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Changes in Appetite and Eating Behavior Associated with the Combination of Sibutramine and Behavior Therapy

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CHANGES IN APPETITE AND EATING BEHAVIOR ASSOCIATED WITH THE COMBINATION OF SIBUTRAMINE AND BEHAVIOR THERAPY

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Dissertation Approval

This is to certify that the thesis presented to us by Raymond Carvajal

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Abstract

This archival-data study assessed the potentially complementary mechanisms of action of sibutramine and behavior therapy (also known as lifestyle modification) believed to be responsible for the greater weight loss observed with combining the two approaches than with either approach alone. One hundred and seventy-one subjects were randomly assigned to receive 15 mg of sibutramine per day alone, delivered by a primary-care provider in five brief office visits; behavior therapy alone, delivered by a psychologist in 18 group sessions; and sibutramine (15 mg/day) plus 18 group sessions of behavior therapy (i.e., combined therapy). Mixed effects linear model analysis was used to compare changes in scores among the groups on the Eating Behavior Inventory and on visual analogue scales of appetite. Most of the findings were either significant or in the expected direction. Subjects who received sibutramine alone and behavior therapy alone displayed improvements principally in appetite control and eating behavior, respectively. By comparison, those who received combined therapy displayed improvements in both areas. These results provide evidence that sibutramine and behavior therapy work additively to produce greater weight loss than either therapy alone. Furthermore, they underscore the importance of prescribing weight loss medications in combination with lifestyle modification, an approach that may be facilitated through the integration of behavioral-health providers within primary care.

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Chapter One: Introduction

Statement of the Problem

Obesity has reached epidemic proportions in the United States. Approximately 66% of adults are classified as overweight, of whom 32% are obese (Ogden et al., 2006). The overall health care costs attributable to obesity increased from an estimated $99.2 billion per year in 1995 (Greenway et al., 1999) to an estimated $117 billion per year in 2004 (Stein & Colditz, 2004). The marked rise in obesity is alarming because of the array of adverse medical and psychosocial consequences that often impair the physical and emotional functioning of obese persons. Obesity increases the risk of developing a variety of medical conditions, including hypertension, coronary artery disease, hypercholesterolemia, type 2 diabetes, osteoarthritis, various cancers, sleep apnea, gallbladder disease, and orthopedic complications (Bray, 2004; Brown, Fujioka, Wilson, & Woodworth, 2009; Field, Barnoya, & Colditz, 2002). A considerable amount of psychopathology also is found among obese patients who seek professional assistance with weight loss. Depression, binge-eating disorder, body image dissatisfaction, and impaired health-related quality of life are prevalent in this population (de Zwaan, 2001; Fitzgibbon, Stolley, & Kirschenbaum, 1993; Nauta, Hospers, & Jansen, 2001; Sarwer & Thompson, 2002; Wadden, Womble, Stunkard, & Anderson, 2002). In addition, obese individuals are targets of widespread prejudice and discrimination (Sarlio-Lahteenkorva, 2001; Wadden et al., 2002; Wang, Brownell, & Wadden, 2004).

Several approaches to weight loss have been developed, such as a variety of self-directed diets and commercial programs. Unfortunately, many of these approaches have not been subjected to randomized controlled trials and, thus, lack empirical support (Tsai

& Wadden, 2005; Womble, Wang, & Wadden, 2002). Two approaches that have been empirically validated for the management of obesity include behavior therapy (Foster, Makris, & Bailer, 2005; Wadden, Crerand, & Brock, 2005) and pharmacotherapy (James et al., 2000; Sjostrom et al., 1998; Yanovski & Yanovski, 2002). Behavior therapy promotes weight loss by facilitating the adoption of healthy eating and physical activity behaviors, whereas pharmacotherapy targets weight loss through the use of medications. At the time of the current study, two pharmacological agents – sibutramine (Meridia; Abbot Laboratories, North Chicago, IL) and orlistat (Xenical; Roche Laboratories, Burlington, NC) – were approved by the U.S. Food and Drug Administration (FDA) for the long-term management of obesity. Whereas orlistat remains on the market, sibutramine has since been removed because of its association with adverse cardiovascular events (James et al., 2010).

To achieve optimal weight control, the National Heart, Lung, and Blood Institute (NHLBI) (1998) recommends the use of pharmacotherapy as an adjunct to a comprehensive program of diet, exercise, and behavior therapy. The combination of sibutramine and behavior therapy (which includes diet and exercise), in particular, has been found to produce clinically significant weight loss that exceeds the losses achieved with either sibutramine or behavior therapy alone (Wadden, Berkowitz, et al., 2005). The success of this combination is believed to be attributable to the additive effects of sibutramine and behavior therapy (Wadden, Butryn, & Wilson, 2007). Sibutramine, a serotonin-norepinephrine reuptake inhibitor, appears to modify biological variables related to appetite, such as levels of hunger and satiation (Bray, 2002). These actions

appear to reduce patients' responsiveness or vulnerabilities to food cues. Behavior therapy teaches patients to control external eating-related cues by such methods as storing foods out of sight, avoiding high-risk situations (e.g., fast-food restaurants), and limiting activities while eating (e.g., watching television). It also provides strategies to control eating in response to social or emotional cues (Foster et al., 2005; Wadden, Crerand, et al., 2005). Evidence suggests that sibutramine and behavior therapy have these separate effects (Bray, 2002; Foster et al., 2005; Wadden, Crerand, et al., 2005). However, no study has assessed the potentially complementary mechanisms of action of sibutramine and behavior therapy in a trial that examines these therapies separately and combined.

Purpose of the Study

The purpose of the current archival-data study was to examine changes in appetite and eating behavior associated with the provision of sibutramine, behavior therapy, and their combination. This investigation utilized data that were collected as part of a randomized controlled trial by Wadden, Berkowitz, and colleagues (2005), as previously described. Subjects who received the combination of therapies were expected to display significantly better appetite control and more appropriate eating behavior than subjects who received either therapy alone. Improvements in both appetite control and eating behavior were predicted to account for the greater weight loss observed with combined therapy. The results of this study are expected to provide evidence for these complementary mechanisms of action and to improve the quality of care provided to obese patients in primary care.

Relevance to Cognitive Behavior Therapy

Pharmacotherapy and behavior therapy are two established approaches to the management of obesity. While pharmacotherapy is rooted in the medical model, behavior therapy is based on principles of learning theory (Foster et al., 2005; Wadden, Crerand, et al., 2005). Behavior therapy assumes that eating behaviors are conditioned phenomena that are amenable to modification through the application of behavioral principles and techniques. Accordingly, classical conditioning and operant conditioning serve important functions in treatment (Foster et al., 2005; Wadden, Crerand, et al., 2005). The principle of classical conditioning holds that stimuli that are repeatedly presented before or simultaneously with a particular behavior become associated with that behavior (Pavlov, 1927). The more often two events are paired, the stronger the association becomes, such that the presence of one event automatically triggers the other. For example, eating is often associated with watching television. After repeatedly pairing the act of eating with watching television, simply turning on the television may trigger a craving to eat. Eating may be triggered by a single cue, but it is more typically triggered by several events linked together (Brownell, 2004). Repeatedly pairing eating with different stimuli impairs weight control since these latter events become linked with the consumption of food.

The principle of operant conditioning holds that the frequency at which a given behavior occurs is influenced by its consequences (or reinforcement value) (Skinner, 1953). Behaviors that are rewarded with pleasant consequences are likely to be repeated, while those that yield aversive consequences are likely to be extinguished. For example, if an obese man were to experience joy from eating ice cream, then he likely would have

difficulty modifying this behavior because of the positive reinforcement that is gained from eating ice cream. If he were to experience soreness and exhaustion after exercising, then he likely would feel compelled to abandon his exercise efforts in order to avoid these unpleasant consequences. In total, identifying the antecedents and consequences that maintain unhealthy eating and physical activity behavior (through a functional analysis of behavior) represents a central goal in behavior therapy (Foster et al., 2005; Wadden, Crerand, et al., 2005).

While the principal goal of behavior therapy is to promote healthful changes in eating and physical activity behavior, maladaptive cognitions related to weight management are also addressed in treatment. Cognitions that commonly undermine efforts to lose weight tend to be dichotomous, catastrophic, and overgeneralized (Brownell, 2004; Wadden, Crerand, et al., 2005). These types of distorted thinking may be manifested through the establishment of unrealistic eating and weight loss goals, self-criticism in response to overeating or gaining weight, and/or hopelessness about controlling weight (Wadden, Crerand, et al., 2005). Such cognitions, all of which impair the ability to induce and/or maintain weight loss, are identified and modified during the course of behavior therapy.

The subjects who received behavior therapy during the original trial (Wadden, Berkowitz, et al., 2005) followed versions of a manualized, behavioral weight loss program (i.e., Brownell, 1998; Brownell & Rodin, 1990; Brownell & Wadden, 1999). Components of this program included (a) self-monitoring food intake and physical activity behaviors, (b) addressing and establishing realistic weight loss goals, (c)

modifying eating behaviors (e.g., portion sizes, times of eating, speed of eating), (d) controlling the external environment involving food (i.e., stimulus control), (e) increasing programmed activity and lifestyle activity, and (f) modifying maladaptive cognitions related to weight control. The functions of these behavioral interventions are discussed in Chapter Two.

Chapter Two: Literature Review

Definition of Obesity

Obesity is defined as an excess of adipose tissue that results from a consistently greater energy intake than expenditure (Grilo, 2006). It commonly is measured by calculating the body mass index (BMI), which is computed by dividing weight in kilograms by height in meters squared (kg/m^2) (Field et al., 2002; Foster & Kendall, 1994). The NHLBI (1998) recommends using BMI to assess obesity because it generally correlates well with amount of adipose tissue. In addition, BMI accounts for one's height, a critical factor that is not directly considered when assessing weight with pounds or kilograms, and therefore serves as a better predictor of body fatness. Epidemiological studies often use BMI to assess the relationship between weight and morbidity, and current public health recommendations related to weight status are based on BMI.

According to the NHLBI (1998), persons with a BMI of 18.5 to 24.9 kg/m^2 are considered to have a healthy weight. Individuals with a BMI below 18.5 kg/m^2 are classified as underweight, whereas those with a value of 25.0 to 29.9 kg/m^2 are classified as overweight. Overweight status, defined as weighing more than a standard level for age and height, confers a heightened risk of morbidity (NHLBI, 1998). Persons with a BMI equal to or greater than 30.0 kg/m^2 are considered to have excessive body fat and, thus, are classified as obese. Obesity is subdivided into three classes, which are determined by BMI and relate to disease risk (NHLBI, 1998). Class I obesity represents mild obesity (30.0 – 34.9 kg/m^2), Class II obesity represents moderate obesity (35.0 – 39.9 kg/m^2), and Class III obesity represents severe/extreme obesity ($\geq$ 40 kg/m^2). The risk of obesity-

related morbidity and mortality increases linearly with BMI (Fabricatore & Wadden, 2006).

While BMI is considered a valuable tool in assessing overall disease risk, the risk of adverse health outcomes associated with BMI, including mortality, varies with age, sex, race/ethnicity, and socioeconomic status (Havas, Aronne, & Woodworth, 2009). This variation may reflect population-specific differences in body composition, fat distribution, and genetic susceptibility. Because height affects BMI nonlinearly, BMI also may provide an inaccurate measure of adipose tissue in very tall or very short people (Rothman, 2008). In addition, BMI may overestimate obesity in muscular persons and may underestimate obesity in elderly persons (Grilo, 2006). Clinical judgment and the use of other assessment tools, including waist circumference and waist-to-hip ratio, are available to help clinicians develop a more complete picture of the health risks associated with obesity. Additional factors to consider when assessing these risks include patients' global health, family histories, and current lifestyles (Havas et al., 2009).

