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Behavioral Weight Loss Treatment for Youth Treated With Antipsychotic Medications

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Abstract

Background: Youth who are being treated with antipsychotic medications are at increased risk for the development of obesity and type 2 diabetes. Behavioral weight loss treatments show promise for reducing obesity and diabetes risk among adults treated with these drugs, but such treatments have not previously been studied in youth.
Objective: We describe a rationale for behavioral weight loss intervention for high-weight youth being treated with antipsychotic medications. We report behavioral, anthropomorphic, and metabolic findings from a case series of obese adolescents taking antipsychotic medications who participated in a short-term, family-based behavioral weight loss intervention.
Methods: We adapted the Traffic Light Plan, a 16-week family-based weight loss intervention that promotes healthy energy balance using the colors of the traffic light to categorize the nutritional value of foods and the intensity of physical activity. We then added a social and ecological framework to address health behavior change in multiple social contexts. The intervention was administered to three obese adolescents with long-term antipsychotic medication exposure. The efficacy of the intervention was evaluated with a battery of anthropomorphic and metabolic assessments, including weight, body mass index percentile, whole body adiposity, liver fat content, and fasting plasma glucose and lipid levels. Participants and their parents also filled out a treatment satisfaction questionnaire after study completion.
Results: Two boys and one girl, all of whom were 14 years old, participated in this study. All three participants attended all 16 sessions of the intervention and experienced beneficial changes in adiposity, fasting lipid levels, and liver fat content associated with weight stabilization or weight loss. Adolescents and their parents all reported a high level of satisfaction with the treatment.
Conclusions: Family-based behavioral weight loss treatment can be feasibly delivered and is acceptable to youth taking antipsychotic medications and their families. Randomized controlled trials are needed to fully evaluate the effectiveness and acceptability of these treatments for these individuals.

ClinicalTrials.gov Identifier: *NCT01222494*

Keywords: pediatric obesity; antipsychotics; at-risk youth; weight loss treatment

Introduction

Pediatric obesity is a rising public health concern that is associated with the early onset of cardiovascular disease risk conditions such as fatty liver and diabetes (1-3). Children with psychiatric conditions may be particularly vulnerable to the development of obesity and related adverse health conditions (4). The increased risk for obesity in psychiatric populations is exacerbated by the use of second-generation antipsychotic medications (hereafter referred to as *antipsychotics*), which increase the risk for weight gain and related adverse changes in lipid and glucose metabolism (5,6). Youth who are being treated with antipsychotics are more than twice as likely as children in the general population to develop obesity-related cardiometabolic risk conditions like diabetes, hypertension, and hyperlipidemia (7-9). For populations in which obesity is the result of medical treatments, first-line treatment strategies include the discontinuation of agents that cause or contribute to weight gain and substitution with a lower-risk agent if one is available (10; *p. 2489*). Although antipsychotic discontinuation in youth is associated with weight loss, it may come at the price of psychiatric symptom recurrence, including aggressive or self-injurious behavior (11-13). Therefore, it is imperative to identify strategies to mitigate weight gain when maintenance treatment with antipsychotics is necessary.

The putative mechanisms of antipsychotic-induced weight gain are related to the medications' combination of dopamine blockade at D2 receptors, antagonism or inverse agonism at 5HT2C serotonin receptors, antagonism at 5HT2A serotonin receptors, antagonism at alpha-1A adrenergic receptors, and especially antagonism at histamine-1 receptors (14). Blocking the activity of dopamine—particularly in the subcortical, limbic, and striatal areas of the brain—leads to an upregulation of postsynaptic receptors as well as increased dopamine within the synaptic cleft, which may create a "reward deficiency" syndrome that prevents satiety (15). Serotonin receptor inverse agonism or antagonism may lead to decreased satiety and hyperphagia (16,17). Finally, weight gain has long been associated with centrally active drugs that have high affinity for the histamine-1 receptor, and H1 antagonism is known to increase feeding (18,19) and sedation, with predictable reductions in caloric expenditure (14). Although treatment-related weight gain is pharmacologically driven, it could potentially be addressed by behavioral strategies that affect decreased satiety, increased food seeking, and sedentary behavior. Core principles of behavioral weight loss that may impact satiety and activity level typically involve food and activity substitutions, with progressive goal setting and reinforcement to reach the identified terminal health behavior targets and to change food and activity preferences.

