyslipidemia, and obesity, increasing risk of diabetes and cardiovascular disease.[1–4] Weight gain also contributes to an estimated 50% medication nonadherence rate in patients treated with SGAs, potentially increasing psychiatric relapse up to 5-fold.[5] A practical and relatively inexpensive solution is needed to address SGA-associated weight gain and obesity with its related medical and psychiatric sequelae.

The existing literature indicates that a variety of educational, behavioral, and pharmacologic interventions can have a positive impact on obesity among those with SMI.[6–12] However, most trials have been either uncontrolled or of relatively short duration. Our 12-month randomized, controlled, parallel, superiority study examined the efficacy of a multimodal behavioral intervention, based on the Lifestyle Balance Program[13,14] of the Diabetes Prevention Program (DPP), in a large sample of SMI patients. Our hypotheses were that subjects with SMI and SGA-associated obesity who participated in active treatment would lose more weight, improve health knowledge, and have improved psychiatric symptoms than those in a usual care control group. Other hypotheses, regarding effects on treatment adherence and lifestyle changes, are still under investigation.

METHOD

Participants

The study, consistent with the principles of the Belmont Report, was approved by a VA Greater Los Angeles Institutional Review Board and registered with ClinicalTrials.gov (identifier: NCT00344500). From November 2005 to August 2008, 225 volunteers were screened from psychiatric clinics at the Veterans Hospital in West Los Angeles. A sample size of n = 60 per group was determined assuming a conventional medium effect size,[15] 2-tailed α set at 0.05, and desired power of 80. After the procedures and possible side effects were fully explained, 122 volunteers were willing and able to give consent and per their medical records met the following inclusion criteria: (1) *DSM-IV*–diagnosed SMI

Clinical Points

- Antipsychotic medication–associated obesity can compound morbidity and mortality for persons with severe mental illness. Simple-to-implement behavioral programs are needed to offer practical and inexpensive solutions.
- Clinicians can help their patients with this Lifestyle Balance program to reduce weight and improve depression and negative mental health symptoms.

(schizophrenia, schizoaffective disorder, bipolar disorder, or posttraumatic stress disorder with psychotic symptoms), (2) an increase of ≥7% body weight or body mass index (BMI) > 25 while taking SGAs, and (3) age 18–70 years (Figure 1). After complete description of the study to the subjects, written informed consent was obtained. Patients were paid $10 per study visit.

Randomization

Clinical raters were masked to randomization. Coordinators assigned subjects by computer-generated random numbers, with balanced allocation ratio (1:1), to either a Lifestyle Balance (LB) intervention or a Usual Care (UC) group. Plans to stratify by medications were not implemented due to statistical power concerns. Medication management was provided by nonstudy clinicians who could change medications or dosages as clinically necessary. However, subjects were terminated from the study if they discontinued antipsychotic use. Fourteen subjects in the UC group were switched to LB after 6 months of UC participation at their request. These change-over subjects were not included in any analyses involving the UC group.

Interventions

The LB program (n = 60) consisted of 8 weekly education classes, dietary monitoring, recommendations for 30 minutes of exercise 5 days per week, and individual coaching on nutrition and healthy lifestyles. Core classes, derived from the DPP website,[13] were followed by monthly booster classes for the remainder of the year. Subjects and/or caregivers maintained food and exercise diaries that were reviewed individually along with the subjects' individualized goals for the first 8 weeks and monthly thereafter until week 52. Subjects were quizzed at weeks 8, 26, and 52 about exercise and healthy eating habits. Small rewards (eg, $10 gift certificates) were provided for achieving weight loss and exercise goals. DPP instructions for fat and calorie restriction were recommended with a goal of achieving weight loss through a 500-calorie daily deficit. LB participants' caregivers also received support from program dietitians. Group exercise activities led by LB instructors were offered, but optional. Subjects were primarily guided by staff to exercise options within the VA clinics and the community.

Subjects randomized to UC (n = 62) were encouraged to exercise and eat healthy and were given publicly available, printed self-help materials regarding weight loss, exercise, and nutrition. Follow-up visits for weight measurement, data collection, and completion of questionnaires were scheduled at the same intervals as for LB subjects.