Prevalence of Obesity

The prevalence of obesity is growing at a rapid pace in the United States. Data from the National Health Examination Survey (NHES) and the National Health and Nutrition Examination Survey (NHANES) demonstrate a steady rise in obesity rates over the second half of the 20th century (Ogden et al., 2006). Obesity in the United States increased in prevalence from 13.4% in 1960 to 30.9% in 2000 (Flegal, Carroll, Ogden, & Johnson, 2002). Similar increases were observed in men and women across all age groups and across all racial/ethnic populations during this span (Flegal et al., 2002;

Hedley et al., 2004). Although the prevalence of obesity is higher in women than men, recent statistics suggest that obesity rates are stabilizing (but not declining) among women while continuing to climb among men (Ogden et al., 2006). It is estimated that 34.1% of adults, ages 20 years and older, currently are overweight and that 32.2% are obese (Ogden et al., 2006). An estimated 4.8% of the adult population is extremely obese (BMI $\geq$ 40 kg/m^2).

The rate of overweight children and adolescents in the United States also has risen dramatically. Overweight prevalence among these populations, on average, has tripled since the mid-1970s (Centers for Disease Control and Prevention, 2006a). In 2003-2004, 13.9% of children, ages 2 to 5 years, were overweight (BMI $\geq$ sex-specific 95th percentile), compared to 5% of same-aged peers in 1976-1980. An estimated 18.8% of 6- to 12-year-olds and 17.4% of 12- to 19-year-olds were overweight in 2003-2004, compared to 6.5% and 5% of these populations in 1976-1980. These statistics are alarming, given reports that obesity that develops in childhood is associated with severe obesity in adulthood (Whitaker, Wright, Pepe, Seidel, & Dietz, 1997).

In the United States, the prevalence of obesity in most racial/ethnic populations is higher than in the non-Hispanic White population. In 2003-2004, 45% of non-Hispanic Black adults and 36.8% of Mexican-American adults were classified as obese, compared to 30.6% of non-Hispanic White adults (Ogden et al., 2006). The prevalence of children and adolescents who were overweight, or at-risk for overweight, also was higher in non-Hispanic Black and Mexican-American populations than in the non-Hispanic White population (Ogden et al., 2006). The effects on weight of certain genetic and cultural

factors associated with different racial/ethnic groups may account for these differences in prevalence (Kumanyika, 2002). In addition, persons of lower socioeconomic status are found to display higher rates of obesity than those of higher socioeconomic status, owing, in part, to the greater consumption of inexpensive, energy-dense foods by members of impoverished populations (Drewnowski & Specter, 2004). The inverse relationship between income and obesity in the United States, however, appears to be weakening, and recent trends suggest that persons of any socioeconomic status are becoming increasingly susceptible to weight gain (Zhang & Wang, 2004).

Etiology of Obesity

Genetic Factors

The contributions of genetics to weight status have been established through studies of family relationships, parents and offspring, and twins and adopted children (Farooqi & O'Rahilly, 2006; Marti, Moreno-Aliaga, Hebebrand, & Martinez, 2004). These investigations show that genetics play a significant role in the development of obesity. It is estimated that 40 to 70% of the variation in BMI is heritable (Farooqi & O'Rahilly, 2006; Marti et al., 2004). Although certain cases may be explained by monogenic mutations, obesity is considered primarily a polygenic condition (Farooqi & O'Rahilly, 2006; Marti et al., 2004). Based on the latest update of the human obesity gene map (Rankinen et al., 2006), 127 different candidate genes have been associated with obesity. Genetic predisposition is widely assumed to affect both energy intake and energy expenditure (Marti et al., 2004).

A variety of genetic products, such as cholesystokin (CCK), peptide YY (PYY_{3-36}), and glucagon-like peptide (GLP-1), has been shown to affect energy balance (Korner, Woods, & Woodworth, 2009). Two peptides – leptin and ghrelin – have gained particular attention with respect to their homeostatic effects (Klok, Jakobsdottir, & Drent, 2007; Korner et al., 2009). Leptin is a protein that is produced and released into the circulatory system by the body's adipose tissue. It primarily serves as a feedback mechanism that inhibits appetite and decreases food intake via interactions with neurons in the hypothalamus. Interestingly, obese persons tend to have high circulating levels of leptin (Klok et al., 2007; Korner et al., 2009). Leptin injections do little to induce weight loss in these individuals. Thus, researchers have surmised that obese persons likely are resistant to the effects of leptin (Klok et al., 2007; Korner et al., 2009).

Ghrelin is a 28–amino acid peptide that is synthesized mainly in the stomach and small intestines before meals and during periods of food deprivation (Klok et al., 2007; Korner et al., 2009). The effects of ghrelin on energy balance are essentially opposite to those of leptin. Ghrelin operates through the hypothalamus to attenuate the effects of leptin and to increase hunger and food intake (Klok et al., 2007; Korner et al., 2009). Obese persons do not lose sensitivity to ghrelin; in fact, they may be oversensitive to it. Circulating levels of ghrelin tend to increase as obese persons lose weight, a reaction that represents a physiological adaptation to the positive energy balance associated with obesity (Klok et al., 2007; Korner et al., 2009). Thus, ghrelin appears to contribute to the long-term regulation of body weight by adapting its secretions to changes in weight (Klok et al., 2007; Korner et al., 2009).

Genetic predisposition also appears to contribute to obesity by affecting energy expenditure (Marti et al., 2004). The amount of energy expended per day is the product of three factors: (a) resting metabolic rate (i.e., energy expended when resting in a fasting state under ambient conditions), (b) physical activity (i.e., energy expended through spontaneous and voluntary physical activity), and (c) thermic effect of food (i.e., energy expended when digesting and absorbing food). Approximately 50 to 70% of daily energy expenditure is attributable to resting metabolic rate; 20 to 40% to physical activity; and 10% to the thermic effect of food (Tataranni & Ravussin, 2002). Genetic differences across these variables have been shown to affect weight (Bouchard, 2007; Foster, Wadden, & Vogt, 1997b; Tataranni & Ravussin, 2002; Zurlo, Larson, Bogardus, & Ravussin, 1990).

Environmental Factors

The obesity epidemic is considered largely the product of a toxic environment that surrounds Americans with inexpensive, high-calorie foods (Horgen & Brownell, 2002). The dramatic rise in obesity rates is evidence that environmental factors, in addition to genetic determinants, independently affect energy balance (Marti et al., 2004). Highly palatable, energy-dense foods in large portion sizes have become readily available in most regions of the United States (Young & Nestle, 2002). The number of fast-food restaurants offering tremendous portions of fatty foods has more than doubled since the mid-1970s (Austin et al., 2005; Chou, Grossman, & Saffer, 2004). Convenience stores are stocked continually with ever-increasing portions of sugary snacks (Booth, Pinkston, & Poston, 2005). Not surprisingly, obesity rates have risen in parallel with these changes

in the food environment (Astrup, 2005; Nielsen & Popkin, 2003), and recent statistics confirm that Americans are consuming more calories now than in previous decades (Kant & Graubard, 2006). Between 1971 and 2002, the number of calories consumed by Americans increased by an estimated 12% (Kant & Graubard, 2006).

Several studies have demonstrated that larger portion sizes are associated with greater energy intakes (Diliberti, Bordi, Conklin, Roe, & Rolls, 2004; Rolls, Morris, & Roe, 2002; Wansink & Cheney, 2005; Wansink & Kim, 2005). Diliberti et al. (2004) reported that diners who purchased larger portions of a pasta entrée increased their total consumption of the entrée by 43% and of the entire meal by 25%, compared with those who purchased standard portions of a pasta entrée. Wansink and Kim (2005) found that persons who were given a large container of popcorn consumed 45.3% more popcorn than those who were given a medium container of popcorn. Even when the popcorn was stale, subjects consumed 33.6% more popcorn when it was from a large container. Similarly, Wansink and Cheney (2005) observed that persons who served themselves from large serving bowls at a Super Bowl party consumed 56% more food than those who served themselves from medium serving bowls. These studies clearly demonstrate that being offered or served large portion sizes is associated with excessive eating.

The greater availability and consumption of sugar-based drinks also has contributed to increased obesity rates across the nation. From 1977 to 2001, the amount of energy consumed from sweetened beverages increased by 135%, which translated to the consumption of an additional 278 kilocalories per day (kcal/day) (Karppanen & Mervaala, 2006). The greater consumption of sugar-based drinks may be explained by

increases in sodium intake, and subsequent levels of thirst, experienced by Americans in recent decades (Karppanen & Mervaala, 2006). The impact of sugar-based drinks on childhood obesity is particularly concerning. In school-aged children, the incidence of obesity is 1.6 times greater with each serving of sweetened drinks consumed per day (Ludwig, Peterson, & Gortmaker, 2001). Unfortunately, a number of public schools continue to house soft-drink vending machines in their cafeterias (Johnston, Delva, & O'Malley, 2007).

The obesity epidemic also has been influenced by a shift in the percentages of meals prepared at home to meals eaten outside of home (Wolf & Woodworth, 2009). A greater frequency of consuming meals at fast-food restaurants, in particular, has paralleled the weight gain observed among Americans (Astrup, 2005; Nielsen & Popkin, 2003). In a 15-year prospective analysis, Pereira et al. (2005) found that subjects who ate meals at fast-food restaurants more than twice weekly gained an extra 4.5 kg and had a two-fold greater increase in insulin resistance than those who ate less than one meal per week at these restaurants. In addition, McCrory et al. (1999) found that the frequency of eating foods at restaurants that served high-fat options, such as fried chicken, fried fish, burgers, pizza, Chinese food, and Mexican food, was directly associated with body fatness, along with higher levels of total fat and saturated fat intake and a lower level of fiber intake. Eating outside of the home, therefore, appears to increase the risk of consuming large portions of unhealthy, energy-dense foods.

Reductions in energy expenditure have accompanied increases in energy intake among Americans (Blair & Church, 2004). With advancements in technology, such as

motorized transport and labor-saving devices, Americans defaulted to increasing amounts of sedentary behavior over the second half of the 20th century (Dzewaltowski, 2008). Currently less than 30% of Americans are physically active on a regular basis (Kruger, Yore, & Kohl, 2007), despite indications that persons who are physically active are significantly less likely to be obese, to become obese, and to experience obesity-related health consequences (Grilo, 2006). Unfortunately, the trend towards physical inactivity appears to begin in childhood, as less than 10% of public schools provide physical-activity classes on a daily basis (Centers for Disease Control and Prevention, 2006b). The lack of physical activity offered in schools, combined with evidence that children are direct targets of marketing by food companies (Story & French, 2004), provides an environment ripe for the development of obesity in youth. To combat childhood obesity, the CDC recently has recommended that schools allot additional time for physical activity, integrate nutritional education with physical activity, include noncompetitive sports (e.g., dance) in physical-education curricula, and educate students on the effects of sedentary behavior on health (Katz et al., 2005).

Psychological Factors

The psychological causes of obesity are less understood than the physiological and environmental determinants. Research primarily has focused on the association between obesity and depression (Simon et al., 2006). Depression, in its typical form, is associated with weight loss, whereas weight gain is characteristic of atypical depression (American Psychiatric Association, 2000). Weight gain that accompanies depression may be attributable to a variety of factors, including increased appetite, reduced physical

activity, increased binge eating, and the side effects of antidepressant medications (Simon et al., 2006). While the presence of depression has been found to predict obesity (Blaine, 2008; Hasler et al., 2004), the presence of obesity also has been found to predict depression (Roberts, Deleger, Strawbridge, & Kaplan, 2003). Thus, there appears to be a complex bi-directional relationship between depression and weight, such that obesity may be either a cause or a consequence of depressed mood (Stunkard, Fernstrom, Price, Frank, & Kupfer, 1990). A variety of behavioral, cognitive, physiological, and social mechanisms may be responsible for these causal pathways (Markowitz, Friedman, & Arent, 2008).