Intensive behavioral weight loss and lifestyle modification programs have been successfully adapted for use in adults with psychotic disorders and other severe mental illnesses who are taking antipsychotics (20-22). One particularly successful weight loss intervention has incorporated psychosocial and cognitive rehabilitation strategies into a health education framework in a setting in which patients received mental health care and social support (23)). Social ecological approaches to health behavior change in psychiatric populations consider the adjustment, coping, and adaptive functioning of the individual within a social and cultural context (24). This focus on facilitating the individual's involvement in and impact on the environment as an agent of change is thought to enhance the likelihood of the sustained improvement of health behaviors. Social ecological models of pediatric health behavior change include the family as an integral part of the child's immediate environment and promote the development of parent-facilitated social networks that support health behavior change and that address social barriers to engaging in health behavior change (25,26). Weight loss treatments that make use of a social ecological approach to health behavior change may be ideally suited to promoting health behavior change in mentally ill youth, because psychosocial barriers to participation may be more pronounced as compared with populations of non-psychiatrically ill individuals. Family is part of the first and perhaps most important layer of social ecology in the lives of children, and thus social ecological approaches that focus on the involvement of social supports, including family, may be of primary importance for individuals who face psychiatric illnesses as barriers to health behavior change.

Family-based behavioral weight loss treatment (FBT) is considered a first-line treatment for the management of pediatric obesity (27,28). Published meta-analyses have documented that such interventions lead to improved weight outcomes among children and adolescents (29,30). However, these reports also highlight the need for studies that evaluate treatment-related changes in metabolic parameters and that test strategies for enhancing real-world intervention delivery, particularly in at-risk populations such as individuals with psychiatric illnesses who are treated with antipsychotics (31). To our knowledge, two studies that included behavioral weight loss as part of the study design have been conducted in overweight or obese youth treated with antipsychotics (32,33). However, we are aware of no published studies evaluating the feasibility and

efficacy of family-based behavioral weight loss interventions in this population nor of any studies that measure the impact of such interventions on metabolic health outcomes.

The present report describes a modified FBT approach to weight loss among youth taking antipsychotics and reports on the first three participants in a randomized controlled trial to evaluate the efficacy of FBT for weight loss in youth between the ages of 6 and 18 years treated with antipsychotics. The design of this study involves delivering weekly FBT to youth with psychiatric illnesses treated with antipsychotics as compared with otherwise healthy but overweight or obese youth, with a monthly standard-of-care reference group treated with antipsychotics. The primary outcomes of this study include gold-standard measures of body composition and metabolism: changes in total percentage of body fat and liver fat, measured respectively via dual energy X-ray absorptiometry and magnetic resonance spectroscopy; common clinical measures, such as body mass index (BMI) and BMI percentile; vital signs; and fasting plasma lipid and glucose values. We hypothesize that individuals treated with antipsychotic agents can successfully participate in behavioral weight loss treatment without adverse weight or metabolic outcomes. Here, we describe the weekly FBT program adapted for use in youth treated with antipsychotics to incorporate a social ecological approach, and we report changes in weight and other measures of metabolic health in the initial three patients who completed the weight loss treatment.

Participants

Three adolescent participants were recruited from the Washington University School of Medicine Child and Adolescent Psychiatry Outpatient Clinic. In all cases, the participant's pediatrician or primary care provider was notified of study participation and provided medical assent. Outpatient weights and heights collected during the year prior to study enrollment were obtained for all participants from their primary care provider or treating psychiatrist. Inclusion criteria for the overall study included the following:

1) overweight (BMI percentile ≥85) or obese (BMI percentile ≥95) youth between the ages of 6 and 18 years;
2) any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* diagnosis;
3) at least 6 continuous months of treatment with antipsychotics;
4) documented weight gain that was greater than expected (e.g., crossing a percentile line on the BMI growth chart);
5) evidence of psychiatric stability (i.e., no inpatient hospitalizations during the previous 6 months and no changes in psychotropic medication doses for 4 weeks);
6) consenting adult caregiver willing to participate in the study; and
7) ability to provide assent for participation as evidenced by documented or clinically estimated intelligence quotient of 70 or higher.