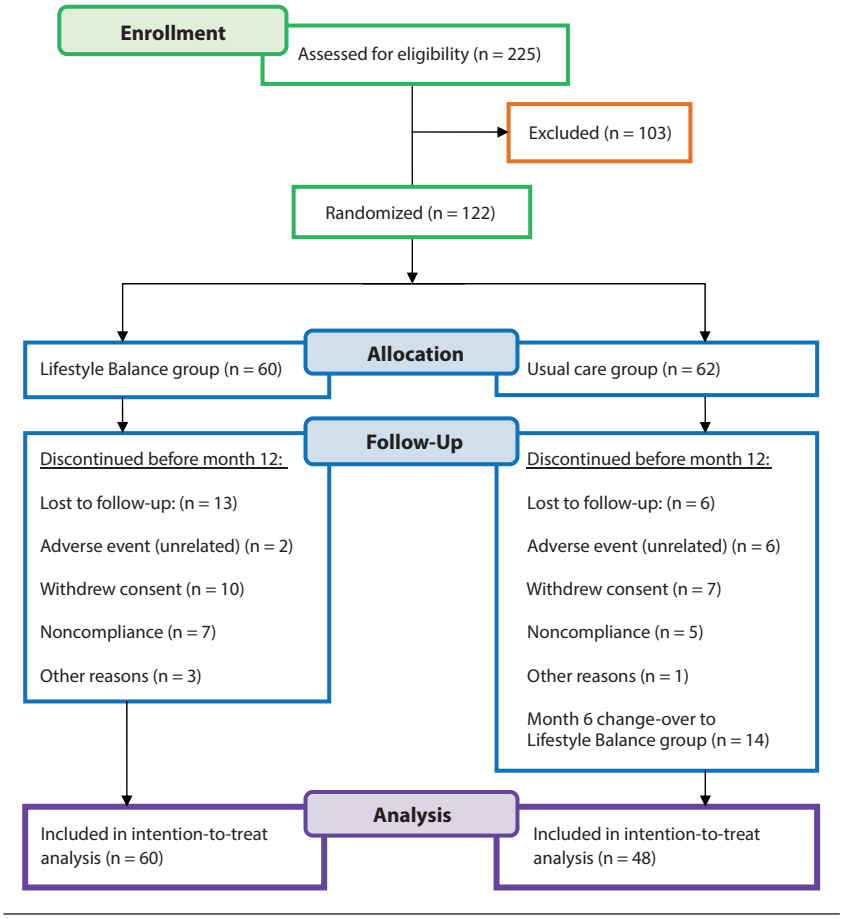
Measures

Subjects had a physical examination and Framingham cardiac risk assessment[16] at baseline and final visits. Vitals and anthropometric measures, including body fat percentage obtained using the bioelectrical impedance analysis (Fat Loss Monitor HBF-306, Omron Healthcare, Inc, Lake Forest, Illinois), were taken at every visit. Laboratory tests for glucose, hemoglobin A1c, lipids, and urine protein and creatinine were completed at baseline and quarterly thereafter. The study physician performed clinical assessments at baseline and months 2, 6, and 12, including the 24-item Brief Psychiatric Rating Scale (BPRS),[17] the Clinical Global Impressions scale (CGI),[18] and the Hamilton Depression Rating Scale (HDRS).[19] Heinrich's Quality of Life scale (QOL)[20] and the Structured Clinical Interview Diagnostic Checklist for *DSM-IV* Axis I Disorders (SCID-I)[21] were administered at baseline and termination. Negative symptoms were quantified using the BPRS negative symptom subscale (emotional withdrawal, motor retardation, and blunted affect), insight was measured with the Self-Appraisal of Illness Questionnaire (SAIQ),[22] and motivation was assessed using the Motivational Interview to Assess Stage of Change (MI).[23,24] We also designed a 24-item mixed multiple choice and true/false Healthy Lifestyles Knowledge Quiz (HLQ; available from the authors on request) to assess general knowledge of the information provided to all subjects.