Obesity-Related Comorbidities

Medical Comorbidities

Obesity can have detrimental effects on almost every major organ system in the human body and increases the risk of a variety of medical conditions, potentially leading to early mortality (Bray, 2004; Brown et al., 2009; Field et al., 2002). In an alarming analysis (Olshansky et al., 2005), the gains in life expectancy achieved in the United States during the 20th century are projected to decline as a result of the adverse health consequences of obesity. There is a strong relationship between weight gain and premature death, with cardiovascular disease representing the principal cause of death among obese patients (Van Gaal, Mertens, & De Block, 2006). Obesity increases the risk of developing a variety of cardiovascular risk factors, including hypertension, hypercholesterolemia, and type 2 diabetes (Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). The risk of developing various cancers (e.g., esophageal, colorectal,

gallbladder, breast, uterine) increases with excess weight, and BMI correlates significantly with death from all cancers (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003). Obesity is associated with pulmonary diseases and musculoskeletal problems, such as obstructive sleep apnea and osteoarthritis (Coughlin, Mawdsley, Mugarza, Calverley, & Wilding, 2004; Wearing, Hennig, Byrne, Steele, & Hills, 2006). Finally, obesity predisposes patients to complications with gastrointestinal and hepatic functioning (e.g., gallbladder disease), reproductive functioning (e.g., polycystic ovary syndrome, erectile dysfunction), and dermatologic functioning (e.g., acanthosis nigricans) (Bray, 2004; Brown et al., 2009; Field et al., 2002).

Obesity also is associated with the metabolic syndrome, a cluster of cardiometabolic factors that increases the risk of heart attack, stroke, and type 2 diabetes (Despres & Lemieux, 2006). These risk factors, as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), include elevated waist circumference (men = > 102 cm, women = > 88 cm); elevated blood pressure (≥ 130/≥ 85 mmHg); elevated triglyceride concentrations (≥ 150 mg/dL); high fasting glucose concentrations (≥ 110 mg/dL), and low high-density lipoprotein (HDL) cholesterol levels (men = < 40 mg/dL, women = < 50 mg/dL). The metabolic syndrome is associated with increased risks of cardiovascular mortality and all-cause mortality (Hunt, Resendez, Williams, Haffner, & Stern, 2004).

With the rapid rise in childhood and adolescent obesity in the United States, obesity-related comorbidities, many of which were previously observed primarily in adults, are becoming increasingly common in younger populations (Dietz & Robinson,

2005). The incidences of sleep apnea and gallbladder disease in children and adolescents tripled between the late 1970s and late 1990s. Type 2 diabetes now accounts for as many as 45% of all newly diagnosed cases of diabetes in pediatric populations. The risk factors associated with cardiovascular disease, such as elevated blood pressure and dyslipidemia, also are increasing in children (Dietz & Robinson, 2005). Fortunately, the significance of obesity prevention in children has been recognized by several public health organizations in recent years, including the Robert Wood Johnson Foundation, which has vowed to devote $500 million in funds to combat childhood obesity and to reverse the obesity epidemic in American children by 2015 (Havas et al., 2009).

Psychosocial Comorbidities

Several psychosocial complications are related to obesity. Obese individuals experience an abundance of prejudice and discrimination across many domains of living (Sarlio-Lahteenkorva, 2001; Wadden et al., 2002; Wang et al., 2004). Negative attitudes toward obese persons have been documented across education, employment, and social settings (Grilo, 2006). In the workplace, for example, obese persons face discrimination in several areas, including selection, placement, compensation, and promotion (Roehling, 1999). Such bias appears to be especially pronounced for overweight women (Pingitore, Dugoni, Tindale, & Spring, 1994). Gortmaker, Must, Perrin, Sobol, and Dietz (1993) found that women who were overweight completed fewer months of school, were less likely to be married, and had lower household incomes than nonoverweight women, despite displaying comparable intellectual aptitudes. Overweight children and adolescents are not immune to the effects of prejudice and discrimination, as they tend to

have fewer friends, to be excluded from games and sports, and to be teased more often than their nonoverweight peers (Pierce & Wardle, 1997). It has long been known that children as young as 10 years of age display negative bias toward their overweight peers (Richardson, Goodman, Hastorf, & Dornbusch, 1961), a finding that was replicated more recently by Latner and Stunkard (2003). Prejudice towards the obese population is so prevalent that even some health care professionals have been found to endorse negative attitudes toward obese patients, viewing them as overindulgent, lazy, and noncompliant (Foster et al., 2003; Teachman & Brownell, 2001).

Obese patients who seek professional assistance with weight loss tend to experience significant psychopathology (Fitzgibbon et al., 1993; Wadden et al., 2002). Binge-eating disorder (BED) has been found to affect 10 to 15% of patients who seek weight loss treatment (Stunkard, 2002), as compared with 1.2% of the general population (prevalence rates vary based on measurement criteria) (Hudson, Hiripi, Pope, & Kessler, 2007). BED currently is proposed as a diagnosis requiring further study in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)* (American Psychiatric Association, 2000). BED is characterized by episodes of eating, in a discrete period of time, an amount of food that is objectively larger than most people would eat under similar conditions. These episodes are accompanied by a sense of loss of control of eating. Indicators of loss of control include eating very rapidly, eating until uncomfortably full, eating when not physically hungry, eating alone out of embarrassment, and feeling disgusted or guilty after overeating. BED is differentiated from bulimia nervosa by the absence of inappropriate compensatory behaviors, such as

purging, fasting, or excessive exercise. Compared to those without BED, obese patients with BED display more symptoms of depression and borderline personality disorder, along with a significantly greater lifetime prevalence of any Axis I disorder, including substance abuse or dependence (de Zwaan, 2001; Wadden et al., 2002).

Night-eating syndrome (NES) is another condition found among obese patients in clinical settings. The prevalence of NES ranges from 1.5 to 6% in the general population and from 6 to 16% in obese patients who seek weight loss treatment (Stunkard et al., 2009). NES is not currently defined as an eating disorder in the *DSM-IV-TR* (2000), although recognition of its principal characteristics has increased over the past decade. First identified by Stunkard and colleagues in 1955 (Stunkard, Grace, & Wolff, 1955), NES is defined by two core diagnostic criteria: (a) evening hyperphagia, defined as the consumption of at least 25% of daily food intake after the evening meal, and/or (b) presence of nocturnal awakenings with ingestions of food several times per week (Stunkard et al., 2009). Patients with NES experience a shift in the normal circadian rhythm of food consumption toward later in the day and, thus, experience a delay of appetite in the morning, overconsumption of food at night, and sleep onset and sleep maintenance insomnia. In addition, patients with NES experience more psychiatric comorbidity than patients without NES, including depressed mood, low self-esteem, and substance-use disorders (Stunkard et al., 2009).

Depression represents another condition found among those who seek treatment for weight loss, affecting approximately 10% of obese patients in clinical settings (Wadden et al., 2000). As previously described, the relationship between obesity and

depression is complex. Depressed mood is positively correlated with BMI (de Zwaan, 2001; Wadden et al., 2002) and may be either a cause or a consequence of obesity (Stunkard et al., 1990). Depression is very common among extremely obese patients, such as those who present for bariatric surgery (Wadden, Sarwer, et al., 2007). Persons with a BMI of 40 kg/m^2 or greater are approximately 5 times more likely to have experienced a major depressive episode than those of average weight (Onyike, Crum, Lee, Lyketsos, & Eaton, 2003). In addition, the risk of attempted suicide increases as BMI exceeds 40 kg/m^2 (Dong, Li, Li, & Price, 2006). Dong et al. (2006) found that compared to the general population, the risk of attempted suicide is 87% higher for persons with a BMI of 40 to 50 kg/m^2 and 122% higher for those with a BMI greater than 50 kg/m^2. The adverse psychological reactions of extremely obese persons may be attributable to their severe impairment in health-related quality of life, as well as to their heightened exposure to prejudice and discrimination (Fabricatore, Wadden, Sarwer, & Faith, 2005; Wadden et al., 2002).

Finally, obesity is associated with body image dissatisfaction, which is widely considered a function of Western society's pervasive emphasis on thinness as the ideal (Grilo, 2006). Although the degree of disturbance varies across different subgroups of the population (Kumanyika, Wilson, & Guilford-Davenport, 1993), the prevalence of body image dissatisfaction has increased dramatically in men and women since the 1970s (Sarwer & Thompson, 2002). Body image dissatisfaction has become so common that it has been termed a "normative discontent" (Rodin, Silberstein, & Striegel-Moore, 1985). There appears to be a relationship between body image dissatisfaction and increased

psychological distress, including low self-esteem and depressive symptoms (Foster, Wadden, & Vogt, 1997a). A minority of obese patients who seek weight loss treatment are likely to suffer from clinically significant depression as a result of their body image concerns (Sarwer, Wadden, & Foster, 1998; Wadden et al., 2002). In addition, patients who endorse a negative body image may have difficulty controlling their weight in the long term (Cooper & Fairburn, 2002). Interestingly, the severity of obesity does not appear to influence the severity of body image dissatisfaction or the relationship between body image dissatisfaction and psychological symptoms (Sarwer et al., 1998).

Treatment Approaches

There are three general approaches to the management of obesity. The first approach is behavior therapy, also known as behavioral weight control or lifestyle modification. Behavior therapy is considered the first-line approach to obesity (NHLBI, 2000; Phelan & Wadden, 2002). It consists of diet, physical activity, and behavior modification (Foster et al., 2005; Wadden, Crerand, et al., 2005). Pharmacotherapy represents another approach to obesity. The use of medications is indicated for patients with a BMI equal to or greater than 30 kg/m^2, or for those with a BMI of 27 to 29.9 kg/m^2 who exhibit obesity-related medical comorbidities (NHLBI, 2000). The third approach to obesity is surgical intervention. Weight loss surgery is reserved for patients with a BMI equal to or greater than 40 kg/m^2, or with a BMI of 35 to 39.9 kg/m^2 in the presence of comorbid conditions (NHLBI, 2000).

Behavior Therapy

Behavior therapy is considered the cornerstone of treatment for obesity (Foster et al., 2005; Wadden, Crerand, et al., 2005). The goal of behavior therapy is to modify patients' eating and physical activity behavior in order to achieve clinically significant weight loss and health improvements. Behavior therapy consistently has been shown to produce these favorable outcomes (Foster, 2006; Wadden, Crerand, et al., 2005; Wing, 2002).

Originating from learning theory in the late 1960s, behavior therapy assumes that eating and physical activity behavior are learned phenomena that are amenable to behavior modification through the application of behavioral principles and techniques (Foster et al., 2005; Wadden, Crerand, et al., 2005). Classical conditioning and operant conditioning, therefore, serve important functions in treatment (Foster et al., 2005; Wadden, Crerand, et al., 2005), as previously described. Identifying and modifying the conditions that maintain unhealthy eating and exercise behavior are central goals in therapy (Foster et al., 2005; Wadden, Crerand, et al., 2005).

Treatment typically is delivered to closed groups of 10 to 20 patients on a weekly basis for 16 to 26 weeks, followed by monthly or every-other-month maintenance sessions (Foster et al., 2005; Wadden, Crerand, et al., 2005). Sessions usually last from 60 to 90 minutes. This approach allows time for patients to achieve a 10% loss of initial weight during the course of treatment, which is considered a clinically significant weight loss (NHLBI, 1998). Renjilian et al. (2001) found that group therapy induced larger initial losses (approximately 2 kg) than individual therapy, even among patients who

preferred individual treatment but were randomly assigned to receive group care. Group therapy allows patients to receive mutual support and to engage in healthy competition with each other, which may account for the greater losses achieved with this modality. In addition, group therapy is more cost-effective than individual therapy (Wadden, Crerand, et al., 2005).

Behavior weight loss interventionists consist of behavioral psychologists, registered dietitians, exercise specialists, and other health-related professionals (Wadden, Crerand, et al., 2005; Wadden & Osei, 2002). Patients are expected to assume an active role in treatment and, thus, are prescribed homework assignments on a regular basis. These assignments are tailored toward modifying their eating, physical activity, and thinking habits. Group sessions principally are devoted to reviewing their homework assignments and problem solving their difficulties with implementing behavioral changes. A different educational topic related to healthful behaviors is presented by the group leader at each session, and patients are encouraged to integrate this information into their weight control efforts. Patients are weighed at each session as a measure of their adherence to and progress in treatment (Wadden, Crerand, et al., 2005; Wadden & Osei, 2002).