Exclusion criteria included the following:

1) youth who were not overweight or obese by BMI percentile;
2) age outside the specified range of 6 to 18 years;
3) no presence of any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* diagnosis;
4) less than 6 months of antipsychotic treatment;
5) active suicidality or substance use disorders;
6) lack of psychiatrically stability and/or antipsychotic treatment deemed in-appropriate;
7) no consenting adult caregiver able to participate in the study; and
8) estimated or documented intelligence quotient of less than 70.

Concurrent treatment with selective serotonin reuptake inhibitors and attention-deficit/ hyperactivity disorder medications (including stimulants, Atomoxetine, or alpha-agonist agents below a total daily dose of 2 mg/kg methylphenidate equivalent) was permitted to increase the generalizability of results. A large portion of youth treated with antipsychotics are concurrently treated with selective serotonin reuptake inhibitors, stimulants, and other psychotropic medications (34). More specifically, the use of antipsychotics for treatment-resistant attention-deficit/hyperactivity disorder is increasingly common (35).

Study Assessments

Participants were youth between the ages of 6 and18 years who were enrolled in the National Institute of Mental Health–funded "Measurement of Cardio-metabolic Risk in Antipsychotic Treated Youth" study. This is a randomized controlled trial to evaluate metabolic changes in overweight or obese youth treated with antipsychotics during behavioral weight loss treatment as compared with obese or overweight but otherwise healthy controls undergoing the same behavioral weight loss treatment. All participants underwent a clinical evaluation by a study psychiatrist to ensure psychiatric stability and the appropriateness of continued antipsychotic treatment during study participation. Diagnoses were based on *Diagnostic and*

Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria and corroborated with records of previous psychiatric treatment. A consensus study diagnosis was based on the preponderance of clinical and study data. Baseline assessments were conducted within one month of study enrollment, and endpoint assessments were conducted within two weeks of completing the 16-week weight loss treatment. All blood draws and physical study assessments were performed at the Washington University Pediatric Research Unit; imaging was performed at the Center for Clinical Imaging in Research and at the Nutrition Obesity Research Center and included the following: height and weight measurements performed on a calibrated stadiometer (Seca 240 Wall-Mounted Stadiometer, Germany) and scale (Seca 684 Digital Multifunctional Scale, Germany), respectively, by a trained research nurse whole body fat percentage measured using dual energy X-ray absorptiometry (Delphi W densitometer equipped with version 12.4 software; Hologic, Waltham, MA); intrahepatic triglyceride content determined at baseline and at the study endpoint by proton magnetic resonance spectroscopy with a 1.5 T scanner (Magnetom Sonata; Seimens, Erlangen, Germany), with all frequencies (i.e., chemical shifts) measured relative to the principal water ^{1}H resonance; and fasting plasma lipid (i.e., total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride) and glucose levels. Weekly treatment weights were measured on a digital office-based scale (Health o meter, Sunbeam Products Inc., Boca Raton, FL). BMI, BMI percentile, and BMI Z-score were calculated from medical records for each subject at 12 and 6 months prior to study enrollment and at the baseline and endpoint study assessments. The Washington University in St. Louis Institutional Review Board approved this study.

Treatment Description

FBT is an evidence-based intervention that consists of weekly sessions for 12 to 24 weeks and that includes individual family member weigh-ins, meetings with a trained interventionist, and separate parent and child groups (36). FBT targets family support and restructuring of the home environment to enable healthier behaviors while establishing self-regulatory behaviors to promote weight management. A weight loss goal range of 0.5 to 2 lb per week is set for both participating children and adults; this range is in line with evidence-based childhood obesity treatment (37) and recommenddations for healthy child development and weight management /27,38). Expected annual weight gain during normal growth and development varies on the basis of age and gender and can range from 2 to 3 lb per year in prepubertal and postpubertal youth to 8 to 12 lb per year during the prepubertal and pubertal growth stages, with weight gain being higher in prepubertal females as compared with males and higher in pubertal males as compared with females (39,40). For individuals who are already at a high weight, the range of 0.5 to 2 lb per week is a safe weight loss range for all ages and stages of growth. Core components of behavioral weight loss strategies include education about energy balance, shaping behaviors to promote stimulus control, and self-monitoring. The Traffic Light Plan is used as a framework to help families shift their energy intake and expenditure with the use of a classification system in which the nutritional values of foods and the intensity values of activities are coded as RED for "stop and think" to indicate the least healthy options, YELLOW for "caution" to indicate moderately healthy options, and GREEN for "go" to indicate the healthiest options (41-44). Both participating parents and youths are asked to self-monitor their daily food intake and physical activity. Youth and their participating parents are asked to select from a list of behavioral rewards (which exclude options related to food or sedentary behavior) for accumulating points when weekly goals are met. Child and parent weights are measured during each in-person session.