Statistical Analysis

Our primary, intention-to-treat statistical analysis was performed with SPSS using a general linear mixed model (GLMM) as the primary analysis for repeated measures. We chose the GLMM because it offers several advantages in the analysis of longitudinal data. It is a full information maximum likelihood approach that permits inclusion of all the available data and provides unbiased parameter estimates even if there are missing data under the condition that the data are missing at random. The GLMM approach assumes that every patient is on a specific trajectory over time and that both the slope and the shape of this trajectory are a potential function of group membership or other person-level covariates. Using a likelihood ratio test, we compared different options to model these trajectories (eg, quadratic, cubic, linear) and found that a linear model, which assumes that the same rate of change is maintained over the whole study, provided a good fit to the data. We therefore used a linear model of the average rate of change over time (slope) for all comparisons. To illustrate the magnitude of difference between slopes for major outcomes, we report the estimated difference at 12 months between 2 hypothetical participants with identical baseline characteristics other than study group assignment.

Figure 1. Recruitment and Participation Flowchart



RESULTS

Demographics

At baseline, there were no statistically significant differences in demographic, clinical, or metabolic characteristics between the UC and LB groups (Tables 1, 2, and 3, respectively). Both LB and UC groups had high rates of diabetes, hypertension, and dyslipidemia, but there were no significant differences between groups.

Weight and Metabolic Changes

As an initial step, we determined the proportion of participants who lost 5% and 7% of their baseline body weight over the course of the study in the 2 arms. In the UC arm, 19% of the participants lost 5% of their body weight, and 12% lost 7% of their body weight. In the LB arm, 1.7 times more people lost 5% of their body weight (33%), and 1.5 times more people lost 7% of their body weight (22%). These differences are not statistically significant from each other ($\chi^2_1 = 2.9$, $P = .09$, and $\chi^2_1 = 1.6$, $P = .21$, respectively).

Analyzing the complete dataset and leveraging the repeated measurements design of this study revealed significant differences in the predicted trajectory of mean weight change between UC and LB subjects over 12 months (treatment × time interaction: $F_{1,1275} = 68.75$, $P < .01$) (Figure 2). These significant differences persisted after adjusting for baseline weight. Based on the GLMM, the differences between 2 matched patients were such that an LB participant would be expected to lose an average of 4.6 kg over a year, while a UC participant would gain an average of 0.6 kg in the same time period. BMI trajectories were also significantly different between the 2 groups (treatment × time interaction: $F_{1,1135} = 76.34$, $P < .01$). On average, an LB participant would be expected to lose 1.7 BMI points over a year, while a matched UC participant would gain 0.6 BMI points. Change in body fat percentage followed the same pattern, with an expected 2% body fat reduction for an LB subject vs a 1.5% gain for a matched UC subject (treatment × time interaction: $F_{1,1149} = 61.8$, $P < .01$).

Laboratory tests measuring glucose and lipids showed no statistically significant differences in trajectories between the 2 treatment groups, with the exception of HDL cholesterol (treatment × time interaction: $F_{1,1159} = 4.3$, $P = .015$), for which a mean increase of 6.4 mg/dL was predicted among LB subjects over a year compared to a 0.1-mg/dL increase in the UC group.

Psychiatric Symptoms

Psychiatric symptoms were included as time-varying covariates in the GLMM to explore relationships between

Table 1. Demographics

	Usual Care Group (n = 48)		Lifestyle Balance Group (n = 60)	
	n	%	n	%
Sex				
Male	42	87.5	54	90.0
Female	6	12.5	6	10.0
Ethnicity				
African American or black	24	50.0	25	41.7
Asian or Pacific Islander	0	0.0	2	3.3
Caucasian, white	19	39.6	24	40.0
Hispanic, Latino, or Spanish origin	3	6.3	6	10.0
Native American or Alaska native	0	0.0	0	0.0
Mixed heritage or other	2	4.2	3	5.0
Living situation				
Own home	0	0.0	1	1.7
Rental home/apartment	6	12.5	16	26.7
With relatives	2	4.2	1	1.7
Board and care	40	83.3	42	70.0
Homeless	0	0.0	0	0.0
Marital status				
Married	8	16.7	4	6.7
Single/cohabiting	24	50.0	27	45.0
Divorced/widower	16	33.3	29	48.3
Education				
No diploma	3	6.3	5	8.3
High school diploma/GED	36	75.0	47	78.3
Bachelor's or equivalent degree	9	18.8	6	10.0
Higher professional degree	0	0.0	2	3.3
Occupation				
Paid work	3	6.3	6	10.0
Unpaid work	3	6.3	1	1.7
None	42	87.5	53	88.3

Abbreviation: GED = general educational development.