There are several key components of behavior therapy. Recording food intake and physical activity through the use of detailed, self-monitoring forms is perhaps the most important aspect of treatment (Wadden, Crerand, et al., 2005). Studies consistently demonstrate an association between recording food intake and improved weight control (Berkowitz, Wadden, Tershakovec, & Cronquist, 2003; Head & Brookhart, 1997;

Wadden, Crerand, et al., 2005). Obese patients tend to underestimate their food intake by approximately 40 to 50% per day, which is attributable to their difficulty in estimating portion sizes, macronutrient compositions, and calorie contents of food (Lichtman, Pisarka, & Berman, 1992). Keeping food records reduces (but not eliminates) their tendency to underestimate energy intake and, thus, improves their ability to lose weight (Wadden, Crerand, et al., 2005). Patients initially are instructed to record the types, amounts, and calorie values of food consumed per day. As therapy progresses, they are asked to include the times, places, and emotions associated with their eating in order to elucidate patterns that may be contributing to their obesity, as well as to identify strategic points of intervention for the therapist. Self-monitoring often reveals behaviors of which patients were previously unaware (e.g., grazing on sugary snacks), which consequently helps them focus their efforts on modifying these behaviors (Wadden, Crerand, et al., 2005).

Dietary change represents another component of behavior therapy (Wadden & Osei, 2002; Wing, 2002). The NHLBI (1998) recommends that overweight and obese patients follow a portion-controlled, low-calorie diet and reduce their calorie intake by approximately 500 kcal/day. This guideline generally translates to the consumption of 1,000 to 1,500 kcal/day for obese women and 1,500 to 1,800 kcal/day for obese men, although patients' exact calorie goals are based on their baseline energy requirements (Wadden & Osei, 2002). Patients also are expected to limit their fat intake to no greater than 30% of total kcal/day. Additional dietary prescriptions are based on the latest dietary

guidelines by the Department of Health and Human Services (HHS) and the Department of Agriculture (USDA) (e.g., 2005 Dietary Guidelines for Americans).

Diets that prescribe fewer than 800 kcal/day, known as very-low-calorie diets (VLCDs), have been shown to induce weight loss that is nearly double the size of that achieved with conventional diets consisting of 1,200 to 1,500 kcal/day (Tsai & Wadden, 2006). However, patients who are prescribed VLCDs usually regain 35 to 50% of their weight within the first 2 years following treatment. As a result, few statistically significant differences in weight losses have been detected at follow-up between patients treated with VLCDs and those treated with more balanced-deficit diets (1,000 to 1,500 kcal/day) (Wadden & Osei, 2002). Patients prescribed VLCDs also require careful medical supervision, particularly in monitoring the development of gallstones, and incur high expenses owing to the cost of ongoing medical care. Thus, VLCDs do not appear to offer any significant advantages over more balanced-deficit diets in the long term (Wadden & Osei, 2002).

A variety of dietary strategies may be used in behavior therapy. No single approach works for every patient because of the diverse needs of obese individuals (Aronne, 2002; Kumanyika, 2002). Examples of dietary options include meal replacement products (i.e., prepackaged meals, shakes, and snack bars) and structured meal plans. The use of meal replacement products, in conjunction with low-fat, low-calorie diets, has been shown to facilitate the induction and maintenance of weight loss in short- and long-term trials (Ditschuneit, Flechtner-Mors, Johnson, & Adler, 1999; Flechtner-Mors, Ditschuneit, Johnson, Suchard, & Adler, 2000). Replacing one or two

meals per day with meal replacement products also has been found to produce greater weight loss than isocaloric diets composed of conventional foods (Heymsfield, van Mierlo, van der Knapp, Heo, & Frier, 2003). The benefits of these products derive from their fixed quantity and calorie content, which facilitate dietary adherence. Replacing conventional meals and snacks with calorie-specific products removes the error, and subsequent weight gain, associated with underestimating calorie intake. In addition, these products simplify food choices, require minimal preparation, and prevent exposure to unhealthy foods, all of which facilitate weight control (Tsai & Wadden, 2006).

Structured meal plans, also known as portion-controlled servings of conventional foods, offer an alternative to meal replacement products. This approach consists of providing patients with calorie-specific menus, recipes that use conventional food, and grocery lists, thereby exposing patients to models of healthful eating (Fabricatore & Wadden, 2006). The goal of this approach is to impose greater structure on patients' eating behaviors in order to improve their dietary adherence. Studies show that the use of structured meal plans, like meal replacement products, produces greater weight loss than isocaloric, self-selected diets (Jeffery et al., 1993; Wing et al., 1996).

Although patients in behavior therapy are traditionally prescribed a low-fat diet, debate currently exists over whether low-carbohydrate diets lead to greater weight loss than low-fat diets. Low-carbohydrate diets, such as the Atkins diet (Atkins, 1998), promote a state of ketosis by allowing for the unlimited consumption of protein and fat at the expense of carbohydrates. Despite the unlimited amount of protein and fat intake allowed, dieters appear to reduce their overall calorie intake, which may be attributable to

increased satiation (from high protein intake) and/or decreased dietary variability (Makris & Foster, 2005). Studies comparing the efficacy of low-carbohydrate diets and low-fat diets show greater weight loss at 6 months with low-carbohydrate diets but no differences in weight loss at 12 months (Nordmann et al., 2006). Two recent studies, however, have demonstrated greater loss with low-carbohydrate diets at 12 months (Gardner et al., 2007; Shai et al., 2008). The safety concerns associated with consuming large amounts of saturated fat, including elevations in low-density lipoprotein (LDL) cholesterol and risk of cardiovascular disease, must be weighed against the potential benefits of following a low-carbohydrate diet (Astrup, Larsen, & Harper, 2004).

Another component of behavior therapy includes establishing realistic weight loss goals with patients, along with increasing their appreciation of achieving a modest loss. A loss of 5 to 10% of initial weight can substantially decrease the risk of obesity-related diseases and improve the health outcomes of obese patients (Foster, 2006; Wadden, Crerand, et al., 2005; Wing, 2002). Research shows that patients generally achieve losses of 8 to 10% of initial weight during the first 6 months of treatment, well within the parameters of a clinically significant outcome (NHLBI, 1998). The health benefits of modest loss were clearly demonstrated in a landmark trial by the Diabetes Prevention Program (DPP) Research Group (Knowler et al., 2002). Over a mean follow-up period of 2.8 years, the DPP found that an intensive lifestyle intervention program (behavior therapy), designed to induce a loss of 7% of initial weight, successfully reduced the incidence of type 2 diabetes by 58% in overweight subjects with impaired glucose tolerance compared with a placebo group (Knowler et al., 2002). In addition, behavior

therapy was significantly more effective than metformin therapy in reducing diabetic risk among subjects. A follow-up study currently is being conducted by the National Institutes of Health (NIH) to determine the long-term effects of lifestyle modification on morbidity and mortality in overweight and obese individuals who already have developed type 2 diabetes (Ryan et al., 2003).

Maladaptive cognitions related to weight control are also addressed in behavior therapy. As described previously, cognitions that commonly undermine efforts to lose weight tend to be dichotomous, catastrophic, and overgeneralized (Brownell, 2004; Wadden, Crerand, et al., 2005). These types of distorted thinking may be manifested through the establishment of unrealistic eating and weight loss goals, self-criticism in response to overeating or gaining weight, and/or hopelessness about controlling weight (Wadden, Crerand, et al., 2005). For example, despite the demonstrated benefits of modest weight loss, many obese patients unrealistically desire a loss of over 25% of initial weight and, thus, may have difficulty accepting a loss that falls below this expectation (Foster et al., 2005; Wadden, Berkowitz, Sarwer, Prus-Wisniewski, & Steinberg, 2001). Others may display marked body image concerns that disrupt their ability to appreciate their weight loss (Cooper & Fairburn, 2002). Cognitive interventions, such as self-monitoring negative thoughts and role playing rational responses, are used in behavior therapy to restructure dysfunctional thoughts about losing weight (Brownell, 2004). Interestingly, owing to the large body of evidence in support of behavior therapy, randomized controlled trials examining the efficacy of cognitive approaches to obesity currently are lacking (Fabricatore, 2007). Although cognitive

therapy is purported to improve long-term weight control (Cooper & Fairburn, 2002), empirical trials are needed to determine the comparative effectiveness of behavior therapy and cognitive therapy in the treatment of obesity.

A large portion of behavior therapy is devoted to modifying patients' eating behavior (Brownell, 2004; Wadden, Crerand, et al., 2005). Maladaptive eating habits have been shown to contribute significantly to weight gain. Eating infrequent meals and at later times in the day, for example, are associated with obesity (Taylor, Missik, Hurley, Hudak, & Logue, 2004). Accordingly, patients are provided instruction on ways to improve their eating behavior. They are taught to control their portion sizes (e.g., weighing and measuring food), to decrease their speed of eating (to improve recognition of fullness), and to eat at regular time intervals (to improve appetite control). In addition, they are taught to avoid other activities while eating, as well as to limit their eating to certain rooms in the home (e.g. kitchen, dining room), in order to prevent and/or extinguish any associations between eating and non-eating-related stimuli (Brownell, 2004).

The principle of stimulus control is applied throughout the course of therapy (Brownell, 2004; Wadden, Crerand, et al., 2005). In the context of obesity treatment, stimulus control refers to the act of controlling the external environment involving food. Patients are encouraged to avoid high-risk venues (e.g., fast-food restaurants, convenience stores, buffets); avoid aisles in grocery stores that contain energy-dense snacks; store high-fat, high-sugar foods out of sight; shop from a food list; keep serving dishes off the table; and serve modest portion sizes (Brownell, 2004; Wadden, Crerand, et

al., 2005). In addition to eliminating triggers to overeating, patients are instructed to add cues to their environment that promote healthful behaviors. For example, placing a pair of sneakers at the front door may serve as a prompt to exercise. Patients are encouraged to use self-reinforcement techniques, such as non-food-related rewards, to strengthen the frequency of these behaviors (Brownell, 2004; Dietz & Robinson, 2005; Nauta et al., 2001).

In addition to limiting their energy intake, patients are instructed to increase their energy expenditure through physical activity. While physical activity alone is of limited benefit in inducing weight loss, it is a critical component in the long-term management of weight (Jakicic & Otto, 2005; Wadden, McGuckin, Rothman, & Sargent, 2003; Wing, 1999). Patients who exercise on a regular basis after losing weight are more likely to maintain their losses than are those who do not exercise regularly after losing weight (Wadden et al., 2003). Similarly, patients who achieve greater amounts of physical activity (e.g., 2,500 kcal/week or greater) are more likely to maintain their losses compared with those who achieve lesser amounts of physical activity (Jakicic, Winters, Lang, & Wing, 1999; Jeffery, Wing, Sherwood & Tate, 2003). Exercise confers important health benefits, such as reducing lipid levels, blood pressure, blood glucose, and risk of osteoporosis (Jakicic & Otto, 2005). In addition, it appears to reduce cardiovascular morbidity and mortality, independent of weight loss outcomes (Hu et al., 2004; Lee, Blair, & Jackson, 1999; Wadden, Butryn, & Byrne, 2004).

Behavior therapy encourages patients to increase their programmed activity and lifestyle activity (Brownell, 2004; Wadden, Crerand, et al., 2005). Programmed activity is

defined as structured bouts of exercise, completed in discrete periods of time (i.e., 30 to 60 minutes) at a relatively high intensity (i.e., 60 to 80% of maximum heart rate) (Fabricatore & Wadden, 2006). Examples of programmed activity include jogging, biking, swimming, and scheduled workouts. In contrast, lifestyle activity refers to activity performed as part of one's daily routine (Brownell, 2004). Lifestyle activity includes walking instead of driving, using stairs instead of elevators, and parking farther from building entrances (to achieve more steps). Studies suggest that lifestyle activity may be as effective as traditional structured exercise in improving fitness and weight control (Andersen et al., 1999; Dunn et al., 1999). Lifestyle activity also requires less planning and time commitment than does programmed activity. Thus, lifestyle activity may represent an attractive alternative for patients who do not enjoy or have time to engage in structured exercise.