In the present case series, modifications were made to the existing FBT framework to facilitate delivery in an outpatient psychiatric treatment setting. First, we removed the weekly group meeting and increased contact with the treatment team through a mid-week phone check-in, and we incorporated the group content and skills practice into the individual family sessions. This was done to reduce the total time spent in person per week by families and interventionists and to allow interventionists to provide support and reminders to engage in self-monitoring and health behavior changes throughout the week. We also employed a simplified, one-page food and activity log composed of visual cues for RED and GREEN foods and activities. This was done to simplify food logging for youth who had learning disabilities or other cognitive challenges. We created and used a "taste log" to incentivize trying new GREEN and YELLOW foods and to promote serial desensitization for youth with food aversions or selective eating patterns. In addition, we included an ecological-based social facilitation component in each session to encourage the consolidation of health behavior changes across environmental contexts; we took into account the developmental stage of the participating youth, and we encouraged parents to facilitate the development and use of peer and community networks to support health behavior change. Weekly treatment goals were divided into energy balance, weight loss, and social facilitation

domains, and target ranges for scaled goal attainment were created within each domain. This allowed the interventionist to individualize weekly goals on the basis of child- and family-level characteristics and needs.

Results

Table 1 presents each of the three cases in detail. Common characteristics among participants included age, race, and weight related medical comorbidities (e.g., dyslipidemia, impaired fasting glucose). Additionally, each case presented unique parenting challenges related to either parental or child psychiatric considerations. Quantitative cardiometabolic outcomes are presented in Table 2. Beneficial changes in fasting total cholesterol, low density lipoprotein cholesterol, adiposity, and liver fat content were documented for Participant 1 and Participant 3, who both experienced greater changes in BMI percentile and Z-score as compared with Participant 2. All participants experienced a slowing of weight gain as compared with their pretreatment weight trajectories (Figure 1). No clinically significant changes in fasting glucose and triglyceride values were found. Participating parents and youth reported that they were either "very satisfied" (n = 2) or "somewhat satisfied" (n = 1) with the treatment program at study completion. Two parents reported that they would not suggest any changes to the treatment; one parent suggested the use of a computer or mobile device application for homework and self-monitoring.

Conclusions

Children with mental health conditions—especially those who are treated with antipsychotics—are vulnerable to developing obesity and related health problems. Little research has been conducted regarding weight loss interventions in this population. FBT interventions are low risk and are considered first-line treatments for pediatric obesity, with evidence for long-term sustainability (36). The preliminary results reported here represent, to our knowledge, the first reported for a behavioral weight loss intervention adapted for use in youth treated with antipsychotics.

The primary goal of this pilot study was to demonstrate the feasibility of delivering a behavioral weight loss treatment to families of youth with psychiatric conditions. All participants experienced a beneficial change in or stabilization of their BMI percentile and Z-score as compared with pretreatment conditions, and these changes are similar to those of previous FBT studies (25). Although greater weight loss was associated with greater changes in metabolic parameters, it is notable that small reductions in weight were associated with measurable improvements in portions of the lipid panel and in liver fat content. Finally, each of the three cases involved a parenting component that challenged the family's ability to maintain a healthy weight, which suggests that a family-based approach may be useful in this population to support parents who want to help their children make health behavior changes (Table 1).