Table 2. Baseline Clinical Characteristics

	Usual Care Group (n = 48)		Lifestyle Balance Group (n = 60)	
	n	%	n	%
Medical comorbidity				
Hypertension	27	56.3	33	55.0
Dyslipidemia	23	47.9	32	53.3
Diabetes	11	22.9	15	25.0
Metabolic syndrome	25	52.1	40	66.7
Obesity	32	66.7	40	66.7
Required ETT	5	10.4	7	11.7
SCID diagnosis				
Schizophrenia	28	58.3	21	35.0
Schizoaffective disorder	8	16.7	12	20.0
Bipolar disorder	9	18.8	23	38.3
Other	3	6.3	4	6.7
Antipsychotic (weight gain risk)				
Olanzapine/clozapine (high)	11	22.9	5	8.3
Risperidone/quetiapine (medium)	20	41.7	24	40.0
Aripiprazole/ziprasidone (low)	7	14.6	21	35.0
Other	3	6.3	2	3.3
Multiple	7	14.6	8	13.3
	Mean	SD	Mean	SD
Age, y	49.58	9.1	49.67	6.9
Length of illness, y	20.5	11.8	18.86	11.8
Age at onset, y	28.21	10.12	30.47	11.5
Baseline psychopathology ratings				
BPRS, total	33.4	8.0	34.9	8.8
CGI rating	3.4	0.8	3.4	0.8
HDRS, total	10.0	5.9	12.7	7.4
QOL, total	54.7	18.9	61.1	22.4
SAIQ, total	76.6	9.18	79.1	9.4
ASC,[25] total	26.2	3.7	25.6	3.7
MI rating	2.9	0.7	2.9	0.7

Abbreviations: ASC = Antipsychotic Side-effect Checklist, BPRS = 24-item Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, ETT = exercise tolerance test, HDRS = Hamilton Depression Rating Scale, MI = Motivational Interview to Assess Stage of Change, QOL = Heinrich's Quality of Life scale, SAIQ = Self-Appraisal of Illness Questionnaire, SCID = Structured Clinical Interview Diagnostic Checklist.

Table 3. Baseline Metabolic Findings[a]

	Usual Care Group (n = 48)		Lifestyle Balance Group (n = 60)	
	Mean	SD	Mean	SD
Vital signs				
Weight, kg	106.7	15.6	105.3	21.0
BMI	34.3	4.8	34.1	5.3
Waist circumference, cm	119.1	11.4	117.1	14.5
Percent body fat	30.2	6.6	30.8	5.7
Laboratory tests				
BP systolic sitting, mm Hg	123.5	11.9	126.7	13.3
BP diastolic sitting, mm Hg	82.4	10.6	83.1	10.4
Glucose, mm/dL	114.6	60.0	103.9	38.6
HDL, mm/dL	37.5	9.1	37.3	8.9
Triglycerides, mm/dL	161.5	101.4	161.3	117.9
LDL, mm/dL	114.2	36.1	111	30.9
Total cholesterol, mm/dL	184.9	43.8	178.9	38.1
Microalbumin (mg)/creatinine (g)	13.8	26.7	16.12	39.7
Framingham risk, CHD % chance	10.8	7.4	11.2	5.8

[a]No statistically significant differences between the groups.
Abbreviations: BMI = body mass index, BP = blood pressure, CHD = coronary heart disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