Behavior therapy traditionally prescribes 1,000 kcal/week in physical activity, which is roughly equivalent to walking 10 miles per week. Patients who have difficulty achieving this goal are encouraged to schedule exercise in multiple bouts. Jakicic, Wing, Butler, and Robertson (1995) found that subjects who were instructed to engage in multiple, shorter bouts of activity (i.e., four 10-minute bouts of activity) demonstrated better exercise adherence and weight loss at 6 months than those who were instructed to engage in single, longer bouts of activity (i.e., one 40-minute bout). Scheduling exercise in multiple bouts may be especially helpful to patients who are unaccustomed to exercising on a regular basis or to those who are initiating an exercise program for the first time.

Research suggests that completing 2,000 to 2,500 kcal/week in physical activity (e.g., walking 20 to 25 miles per week) results in better weight control than does completing 1,000 kcal/week, as prescribed in traditional behavior therapy (Jakicic et al., 1999; Jeffery et al., 2003; Tate, Jeffery, Sherwood, & Wing, 2007). In 2002, the Institute of Medicine recommended at least 60 minutes per day of moderate activity to manage body weight and avoid weight gain, which subsequently was reflected in the 2005 Dietary Guidelines for Americans (HHS/ USDA, 2006). Sixty minutes of moderate activity per day translates to approximately 2,100 kcal/week in exercise, which is double the recommended dose of physical activity in behavior therapy. Further support of higher amounts of physical activity comes from members of the National Weight Control Registry, a list of persons who have lost at least 13.6 kg (i.e., 30 lb) and have maintained this loss for at least 1 year (Klem, Wing, McGuire, Seagle, & Hill, 1997). Members report an average of 2,800 kcal/week in physical activity, which is roughly equivalent to walking 28 miles per week. The dose of exercise traditionally prescribed in behavior therapy, therefore, appears to be lower than the dose found to ensure long-term weight control.

Because the goal of behavior therapy is permanent weight loss, patients must remain motivated to control their weight beyond the course of treatment. Unfortunately, few patients who lose weight are able to maintain their losses over time (Wadden, Crerand, et al., 2005). Within the first year following behavior therapy, patients tend to regain 30 to 35% of weight initially lost in treatment, and over 50% of individuals return to their baseline weight within 5 years (Wadden, Crerand, et al., 2005). It is difficult for

patients to practice healthful behaviors consistently in face of the variety of compensatory biological and environmental forces that oppose weight loss (Aronne, Wadden, Isoldi, & Woodworth, 2009; Brownell, 2010). Helping patients remain motivated to control their weight, given these conditions, represents a final target in behavior therapy.

The construct of social support has been studied widely in health behavior research in terms of its effects on a variety of medical and psychological conditions (Gallant, 2003; McNeill, Kreuter, & Subramanian, 2006). In terms of its impact on obesity management, Gorin et al. (2005) found that subjects with at least one support partner who had been successful in losing weight displayed greater weight loss at 6, 12, and 18 months than those with no successful partners or those without partners. In another study, 66% of subjects who participated in a behavioral weight loss program with three friends maintained their weight losses at 6-month follow-up, compared with only 24% who participated in treatment alone (Wing & Jeffery, 1999). Research also shows that social support is positively correlated with exercise behavior and exercise intention (Carron, Hausenblas, & Mack, 1996) and that social support independently affects exercise behavior (Fraser & Spink, 2002). Having someone with whom to exercise, for example, increases the probability that one will engage in physical activity (Der Ananian, Wilcox, Saunders, Watkins, & Evans, 2006). Based on these findings, social support appears to facilitate weight control and may help sustain motivation in the long term.

Pharmacotherapy

Pharmacotherapy represents another approach to the management of obesity. The use of medications is indicated for patients with a BMI equal to or greater than 30 kg/m^2,

or with a BMI of 27 to 29.9 kg/m^2 in the presence of obesity-related medical conditions (NHLBI, 2000). Consistent with a stepped-care approach to weight management, medication typically is reserved for patients who have failed to lose weight with diet, exercise, and behavior therapy (Phelan & Wadden, 2002).

The introduction of weight loss medication originally was heralded by the medical community as representing a very promising method of treating obesity. Unfortunately, hopes were derailed after a series of adverse events was observed in association with several agents. In 1934, for example, dinitrophenol was pulled from the market because of its link with cataract and neuropathy (Masserman & Goldsmith, 1934). The use of amphetamine has been banned, restricted, or discouraged because of its potential for abuse or dependence (Huizinga, 2007). Common over-the-counter medications, such as those containing the ephedra herb, have been removed from shelves because of health risks associated with their usage (Huizinga, 2007). Perhaps the most infamous weight loss medication was fenfluramine, which was withdrawn from the market in 1997 because of its link with potentially fatal heart valve abnormalities (Connolly et al., 1997).

Despite a history of safety concerns, newer (and presumably safer) weight loss medications continue to be developed and prescribed (Huizinga, 2007). These medications serve to reduce food intake, affect nutrient absorption, and/or increase energy expenditure. Several anorectic agents are approved by the FDA for short-term use (generally 12 weeks or less), such as phentermine, diethylpropion, and phendimetrazine (Huizinga, 2007). These agents generally affect the availability of anorexigenic

neurotransmitters (most notably, norepinephrine, serotonin, and dopamine) in the central nervous system, which in turn suppresses appetite. The only medication that is currently approved for the long-term management of obesity is orlistat, a gastric and pancreatic lipase inhibitor that reduces the absorption of dietary fat consumed in meals by approximately 30% (Li et al., 2005).

Until recently (and during the time of the current study), sibutramine also was approved for the long-term management of obesity. Sibutramine is a beta-phenylethylamine that inhibits the reuptake of serotonin (5-HT) and norepinephrine (NA) (as well as of dopamine to a very limited extent), thereby increasing their extracellular levels. The 5-$HT_{2A/2C}$, 5-$HT_{2B/2C}$, and 5-HT_{1A} receptors have been implicated in mediating the action of sibutramine on food intake (Jackson, Neeham, Hutchins, Mazurkiewicz, & Heal, 1997; Stricker-Kongrad, Souquet, Jackson, & Burlet, 1996). Research has shown that 5-HT_{1A} antagonists reduce meal size, 5-$HT_{2A/2C}$ agonists fragment the meal, and 5-HT_{2C} agonists decrease rate of ingestion (Chapelot, Marmonier, Thomas, & Hanotin, 2000). A synergy between the action of sibutramine on 5-HT and NA reuptake also has been found to contribute to the potent effect of the drug (Jackson, Pleasance, & Heal, 1998). These actions appear to modify internal hunger and satiation cues (Bray, 2002), thereby facilitating adherence to a reduced-calorie diet. In conjunction with reducing appetite, sibutramine has been shown to increase resting metabolic rate and limit the decline in energy expenditure associated with weight loss (Persky et al., 2004; Walsh, Leen, & Lean, 1999). In total, the effect of sibutramine on weight loss appears to be mediated by both decreased energy intake and increased energy expenditure.

The efficacy of sibutramine has been established in more than a dozen placebo-controlled studies (Arterburn, Crane, & Veenstra, 2004). The use of sibutramine has been shown to produce losses of 5 to 8% of initial weight over the first 6 months of treatment, compared with 1 to 4% with placebo (Bray et al., 1999; Fanghanel, Cortinas, Sanchez-Reyes, & Berber, 2000; Fujioka et al., 2000; Ryan, 2000). At 1 year, sibutramine has been associated with losses of 7 to 10% of initial weight (Bray, 2007). Findings from the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) indicate that sibutramine also facilitates the maintenance of lost weight for up to 2 years (James et al., 2000). Research has found no significant difference in weight reduction among patients treated with sibutramine continuously compared with those treated intermittently over a period of 48 weeks (Wirth & Krause, 2001), suggesting that the intermittent use of the drug could save costs without sacrificing efficacy. Finally, in conjunction with weight loss, sibutramine has been shown to confer significant benefits in improving metabolic outcomes and reducing cardiovascular risk factors (Vettor, Serra, Fabris, Pagano, & Federspil, 2005).

Owing to its sympathomimetic properties, the use of sibutramine is associated with increased pulse rate (4 to 5 beats per minute) and increased systolic and diastolic blood pressure (1 to 3 mmHg) (Bray, 2002). Thus, it is contraindicated for patients with uncontrolled hypertension or cardiovascular disease, such as coronary artery disease, cerebrovascular disease, cardiac arrhythmia, and congestive heart failure. Sibutramine also is contraindicated for those who are already taking medications that inhibit serotonin reuptake. Unlike fenfluramine and amphetamine, respectively, sibutramine has not been

implicated in the development of valvular heart disease (since it does not stimulate serotonin release) and has very low abuse potential (since it does not enhance dopamine release) (Bray, 2002).

Surgical Treatments

Weight loss surgery, known as bariatric surgery, represents the last resort for weight loss in most cases. It generally is reserved for patients with a BMI equal to or greater than 40 kg/m^2, or with a BMI of 35 to 39.9 kg/m^2 in the presence of obesity-related medical comorbidities (NHLBI, 2000). Bariatric surgery essentially involves reducing the size of the stomach, thus limiting calorie intake and producing significant weight loss. Surgical intervention is demonstrated to be the most effective means of inducing and maintaining weight loss in extremely obese patients, displaying the capacity to improve or ameliorate several weight-related conditions (e.g., hypertension, type 2 diabetes, obstructive sleep apnea) (Buchwald et al., 2004).

The most common types of bariatric surgery performed in the United States are gastric bypass and gastric banding (Buchwald, 2005; Steinbrook, 2004). Gastric bypass surgery consists of separating the upper part of the stomach and its connection to the midpart of the small intestine, allowing for food to bypass most of the stomach and the first part of the small intestine. The smaller gastric pouch leads to a faster sensation of satiety, while the bypass of the small intestine results in a limited absorption of calories (and other nutrients). Patients who undergo this procedure must be monitored long term for micronutrient deficiencies resulting from the malabsorptive effects of surgery

(Ledoux et al., 2006). Expected weight loss with gastric bypass is approximately 65 to 70% of excess body weight and approximately 35% of BMI (Buchwald, 2005).

Gastric banding surgery consists of placing a silicone band around the upper part of the stomach, thus creating a small stomach pouch and restricting the amount of food consumed. Unlike the effects of gastric bypass, gastric banding does not limit the absorption of nutrients. The silicone band is also adjustable and reversible (if necessary). Weight loss outcomes are approximately 50% of excess body weight and approximately 25% of BMI (Buchwald, 2005). While gastric banding tends to result in smaller (yet still significant) weight loss than gastric bypass, the former is associated with lower complication and mortality rates. The risk of operative mortality from gastric bypass is about 0.5%, whereas the operative mortality risk from gastric banding is about 0.1% (Buchwald, 2005). With either procedure, patients must adhere to the postoperative diet in order to achieve and maintain optimal weight loss (NHLBI, 2000).

Combination of Pharmacotherapy and Behavior Therapy

The combination of pharmacotherapy and behavior therapy has been found to produce greater weight loss than either approach alone (Wadden et al., 2001; Wadden, Berkowitz, et al., 2005). The superior weight loss achieved with combining these therapies may be attributable to their complementary mechanisms of action. Medication appears to modify internal signals that regulate appetite (Bray, 2002), while behavior therapy helps patients control the external food environment (Foster et al., 2005; Wadden, Crerand, et al., 2005). When combined, these therapies are believed to address a greater number of variables than when used alone, which consequently enhances weight

loss (Wadden, Butryn, et al., 2007). Earlier investigations that compared fenfluramine and lifestyle modification found that patients who received lifestyle modification displayed greater improvements in eating behaviors, cognitions, and adherence to eating schedules (Craighead, 1984; Craighead & Agras, 1991). Another study found that those treated with the combination of phentermine and fenfluramine displayed greater improvements in hunger and evening fullness compared with those who received lifestyle modification (Weintraub et al., 1992). These findings suggest that pharmacotherapy and behavior therapy indeed target different variables.