There are important limitations to note. As a case series, the sample of participants reported here was small and warrants continued evaluation, because the results may not be representative of the general population of children with psychiatric conditions who are overweight or obese. Moreover, these participants were adolescents, and our larger trial addresses both children and adolescents between the ages of 6 to 18 years. Estimates of children's height growth patterns can be used to anticipate the weight-for-height changes needed to achieve normal weight status and to guide weight loss targets on the basis of a youth's age- and sex-specific BMI percentiles (45,46). It is important to note that our presented cases are adolescents with BMIs above the 99th percentile for age and gender at entry; children who are younger and closer to the 85th BMI percentile need to lose less weight to normalize their BMI percentiles as compared with youth who are older and who have a higher degree of obesity (46). Thus, the expansion of our sample to younger children across BMI percentiles in the overweight and obese ranges may provide additional information about treatment response and may indicate whether treatment for this population, which is at risk for continued weight gain, warrants additional adaptation (e.g., whether weight maintenance is more appropriate than weight loss for certain populations)(27,38,46). In addition, there may be important differences in an individual's response to these interventions as a result of gender, ethnicity, age, and sociodemographic variables that are not represented by the individuals discussed in this case series.

Selection bias can confound results in studies of behavior change: individuals who participate in research studies may be more motivated than those in the general population to make health behavior changes. Participant 1 is an example of this and may be quite representative of individuals with mild autism who also have symptoms of attention-deficit/hyperactivity disorder; these individuals are commonly treated with a combination of stimulant and antipsychotic therapy. Although it could be argued that Participant 1 lost weight before starting the FBT as a result of concurrent stimulant therapy, which has a known anorectic effect, stimulants have not been associated with significant weight loss among individuals taking antipsychotics (47,48).

TABLE 1. Participant Characteristics and Case Description

Participant 1 was a 14-year-old Caucasian male diagnosed with PDD-NOS[1] and ADHD,[2] combined type, and Learning Disorder (Reading and Written Expression). He had received psychiatric treatment since age 5, and at study enrollment was taking atomoxetine (Strattera) 100 mg daily, paroxetine (Paxil) 10 mg daily and risperidone (Risperdal) 3 mg daily. Medical comorbidities related to obesity included impaired fasting glucose.[4] Prior to study participation, food limits being set in the home resulted in aggressive behavioral outbursts. Treatment was tailored as follows:

- To address parent modeling of responsive and assertive communication skills, the therapist worked with parents on how to identify and anticipate behavioral triggers prior to setting limits and boundaries.
- To address difficulties with recording foods related to learning disorder, daily family check-ins allowed the participant to narrate or dictate food intake to the participating parent, while the youth utilized Traffic Light Plan materials to identify nutrition data for each food item.

Participant 2 was a 14-year-old Caucasian female diagnosed with Mood Disorder Not Otherwise Specified and GAD.[3] She had received psychiatric treatment since age 7, and at study enrollment was taking quetiapine (Seroquel) 100 mg twice daily and 200 mg at bedtime; sertraline (Zoloft) 150 mg daily. Medical comorbidity related to obesity included hypercholesterolemia.[5] Parental health problems, including limited mobility and mild cognitive impairment impacted the ability to perform key parenting skills (e.g., regular grocery shopping, help with completing self-monitoring logs, facilitation of conversations to promote healthy behaviors at home and with peers). Treatment was tailored as follows:

- To reduce cognitive load, handouts incorporating visual cues and simplified messages regarding the primary message in each meeting were utilized to reinforce session content, and the one-page food and activity log was introduced to simplify self-monitoring.
- To address parental difficulties and communication challenges, the therapists modeled adaptive communication strategies and provided cues for collaborative problem solving.

Participant 3 was a 14-year-old Caucasian male diagnosed with PDD-NOS[1] and ADHD,[2] combined type. He had received psychiatric treatment since age 3, and at study enrollment was taking osmotic-release oral system (OROS)-methylphenidate (Concerta) 54 mg daily, quetiapine (Seroquel) 150 mg twice daily and 100 mg at bedtime and paroxetine (Paxil) 15 mg daily. Medical comorbidity related to obesity included dyslipidemia.[5] This youth began treatment with a significant preference for RED foods, and taste aversion to most GREEN foods. Parents reported weight had gradually become a problem over time because their child had limited taste preferences and became severely agitated when new foods were introduced. Treatment was tailored as follows:

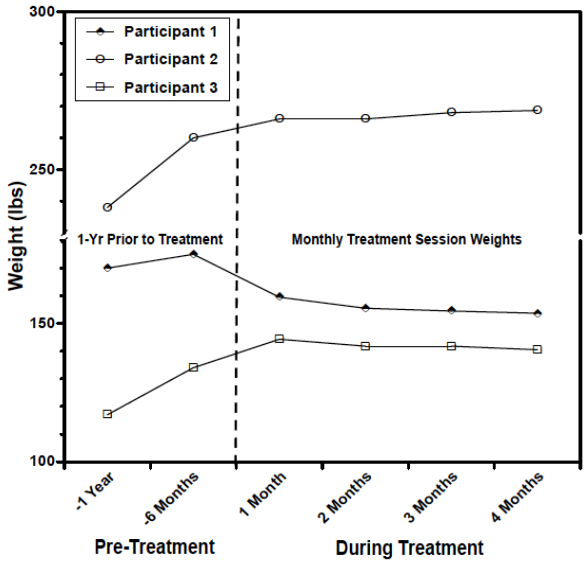
- To address distress about trying new foods related to sensory aversion, the interventionist worked with the family on communication strategies and provided support and education about distress tolerance for parents and youth.
- To engage the youth both during the session and during the week at home and school, a focus of therapy became rewarding attempts to try new GREEN foods using the taste log.

[1] Pervasive Developmental Disorder Not Otherwise Specified
[2] Attention Deficit-Hyperactivity Disorder
[3] Generalized Anxiety Disorder
[4] Defined by American Diabetes Association Criteria (33)
[5] Defined by NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents (34)

TABLE 2. Changes in Metabolic Health During Study Participation

	Participant 1		**Participant 2**		**Participant 3**		**Mean**
	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	**Change (SD)**
Weight (lbs)	165.6	153.7	270.1	268.7	141.8	141.5	-4.53 (6.40)
BMI %ile	91.13	80.94	99.48	99.41	96.16	92.69	-4.58 (5.15)
BMI z-score	1.35	0.88	2.56	2.52	1.77	1.45	-0.28 (0.22)
Fasting Glucose (mg/dL)	103	93	87	86	97	97	-3.67 (5.51)
Fasting Total Cholesterol (mg/dL)	166	145	209	239	160	139	-4.00 (29.44)
Fasting HDL Cholesterol (mg/dL)	57	62	56	60	41	38	2 (4.36)
Fasting Triglycerides (mg/dL)	59	63	93	106	128	70	-13.67 (38.66)
Fasting LDL Cholesterol (mg/dL)	97	70	134	158	93	87	-3 (25.63)
DEXA Total Percent Fat	28.4	24.2	46.9	48.4	35.6	28.6	-3.23 (4.33)
Percent Liver Fat	2.08	0.62	1.92	2.76	3.54	1.31	-0.95 (1.60)

FIGURE 1. Participant Weight Trajectories, 1 year Pre-Treatment and During Treatment



A more likely cause of weight loss before beginning treatment is the motivation for behavioral change. After observing the pretreatment weight trajectory for Participant 1, we modified our study timeline to allow only 2 weeks between baseline testing and starting FBT. Finally, although the potential mechanisms of antipsychotic-related weight gain can be surmised from receptor binding profiles, future studies should evaluate the neurobiological changes associated with antipsychotic treatment and weight loss treatment to develop more effective and individualized weight loss interventions.

Clinical Significance

Our findings demonstrates that a minimally modified FBT intervention can be feasibly delivered to youth with psychiatric disorders and could be disseminated via clinical settings in which weekly encounters with behavioral health providers can occur (e.g., community mental health centers). Although beneficial changes were noted in liver fat, whole body adiposity, fasting total cholesterol, and low density lipoprotein cholesterol levels, definitive conclusions regarding the effectiveness of this intervention cannot be made on the basis of the results of these first three participants. Further study is needed to more definitively determine treatment effectiveness, to clearly identify population- and diagnosis-specific challenges to weight loss, and to determine the most effective strategies for personalizing treatment and mobilizing family member support to promote weight loss success.

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