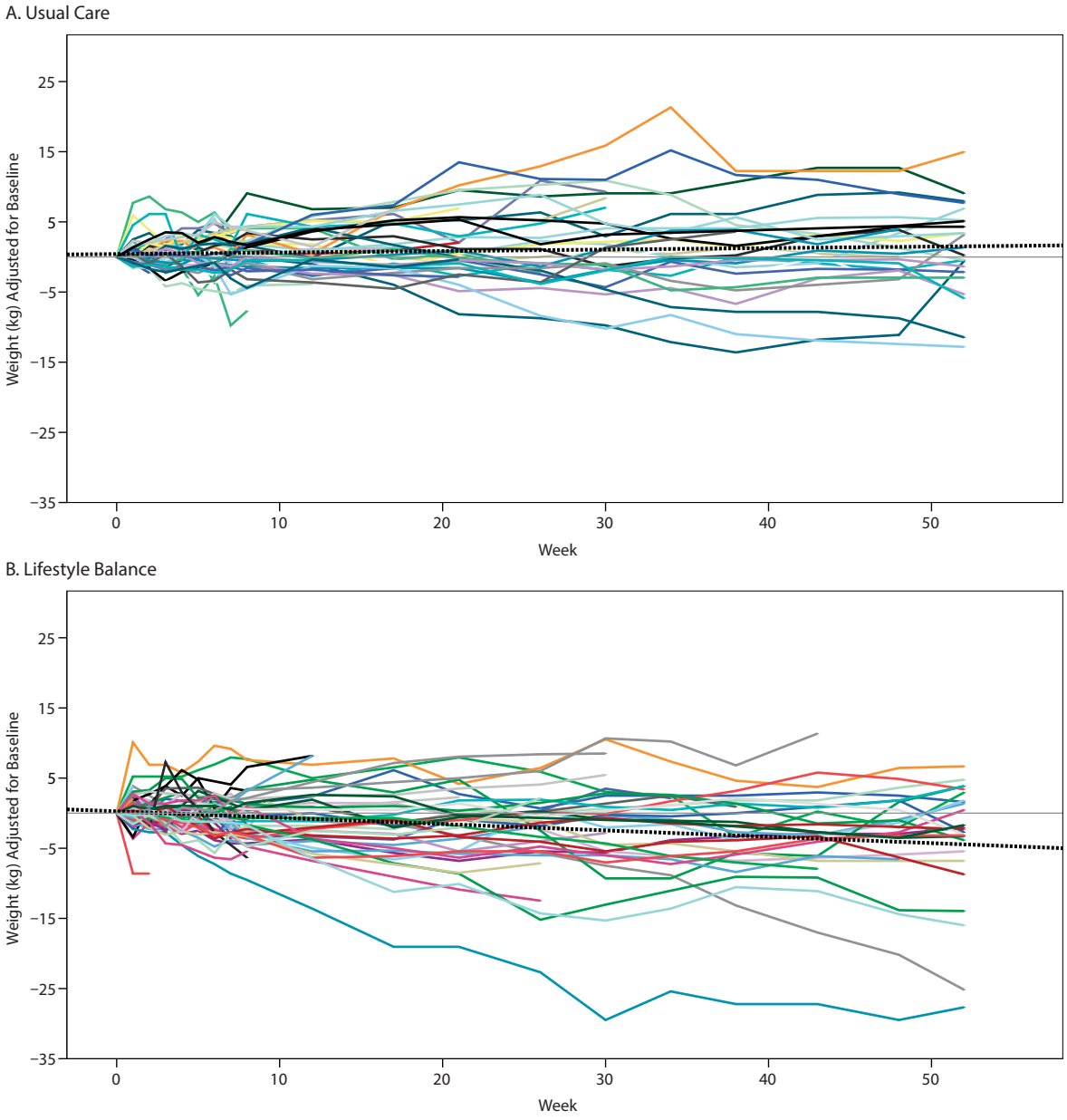
weight change and psychopathology. A significant association was found between declining trajectories of weight change and decreases in symptom severity scores on the HDRS (HDRS × time interaction: $F_{1,1188} = 8.4$, $P < .01$), BPRS total (BPRS × time interaction: $F_{1,1188} = 10.8$, $P < .01$), and BPRS negative symptom cluster (BPRS negative cluster × time interaction $F_{1,1189} = 7.2$, $P < .01$) over time. Conversely, declining weight trajectories were significantly associated with increases in motivation (MI × time interaction $F_{1,1189} = 7.2$, $P < .01$). There was no significant interaction between weight change trajectory and quality of life (QOL × time interaction $F_{1,60} = 3.6$, $P = .06$).

Another primary hypothesis was that LB subjects would gain more knowledge about nutrition and exercise compared to UC subjects. In fact, both LB and UC groups demonstrated statistically significant improvements in HLQ score over time ($F_{1,105} = 7.8$, $P = .006$), with no significant difference in HLQ score change between groups.