Walker, Ballard, and Gold (1977) and Brightwell and Naylor (1979) were among the first groups of investigators to demonstrate the benefits of adding medication (mazinol and phentermine, respectively) to a behavior modification program for the management of obesity. These studies, however, were flawed by limitations in experimental design, sample size, and therapeutic response. Craighead, Stunkard, and O'Brien (1981) are credited with conducting the first large-scale, randomized controlled trial that demonstrated the additive effects of medication and behavior therapy. They found that patients treated with fenfluramine (120 mg/day), in brief monthly office visits, lost an average of 7% of initial weight in 6 months, compared with a loss of 11% among those treated with weekly group behavior therapy. Patients treated with the combination of medication and group behavior therapy lost an average of 16% of initial weight, a significantly greater loss than achieved with either approach alone. Unfortunately, the clinical significance of these findings was limited by the subsequent withdrawal of fenfluramine in 1997.

In 2001, Wadden et al. examined the weight losses associated with the combination of sibutramine and behavior therapy. Fifty-three obese women were randomly assigned to one of three groups, all of which received 1 year of treatment. Subjects in the first condition were prescribed sibutramine (15 mg/day) and received no formal instruction on modifying their eating and physical activity behavior, apart from being instructed to consume 1,200 kcal/day and to exercise regularly. Subjects in the second condition received sibutramine (15 mg/day) and were prescribed the same diet and exercise goals as the first condition. However, those in the second group attended behavior therapy on a weekly basis during the first 4 months of the study and on a monthly basis from months 5 to 12. Subjects in the third condition received the same intervention as the second condition but were also instructed to consume for the first 4 months a portion-controlled diet of 1,000 kcal/day, consisting of liquid meal replacement products (OPTIFAST 800) and frozen-food entrees.

Subjects who were treated with sibutramine alone lost 4.1% of initial weight at the end of 1 year, compared with a loss of 10.8% in subjects who were treated with sibutramine and behavior therapy. Those who received medication in combination with behavior therapy and the portion-controlled diet lost 16.5% of initial weight. Patients who received medication and behavior therapy achieved a significantly greater percentage of their expected weight loss and were more satisfied with changes in their weight, health, body image, and self-esteem than those treated with sibutramine alone. The results of this trial suggested that optimal weight loss and outcome satisfaction are achieved when pharmacotherapy is prescribed in conjunction with major lifestyle changes.

More recently, Wadden, Berkowitz, et al. (2005) found similar results with the combination of sibutramine and behavior therapy. In addition, they demonstrated the efficacy of providing lifestyle modification to obese patients treated with sibutramine in primary-care practice. Two hundred and twenty-four obese adults (BMI = 30 to 45 kg/m^2), ages 18 to 65 years, were randomly assigned to one of four groups, all of which received 1 year of treatment: (a) 15 mg of sibutramine per day, delivered by a primary-care provider (PCP) in eight visits of 10 to 15 minutes each; (b) lifestyle modification, provided by a trained psychologist in 30 group sessions of 90 minutes each; (c) combination of sibutramine (15 mg/day) and lifestyle modification, following the implementation of each therapy combined; and (d) sibutramine (15 mg/day) with brief lifestyle modification counseling delivered by a PCP in eight visits of 10 to 15 minutes each.

The subjects who received sibutramine alone met with their PCPs at weeks 1, 3, 6, 10, 18, 26, 40, and 52. They received a pamphlet that provided tips for healthy eating and physical activity, along with general encouragement from their PCPs, but received no formal weight loss counseling. Patients who received behavior therapy, alone and in combination with sibutramine, attended group meetings on a weekly basis from weeks 1 to 18, meetings conducted every other week from weeks 20 to 40, and a follow-up visit at week 52. Subjects in these groups followed The LEARN Program for Weight Control (Brownell, 1998) for the first 18 weeks of the study, and The Weight Maintenance Survival Guide (Brownell & Rodin, 1990) from weeks 20 through 40. These manuals provide detailed instruction on the behavioral management of obesity in a user-friendly

manner. Patients who received the combination of sibutramine and behavior therapy attended medical visits on the same schedule as those who received sibutramine alone and followed The LEARN Program for Weight Control: Special Medication Edition (Brownell & Wadden, 1999), which is specifically designed for the concurrent use of sibutramine. Finally, subjects who received sibutramine and brief PCP counseling met with their PCP on the same weeks as those who received sibutramine alone but were instructed to follow The LEARN Program for Weight Control: Special Medication Edition (Brownell & Wadden, 1999) and The Weight Maintenance Survival Guide (Brownell & Rodin, 1990) on their own and to review their progress with their PCP at each visit. Subjects in all four conditions were prescribed a diet of 1,200 to 1,500 kcal/day and were encouraged to exercise (i.e., walk) 30 minutes per day on most days of the week.

At 1 year, subjects who received the combination of sibutramine and behavior therapy (combined therapy) lost a mean of 12.1 kg (*SD* = 9.8 kg), compared with a mean loss of 5.0 kg (*SD* = 7.4 kg) among those treated with sibutramine alone, 6.7 kg (*SD* = 7.9 kg) among those treated with behavior therapy alone, and 7.5 kg (*SD* = 8.0 kg) among those treated with sibutramine and brief PCP counseling. Subjects who received combined therapy lost significantly more weight at weeks 18, 40, and 52 than those in the other three conditions. The mean weight loss of subjects who received combined therapy approximately doubled the loss of those who received sibutramine or behavior therapy alone at 1 year. Significantly more subjects in the combined therapy group lost 5% or more (as well as 10% or more) of their initial weight than did those in the other three

groups. Although there were no significant differences in changes in cardiovascular risk factors among the four groups, weight loss at week 52 was correlated with improvements in triglyceride levels, insulin levels, HDL cholesterol levels, insulin resistance, and systolic and diastolic blood pressure.

Based on these results, Wadden, Berkowitz, et al. (2005) concluded that greater weight loss is achieved when sibutramine is used in conjunction with a comprehensive program of diet, exercise, and behavior therapy. The success of this approach was believed to be attributable to the additive effects of sibutramine and behavior therapy. Sibutramine appears to modify the internal environment related to appetite (Bray, 2002), while behavior therapy appears to modify the external environment related to food (Foster et al., 2005; Wadden, Crerand, et al., 2005). Evidence suggests that sibutramine and behavior therapy have these separate effects (Bray, 2002; Foster et al., 2005; Wadden, Crerand, et al., 2005). However, no study has assessed the potentially complementary mechanisms of action of sibutramine and behavior therapy in a trial that examines these therapies separately and combined.

Chapter Three: Hypotheses

Overall Question

The current study was guided by the following question – Is the combination of sibutramine and behavior therapy associated with improvements in appetite control and eating behavior? To answer this question, changes in appetite and eating behavior were compared across three conditions: (a) sibutramine (15 mg/day), (b) behavior therapy (18 group sessions), and (c) combination of sibutramine (15 mg/day) and behavior therapy (18 group sessions).

Hypothesis 1

Ho. There is no difference in eating behavior between subjects treated with behavior therapy, whether alone or in combination with sibutramine, and those treated with sibutramine alone.

H_1. Subjects who receive behavior therapy, whether alone or in combination with sibutramine, will display more appropriate eating behavior than those who receive sibutramine alone.

Rationale. Behavior therapy facilitates the adoption of healthy eating and physical activity behaviors through the application of empirically supported principles and techniques. It teaches patients to control external eating-related cues by such methods as storing foods out of sight, avoiding high-risk situations (e.g., fast-food restaurants), and limiting activities while eating (e.g., watching television). It also provides strategies to control eating in response to social or emotional cues (Foster et al., 2005; Wadden, Crerand, et al., 2005). Therefore, subjects who receive behavior therapy, whether alone or

in combination with sibutramine, are expected to display more appropriate eating behavior (i.e., theoretically facilitative of weight control) than those who receive sibutramine alone.

Hypothesis 2

Ho. There is no difference in appetite control between subjects treated with sibutramine, whether alone or in combination with behavior therapy, and those treated with behavior therapy alone.

H_1. Subjects treated with sibutramine, whether alone or in combination with behavior therapy, will achieve significantly better appetite control than those treated with behavior therapy alone.

Rationale. Sibutramine is a beta-phenylethylamine that inhibits the reuptake of serotonin and norepinephrine (as well as of dopamine to a very limited extent), thereby increasing their extracellular levels. It appears to modify biological variables related to appetite, such as levels of hunger and satiation (Bray, 2002). These actions appear to reduce patients' responsiveness or vulnerabilities to food cues. Therefore, subjects treated with sibutramine, whether alone or in combination with behavior therapy, are expected to display better appetite control (i.e., less food preoccupation, fewer cravings, less hunger, more fullness) than those treated with behavior therapy alone.

Chapter Four: Methods

Design and Design Justification

The study utilized an archival-data design. The data originally were collected as part of a randomized controlled trial (Wadden, Berkowitz, et al., 2005), as described previously, that examined weight loss associated with the provision of sibutramine, behavior therapy, the combination of sibutramine and behavior therapy, and sibutramine plus brief lifestyle counseling by a PCP. Only the results of the subjects who received sibutramine (15 mg/day), behavior therapy (18 group sessions), and the combination of sibutramine (15 mg/day) and behavior therapy (18 group sessions) in the original trial were analyzed in the current study. The results of those who received sibutramine plus brief lifestyle counseling by a PCP in the original trial were excluded from the analysis in order to limit the number of statistical comparisons (thus preserving the alpha level). In addition, the current study examined data from only the first 18 weeks of the original, 12-month trial, since the most reliable data were likely to have been reported by subjects during the initial period of treatment (i.e., months 1 to 5).

Participants

The participants consisted of subjects who participated in three of the four conditions of the original trial, as described under **Design and Design Justification**. The sample included 136 women and 35 men (N = 171), who were randomly assigned to receive sibutramine (n = 56), behavior therapy (n = 55), or the combination of sibutramine and behavior therapy (n = 60). All subjects were between the ages of 18 and 65 years and had a BMI of 30 to 45 kg/m^2 at the start of the original trial.

Inclusion/Exclusion Criteria

The subjects who were eligible to participate in the original trial were free of uncontrolled hypertension (i.e., blood pressure greater than 140/90 mmHg); cerebrovascular, cardiovascular, renal, or hepatic disease; and type 1 or type 2 diabetes. Psychosocial contraindications included bulimia nervosa, substance abuse, clinically significant depression, and current psychiatric treatment. The use of medications known to affect body weight, a weight loss of 5 kg or greater in the preceding 6 months, and the use of selective serotonin-reuptake inhibitors were additional exclusion criteria. Women who were pregnant or breast-feeding at the time of screening also were ineligible for the study.

Screening Procedures to Determine Inclusion/Exclusion Criteria

Subjects of the original trial were screened initially by telephone to determine if they met the inclusion/exclusion criteria. Telephonic screening was conducted by bachelor's-level research assistants following a written protocol. Applicants who met the inclusion/exclusion criteria by telephone were scheduled for an on-site interview with a clinical psychologist at the Weight and Eating Disorders Program (WEDP) at the University of Pennsylvania. During this interview, applicants were informed of the requirements of the study and were asked to provide their informed consent to participate. Those who consented proceeded with the screening process, which included a medical evaluation by the applicants' family physicians and a behavioral evaluation by a clinical psychologist at the WEDP. Candidates who did not meet entry criteria for the study were offered a referral to an appropriate program.

Recruitment

Subjects were recruited for the original trial through the use of public service announcements, notices in local newspapers, and referrals from PCPs in the University of Pennsylvania Health System.

Plan for Informed Consent Procedures

Informed consent from the subjects of the original trial was not required for the current study.

Measures

Eating behavior. The Eating Behavior Inventory (EBI) (O'Neil et al., 1979) was used to assess changes in the practice of weight control behaviors among the three groups. The EBI is a 26-item, self-report scale that is designed to assess behaviors theoretically implicated in weight loss, such as recording food intake, eating slowly, and shopping from a food list (see Appendix A). Items are constructed in the form of first-person statements. Examples include, "I carefully watch the quantity of food that I eat," "I eat at only one place in my home," and "I decide ahead of time what I will eat for meals and snacks." Each item is rated on a 5-point scale according to how often the item is true for the respondent, using the following key: 1 = never or hardly ever, 2 = some of the time, 3 = about half of the time, 4 = much of the time, and 5 = always or almost always. Higher numerical scores reflect more appropriate eating behavior (theoretically facilitative of weight control) than lower numerical scores. The total numerical score provides an index of overall appropriateness of eating behavior.

The EBI generally is a valid, internally consistent, and temporally stable measure of eating behavior (O'Neil et al., 1979; O'Neil & Rieder, 2005). The validity of the scale (individual items and total score) has been demonstrated through several studies, which show correlations between self-reported scores and scores of others who are familiar with the subjects' behaviors; correlations between self-reported scores and self-monitoring data; and sensitivity of self-reported scores to behavioral weight loss treatment (O'Neil et al., 1979; O'Neil & Rieder, 2005). The EBI has a split-half reliability of 0.62 ($p < 0.001$), and all but one item correlate significantly with total score. With the exception of two items, which have exceedingly small variances, test-retest reliability of items ranges from 0.36 to 0.83, with a median of 0.63 (p's < 0.01). Total score test-retest reliability is 0.74 ($p < 0.01$) (O'Neil et al., 1979).

Appetite. Visual analogue scales (Womble, Wadden, Chandler, & Martin, 2003), which have been used to measure appetite since the 1960s (Jordan, Wieland, Zebley, Stellar, & Stunkard, 1966; Silverstone & Stunkard, 1968), were used to assess changes in appetite among the three groups. These scales are composed of 100-millimeter lines with two extreme states anchored at each end (see Appendix B). For example, the question, "How hungry have you felt over the past 24 hours?" is anchored by "Not at all hungry" at one end and "Extremely hungry" at the other end. Subjects are instructed to make a vertical mark across the line corresponding to their level of appetite. Quantification of measurements is done by measuring the distance from the left end of the line to the mark.

Four variables of appetite were assessed in the current study, based on their selection in previous studies of appetite (e.g., Wadden et al., 1997; Womble et al., 2003).

These variables included food preoccupation (amount of time spent thinking about food), cravings (intense desire to consume a particular food), satiation (sensation of fullness), and hunger (drive to eat). Food preoccupation was assessed through the question, "How much were you bothered or distracted by thoughts of food over the past 24 hours?" (Not all all/Extremely bothered); cravings were measured through, "How often did you experience craving to eat particular types of foods over the past 24 hours?" (Not at all/Extremely frequently); satiation was assessed through, "How full did you feel after consuming your meals over the past 24 hours?" (Not at all full/Extremely full); and hunger was measured through, "How hungry have you felt over the past 24 hours?" (Not at all hungry/Extremely hungry).

The validity of these scales has been demonstrated through findings that hunger ratings decrease, while satiation ratings increase, immediately after a laboratory test meal (Blundell & Rogers, 1980); that appetite ratings differ significantly, in anticipated directions, between subjects treated with weight loss medications and placebo (Blundell & Rogers, 1980; Weintraub, Hasday, Mushlin, & Lockwood, 1984); and that appetite ratings correlate significantly with the hunger subscale of the Eating Inventory (Womble et al., 2003), a psychometrically sound measure of hunger (Stunkard & Waterland, 1997). Test-retest reliability of the scales is acceptable (r = 0.61 – 0.85) (Flint, Raben, Blundell, & Astrup, 2000). More recent findings demonstrate excellent test-retest reliability for most scales (r = 0.78 – 0.95) when administered in the short term (i.e., 90 minutes apart) (Womble et al., 2003). These scales have the advantages of being quick, easy to use, and simple to interpret (Stubbs et al., 2000). They also do not require subjects to invoke their

own descriptive terms for the variables being measured and are presented in a standardized format that can be compared under a variety of different experimental manipulations (Stubbs et al., 2000).

Procedure

The procedures of the original trial were described in Chapter Two. The subjects completed the EBI and the visual analogue scales during their clinic visits, which primarily were scheduled in the evening (at the WEDP). The EBI was administered at baseline and week 18, and the visual analogue scales were administered at baseline, week 3, week 6, week 10, and week 18. Scores from these instruments were calculated and inputted into a computer database. Upon receiving permission from the principal investigator of the original trial, Thomas A. Wadden, Ph.D., these data were analyzed in accordance with the goals of the current study.

Analysis of Risk/Benefit Ratio

Potential risk to participants. There was no risk to the subjects of the current study because of its archival-data design.

Potential benefit to participants. There was no benefit to the subjects of the current study because of its archival-data design.

Potential benefit to others. Results of the current study may potentially benefit patients who are obese by improving the management of obesity in primary-care practice. As expected, improvements in both appetite control and eating behavior were found to account for the greater weight loss achieved with the combination of sibutramine and behavior therapy than with either approach alone. Our findings underscore the

importance of using pharmacotherapy in conjunction with a comprehensive program of diet, exercise, and behavior therapy, as recommended by the NHLBI (1998). Our results may encourage PCPs to prescribe weight loss medications in combination with, rather than in lieu of, lifestyle modification, perhaps with the assistance of behavioral health providers integrated within the practice. The outcomes of this study, therefore, may serve to improve the quality of care and subsequent health of obese patients.

Procedure for Maintaining Confidentiality

To ensure patient privacy, the charts of the subjects who participated in the original trial remained in a locked filing cabinet at the Center for Weight and Eating Disorders (formerly the WEDP) at the University of Pennsylvania for the duration of the current study. In addition, code numbers were assigned to each subject to maximize anonymity while analyzing the data.

Chapter Five: Results

Statistical Analyses

The sample used in the present study was a subset of a larger trial that compared weight loss among four different conditions over 1 year (Wadden, Berkowitz, et al., 2005). Analysis of variance revealed no significant differences among the groups in baseline characteristics (see Table 1). The aims of the current study were tested using mixed effects linear model analysis for repeated measures (SAS, Version 9.2 for Windows; SAS Institute, Inc., Cary, NC). For Aim 1, the primary outcome was change in eating behavior among subjects who received sibutramine alone, behavior therapy alone, and combined therapy, as assessed by change in total EBI scores from baseline to week 18. The mixed model for this analysis included time (Baseline, Week 18) and treatment (Sibutramine Alone, Behavior Therapy Alone, Combined Therapy) as the main effects, and a time-by-treatment interaction term. For Aim 2, the primary outcome was change in appetite among the three conditions, as assessed by change in ratings on 100-mm visual analogue scales at four time points. Appetite was measured in terms of food preoccupation, cravings, satiation, and hunger. Partial-correlation analysis that controlled for treatment group indicated that these four appetite variables overlapped yet were conceptually distinct constructs (see Table 2). For each of these variables, change scores were created by subtracting the ratings at baseline from the ratings at week 3, week 6, week 10, and week 18. The mixed model for this analysis included time (Week 3, Week 6, Week, 10, Week 18) and treatment (Sibutramine Alone, Behavior Therapy Alone, Combined Therapy) as the main effects, and a time-by-treatment interaction term.

Table 1

Baseline Characteristics of Subjects in the Three Groups

Variable	Sibutramine alone (n = 56)	Behavior therapy alone (n = 55)	Combined therapy (n = 60)
Sex (number of subjects)			
Female	45	42	49
Male	11	13	11
Race or ethnicity (number of subjects)			
White	32	35	42
Black	22	18	17
Hispanic	2	2	1
Age (years)	42.2 ± 10.2	43.3 ± 9.7	44.2 ± 10.8
Weight (kg)	107.6 ± 14.8	105.1 ± 17.0	108.5 ± 18.6
Height (cm)	167.8 ± 7.7	167.3 ± 8.4	168.8 ± 9.2
BMI (kg/m^2)	38.1 ± 3.9	37.8 ± 4.2	37.9 ± 4.2

Note. Plus-minus values are means ± *SD*. There were no significant differences among the three groups on any of the baseline characteristics at $p \leq 0.05$. Race or ethnicity was self-reported.

Table 2

Correlations of Appetite Ratings Across the Three Groups at Baseline

	Hunger	Food preoccupation	Satiation	Cravings
Hunger	1.0	0.4*	-0.1	0.2*
Food preoccupation	0.4*	1.0	-0.1	0.5*
Satiation	-0.1	-0.1	1.0	-0.2
Cravings	0.2*	0.5*	-0.2	1.0

* Significant correlation at $p \leq 0.01$.

Analysis of variance revealed no significant differences among the means of each appetite variable at baseline. Planned post-hoc pairwise comparisons of the appetite scores were conducted at each time point when significant treatment effects were found. For all analyses, results were considered significant at $p \leq 0.05$. Data are presented as model-based means (± *SE*), unless otherwise indicated.

Eating Behavior

The mean values (± *SE*) on the EBI of the three groups are displayed in Table 3. From baseline to week 18, the means increased from 60.1 ± 1.1 to 63.4 ± 1.2 among those who received sibutramine alone, from 63.0 ± 1.2 to 75.8 ± 1.2 among those who received behavior therapy alone, and from 61.3 ± 1.2 to 73.1 ± 1.1 among those who received combined therapy. There were significant differences in mean change from baseline among subjects who received sibutramine alone compared with those who received behavior therapy alone, $F(1, 157) = 29.52$, $p < 0.0001$, and combined therapy, $F(1, 157) = 23.29$, $p < 0.0001$. No significant difference in mean change was found between the behavior therapy alone and combined therapy conditions, $F(1, 157) = 0.44$, $p = 0.51$. These results clearly indicate an increase in the practice of weight control behaviors among those treated with behavior therapy.

Appetite

Food preoccupation. As shown in Table 4, there was a significant main effect of treatment for the variable of food preoccupation, $F(2, 142) = 3.87$, $p = 0.02$. The mean changes (± *SE*) from baseline, collapsed across time, were -3.6 ± 3.6 among those who received sibutramine alone and -4.8 ± 3.4 among those who received combined therapy.

Table 3

Eating Behavior Inventory Scores at Baseline and Week 18 in the Three Groups

Condition	Baseline	Week 18	Change from baseline
Sibutramine alone (*n* = 56)	60.1 ± 1.1	63.4 ± 1.2	3.3 ± 1.3[a]
Behavior therapy alone (*n* = 55)	63.0 ± 1.2	75.8 ± 1.2	12.9 ± 1.2[b]
Combined therapy (*n* = 60)	61.3 ± 1.1	73.1 ± 1.1	11.8 ± 1.2[b]

Note. Values are model-based means ± *SE*.

[a, b] Values labeled with different letters are significantly different from each other at $p < 0.0001$.

Table 4

Changes in Appetite from Baseline During 18 Weeks of Treatment in the Three Groups

Variable	Sibutramine alone (n = 56)	Behavior therapy alone (n = 55)	Combined therapy (n = 60)
Food preoccupation			
Baseline	42.4 ± 3.1	31.5 ± 3.3	39.3 ± 3.2
Week 3	-4.7 ± 4.3[a]	7.5 ± 4.3[b]	-4.8 ± 4.1[a]
Week 6	-2.8 ± 4.4[ab]	8.2 ± 4.3[b]	-6.1 ± 4.1[a]
Week 10	-6.1 ± 4.2[a]	8.4 ± 4.1[b]	-6.8 ± 3.9[a]
Week 18	-0.9 ± 4.7	6.8 ± 4.6	-1.4 ± 4.3
All weeks from baseline combined	-3.6 ± 3.6[a]	7.8 ± 3.5[b]	-4.8 ± 3.4[a]
Cravings			
Baseline	48.5 ± 3.6	49.0 ± 3.4	52.1 ± 3.0
Week 3	-11.0 ± 4.4[a]	2.3 ± 4.4[b]	-13.9 ± 4.1[a]
Week 6	3.0 ± 4.4[a]	3.0 ± 4.4[a]	-11.7 ± 4.1[b]
Week 10	-4.6 ± 4.8[ab]	2.5 ± 4.7[a]	-13.1 ± 4.4[b]
Week 18	-7.3 ± 4.2	-1.7 ± 4.1	-7.0 ± 3.8
All weeks from baseline combined	-4.9 ± 3.4[ab]	1.5 ± 3.4[a]	-11.4 ± 3.2[b]
Satiation			
Baseline	61.2 ± 2.9	67.2 ± 3.2	62.7 ± 2.9
Week 3	5.9 ± 4.7	-8.8 ± 4.7	2.9 ± 4.4

Variable	Sibutramine alone (n = 56)	Behavior therapy alone (n = 55)	Combined therapy (n = 60)
Week 6	-0.7 ± 3.7	-10.0 ± 3.7	-4.8 ± 3.5
Week 10	0.4 ± 4.3	-10.4 ± 4.3	-1.6 ± 4.1
Week 18	5.8 ± 4.7	-1.7 ± 4.6	-2.7 ± 4.2
All weeks from baseline combined	2.8 ± 3.5	-7.7 ± 3.6	-1.6 ± 3.4
Hunger			
Baseline	50.0 ± 2.8	48.6 ± 2.9	48.7 ± 2.4
Week 3	-12.2 ± 4.2	-3.1 ± 4.1	-6.0 ± 4.0
Week 6	-5.4 ± 4.2	-3.0 ± 4.1	-8.9 ± 3.9
Week 10	-10.0 ± 4.0	-1.6 ± 4.0	-8.3 ± 3.8
Week 18	-2.4 ± 4.6	-3.3 ± 4.5	-5.0 ± 4.2
All weeks from baseline combined	-7.5 ± 3.4	-2.7 ± 3.3	-7.1 ± 3.2

Note. Values at baseline are raw means ± *SE*. Values at weeks 3, 6, 10, and 18 are model-based mean change scores from baseline ± *SE*.