Diagnosis and Medication Status

The LB group included more than twice as many bipolar subjects than the UC group. To determine if diagnosis was a significant factor in weight change, diagnosis was included as a covariate in the GLMM. This revealed a significant effect of diagnosis on the change in weight over time (diagnosis × time interaction: $F_{3,1269} = 16.6$, $P < .01$) and a significant 3-way interaction between the effects of randomization and diagnosis on weight change over time (group × diagnosis × time interaction: $F_{3,1273} = 6.5$, $P < .01$). However, the greatest differences in weight change trajectories between groups were detected among subjects with schizoaffective disorder (mean difference of 0.10 kg/

Figure 2. Participant Weight Changes and Predicted Mean Trajectory of Weight Change[a]



[a]Colored lines represent individual patients. Dotted black line represents the predicted trajectory of mean weight change for an average member of the group based on the mixed model.

wk [SE = 0.10]) and schizophrenia (mean difference of 0.15 kg/wk [SE = 0.11]) rather than those with bipolar disorder (mean difference 0.005 kg/wk [SE = 0.11]) or other diagnoses (mean difference of 0.02 kg/wk [SE = 0.10]). Likewise, post hoc analyses with pairwise contrasts of individual interactions revealed that the significant effect of diagnosis was mainly driven by the greater difference between UC and LB weight change among schizoaffective subjects compared to those with bipolar disorder ($t_{1,273} = 2.93$, $P < .01$) or other diagnoses ($t_{1,273} = 2.45$, $P = .01$). Therefore, the imbalance of bipolar patients did not appear to contribute significantly to differences in weight change between the 2 interventions.

To examine the contribution of antipsychotic medication, we categorized medication status into 3 groups: high risk (olanzapine and clozapine), medium risk (risperidone and quetiapine), or low risk (aripiprazole and ziprasidone) for weight gain. A significant difference in weight change over time was found across medication groups (medication × time interaction: $F_{2,1235} = 3.17$, $P = .04$). Pairwise comparisons revealed that the low-risk group lost significantly more per week on average than the high-risk group (mean difference 0.06 kg/wk, $t_{1,237} = 2.13$, $P = .03$), but not significantly more than the medium-risk group (mean difference of 0.005 kg/wk, $t_{1,237} = 0.15$, $P = .87$). The medium-risk group also

lost significantly more than the high-risk group (mean difference of 0.05 kg/wk, $t_{1,237} = 2.00$, $P = .046$). Although this effect of high-risk medications on weight change was expected, when medication group was used as a GLMM covariate, we found no evidence that medication status significantly affected differential response to LB or UC (treatment × medication × time interaction: $F_{2,1239} = 1.2$, $P = .30$). Although the LB group included 3 times the number of low-risk medication subjects compared to twice the number of high-risk medication subjects in the UC group, the mean difference in weight trajectory between LB and UC groups remained the same across the 3 medication groups. This difference consistently favored LB subjects, with an average weight loss of 0.06 kg/wk compared to UC.

Study Dropouts and Exclusions

Of the 122 subjects randomized, 101 completed the 8 weekly sessions, and 62 completed the full year of the study. This includes 25/60 LB subjects (42%), 25/48 UC subjects (52%), and 12/14 UC subjects allowed to change over to LB but excluded from data analyses (86%). Of the 60 noncompleting subjects, 17 (28%) voluntarily withdrew, and 19 (32%) were lost to follow-up. Twelve (20%) were discontinued due to nonadherence to study procedures. Eight (13%) discontinued due to laboratory abnormalities or adverse events that included psychiatric exacerbations or physical ailments unrelated to study participation, and 4 (7%) terminated for other reasons.

Three consecutive missed study visits or 4 weeks of unresponsiveness to follow-up resulted in termination. Nonadherence to study procedures and loss to follow-up accounted for more than half of terminations. We conducted an exploratory survival analysis using hierarchical Cox regression and all demographic, medical, and treatment variables in a forward search algorithm, but none of the available variables were statistically significant predictors of dropout. The best univariate predictor of dropout is diagnosis, with patients with schizophrenia being more likely to drop out than patients with other diagnoses ($P = .116$, NS). We found no significant adverse effects or evidence of psychiatric worsening related to study participation. Of the 19 total visits offered within the study, LB and UC subjects attended an average of 13.7 and 12.1 sessions respectively. These attendance rates were not statistically significantly different ($F_{1,106} = 1.78$, $P = .18$).

DISCUSSION

This study demonstrated that an adaptation of the DPP's multimodal, behavioral LB Program[13,14] was more effective than usual care in treating SGA-associated obesity. Fifty percent of DPP participants achieved 7% weight loss, and 22% of participants in this study were able to do the same in spite of their SMI diagnosis. Although individual results were variable, GLMM analysis revealed a typical trajectory of statistically significant decreases in weight, BMI, and body fat for LB subjects compared to modest gains in those same parameters for UC, consistent with our primary hypothesis. Contrary to expectations, both groups gained knowledge about healthy lifestyles, without significant differences between them. This underscores the clinical impression that general education about healthy lifestyles may be of limited value and that individualized recommendations with encouragement and incentives might be necessary to achieve actual weight loss.

Limitations to our study were its single-site recruitment, which yielded subjects who were mostly male and all veterans, limitation of statistical power by the change-over group, and a high dropout rate that often troubles behavioral weight loss programs even in the non-SMI population.[26–28] Despite randomization, there were more subjects with bipolar disorder in the LB group and more subjects with schizophrenia in the UC group, but this did not affect our results. Since clozapine is typically reserved for patients with refractory schizophrenia, nearly a quarter of patients in UC were treated with a high-risk antipsychotic. However, we found no evidence of any significant interaction between antipsychotic status and treatment, suggesting that the differential response to UC or LB was not dictated by medication effects. Likewise, although there was a significant interaction between diagnosis and weight change, the bulk of this effect stemmed from the few schizoaffective patients. Therefore, LB appears to be a potentially effective behavioral intervention for patients independent of having schizophrenia vs bipolar disorder and regardless of individual SGA.

Obesity among those with SMI is a major public health problem. Our results, from one of only a handful of randomized controlled trials lasting up to 12 months,[29] add to a growing body of literature that suggests incorporating a multimodal approach involving classes, individual coaching, and rewarding exercise and weight changes in a mental health setting can indeed be an effective way to reduce SGA associated weight gain. Among uncontrolled past studies, Centorrino et al[6] reported declines in blood pressure, weight, and BMI among 17 patients with psychosis who participated in an intensive 24-week program of diet, exercise, and counseling. Kalarchian et al[7] evaluated 27 patients who completed 16 behavioral sessions emphasizing education, a meal plan, exercise recommendations, and self-monitoring over 6 months and achieved a mean weight loss of 3.2 kg. Pendlebury et al[8] followed 93 patients who were offered weekly weight monitoring and group educational sessions over 4 years. Mean weight and BMI declined significantly and correlated with the number of sessions attended.

Among controlled trials, Menza et al[9] associated 52 weeks of nutrition, exercise, and behavioral intervention with significant decreases in weight and BMI among 31 patients with schizophrenia or schizoaffective disorder compared to weight gain among 20 nonrandomized controls. Vreeland and colleagues'[10] randomized controlled study of 31 patients treated with SGAs found that participants in a 12-week intervention incorporating nutrition, exercise, and behavioral modifications had a significant mean loss of 2.7

kg and 0.98 BMI points compared with the control group's mean gain of 2.9 kg and 1.2 BMI points. Wu et al[11] studied 128 inpatients with schizophrenia who gained greater than 10% body weight on SGA treatment. Patients randomized to 12 weeks of lifestyle intervention, pharmacotherapy with metformin, or the combination of both had significantly greater decreases in weight and BMI compared to the placebo group. Finally, Daumit et al[12] recently reported significantly greater weight loss in a randomized, controlled trial among 144 patients with SMI who participated in educational and exercise sessions over 18 months compared to 147 control subjects who received standard information about health, nutrition, and exercise.

In summary, the literature is consistent with our findings that weight loss can continue for an extended period with only occasional booster sessions, routine encouragement, and monitoring. The Lifestyle Balance program is a multimodal behavioral approach that is effective in promoting weight loss. On the basis of these encouraging results, this intervention is being disseminated to other VA health care centers and other clinical settings internationally.

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Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), metformin (Glucophage and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Author contributions: The authors had full access to study data, and Dr Ames takes full responsibility for the integrity of the data.

Potential conflicts of interest: The authors have no conflicts of interest to report.

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