[a, b] Across each row, values labeled with different letters are significantly different from each other at $p \leq 0.05$. Values without letters are not significantly different from the other values.

By contrast, the mean change of those who received behavior therapy alone was 7.8 ± 3.5. These findings indicate, as expected, a decrease in food preoccupation among those who were treated with medication and an increase in food preoccupation among those who were not treated with medication. There were significant differences in mean change among subjects who received behavior therapy alone compared with those who received sibutramine alone, $t(142) = -2.26$, $p = 0.03$, and combined therapy, $t(142) = -2.55$, $p = 0.01$. No significant difference in mean change was found between the sibutramine alone and combined therapy conditions, $t(142) = 0.23$, $p = 0.82$. There was no significant main effect of time, $F(3, 142) = 0.58$, $p = 0.63$, nor a significant time-by-treatment interaction $F(6, 142) = 0.47$, $p = 0.83$.

Post-hoc pairwise comparisons of the data at each time point revealed significant mean change differences from baseline between the behavior therapy alone and sibutramine alone conditions at week 3, $t(142) = -2.0$, $p = 0.05$, and at week 10, $t(142) = -2.48$, $p = 0.01$. The mean change of those treated with behavior therapy alone also differed significantly from the mean change of those treated with combined therapy at week 3, $t(142) = -2.08$, $p = 0.04$, and at week 10, $t(142) = -2.68$, $p = 0.01$. There was a significant difference in mean change between the behavior therapy alone and combined therapy conditions at week 6, $t(142) = -2.41$, $p = 0.02$. No significant mean change differences were found among the groups at week 18.

Cravings. There was a significant main effect of treatment for the variable of cravings, $F(2, 142) = 3.82$, $p = 0.02$ (see Table 4). The mean changes (± *SE*) from baseline, collapsed across time, were -4.9 ± 3.4 among those who received sibutramine

alone and -11.4 ± 3.2 among those who received combined therapy. By comparison, the mean change of those who received behavior therapy alone was 1.53 ± 3.4. Thus, similar to ratings of food preoccupation, subjects who were given sibutramine showed a decrease in cravings, whereas cravings increased among those who were not given medication. Subjects who received combined therapy displayed a significantly different change in means compared with those who received behavior therapy alone, $t(142) = -2.76$, $p = 0.01$. The mean change difference between the sibutramine alone and behavior therapy alone conditions, however, failed to reach significance, $t(142) = -1.34$, $p = 0.18$. These findings suggest that receiving medication without lifestyle counseling resulted in suboptimal control of cravings. No significant difference in mean change was found between the sibutramine alone and combined therapy conditions, $t(142) = 1.38$, $p = 0.17$. There was no significant main effect of time, $F(3, 142) = 1.98$, $p = 0.12$, nor a significant time-by-treatment interaction $F(6, 142) = 1.89$, $p = 0.09$.

Post-hoc comparisons of the data at each time point revealed significant mean change differences from baseline to week 3 among subjects who received behavior therapy alone compared with those who received sibutramine alone, $t(142) = -2.14$, $p = 0.03$, and combined therapy, $t(142) = -2.71$, $p = 0.01$. At week 6, those who received combined therapy displayed significant mean change differences compared with those who received behavior therapy alone, $t(142) = -2.45$, $p = 0.02$, and sibutramine alone, $t(142) = 2.45$, $p = 0.02$. At week 10, there was a significant mean change difference between the combined therapy and behavior therapy alone conditions $t(142) = -2.42$, $p = 0.02$. No significant mean change differences were found among the groups at week 18.

Satiation. In contrast to ratings of food preoccupation and cravings, there was no significant main effect of treatment for the variable of satiation, $F(2, 141) = 2.23$, $p = 0.11$ (see Table 4). There was, however, a significant main effect of time, $F(3, 141) = 3.38$, $p = 0.02$. The mean changes (± *SE*) from baseline, collapsed across the three groups, were -0.03 ± 2.6 at week 3, -5.2 ± 2.1 at week 6, -3.9 ± 2.5 at week 10, and 0.5 ± 2.6 at week 18. The differences in mean change from baseline (with all groups combined) differed significantly from week 3 to week 6, $t(141) = 2.33$, $p = 0.02$, and from week 6 to week 18, $t(141) = -2.47$, $p = 0.01$. These findings indicate that subjects' sensation of fullness generally decreased from week 3 to week 6, before increasing from week 6 to week 18. There was no significant time-by-treatment interaction, $F(6, 141) = 0.97$, $p = 0.45$.

Hunger. With respect to the variable of hunger, results failed to yield a significant main effect of time, $F(3, 142) = 0.77$, $p = 0.51$, or treatment, $F(2, 142) = 0.62$, $p = 0.54$ (see Table 4). Likewise, there was no significant time-by-treatment interaction, $F(6, 142) = 0.80$, $p = 0.57$. The mean changes (± *SE*) from baseline, collapsed across time, were -7.5 ± 3.4 among those who received sibutramine alone, -2.7 ± 3.3 among those who received behavior therapy alone, and -7.1 ± 3.2 among those who received combined therapy.

Chapter Six: Discussion

This archival-data study was designed to explore the potentially complementary mechanisms of action of sibutramine and behavior therapy in the treatment of obese patients. Wadden, Berkowitz, et al. (2005) previously demonstrated that combined therapy produced significantly greater weight loss than either therapy alone. However, the mechanisms of action through which this greater weight loss occurred remained unknown. Wadden and his team believed that the superiority of combined therapy was attributable to the additive effects of each approach. As described previously, sibutramine appears to modify biological variables related to appetite (Bray, 2002), while behavior therapy appears to modify the external environment related to food (Foster et al., 2005; Wadden, Crerand, et al., 2005). When combined, these therapies are believed to address a greater number of variables than when used alone, which consequently enhances weight loss (Wadden, Butryn, et al., 2007). However, no study had assessed the potentially complementary mechanisms of action of sibutramine and behavior therapy in a trial that examined these therapies separately and combined.

We hypothesized that subjects who received behavior therapy, whether alone or in combination with sibutramine, would display more appropriate eating behaviors than those who received sibutramine alone. We also expected that those treated with sibutramine, whether alone or in combination with behavior therapy, would display better appetite control than those treated with behavior therapy alone. We aimed to better understand the mechanisms of action responsible for the greater weight loss achieved with combined therapy and, more broadly, to improve the quality of care provided to

obese patients in primary care. Although we failed to find significant differences across all measures of appetite, the majority of our findings were in the expected direction. Our results support the contention that sibutramine and behavior therapy work additively to produce greater weight loss than either approach alone. Therefore, our study expands upon the original trial by providing an empirically based account for the differences in weight loss among the groups.

With respect to eating behavior, patients who received behavior therapy alone or in combination with sibutramine displayed a significant increase in their practice of weight control behaviors compared with those who received medication alone (see Table 3). Behavior therapy, as expected, appeared to effectively teach patients how to manage their external environment related to food. The effect of treatment was quite robust, as the scores of those treated with behavior therapy were three to four times greater than the scores of those treated with drug alone. As shown in Figure 1, Wadden, Berkowitz, et al. (2005) found that subjects who received behavior therapy, both alone and in combination with sibutramine, achieved significantly greater weight loss at week 18 than those who received medication alone. Our results expand on these findings by suggesting that the differences in weight loss between the groups were attributable, in part, to a greater increase in the practice of weight control behaviors among those treated with behavior therapy.

We cannot identify the behaviors that were most affected by the behavioral intervention, as our primary aim was to examine changes in total score on the EBI.

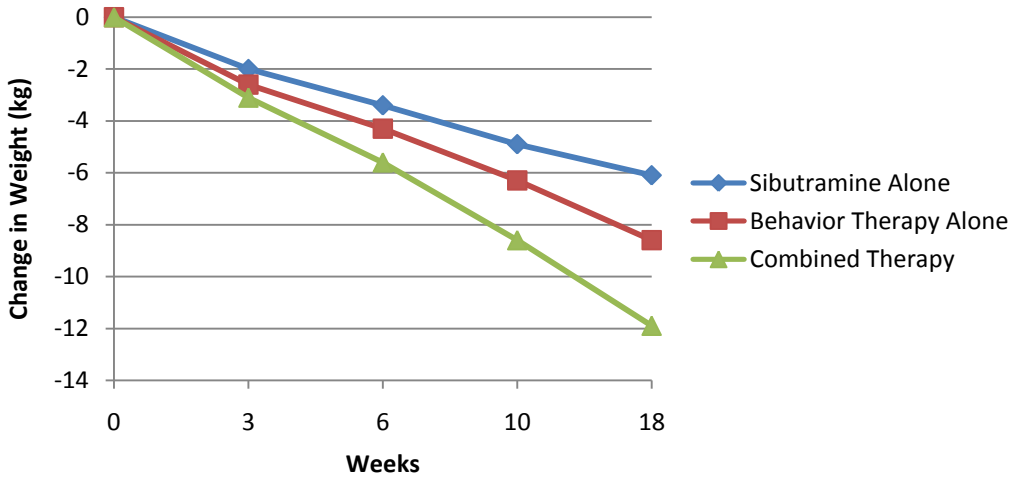

Figure 1. Mean changes in weight (kg) from baseline during 18 weeks of treatment in the three groups, as determined by a last-observation-carried-forward analysis.

However, a secondary analysis performed by the original authors (Wadden, Berkowitz, et al., 2005) showed that those who received behavior therapy alone or in combination with sibutramine completed significantly more food records than those who received medication alone and that keeping these records was positively correlated with weight loss. These findings indicate that those treated with behavior therapy increased their level of self-monitoring, which is a key component of treatment (Wadden, Crerand, et al., 2005). That keeping food records was correlated with weight loss underscores the importance of modifying eating behaviors while attempting to lose weight, rather than relying solely on the effects of a medication (Wadden et al., 1997; Wadden, Berkowitz, et al., 2005).

With respect to appetite, subjects who received sibutramine alone or in combination with behavior therapy reported significantly less preoccupation with food

than those who received behavior therapy alone. Whereas ratings of food preoccupation decreased among patients treated with sibutramine, scores conversely increased among those treated with behavior therapy alone (see Figure 2). Thus, patients who did not receive sibutramine appeared to experience more bothersome thoughts about food, and thus poorer appetite control, than those who were treated with the medication. There was no significant difference in food preoccupation among those treated with sibutramine alone or in combination with behavior therapy, suggesting that the medication decreased food preoccupation equally among these subjects.

As shown in Figure 3, patients who received combined therapy also appeared to experience significantly fewer cravings for food than those who received behavior therapy alone. By contrast, the cravings among those in the latter group increased slightly during treatment. Surprisingly, there was no significant difference in scores between the sibutramine and behavior therapy alone conditions, which was contrary to what we predicted. After differing in the expected directions at week 3, both groups rated their cravings equally at week 6, after which their scores split again in the expected directions. However, the difference in scores between these groups was not significant beyond week 3. These results suggest that while sibutramine may reduce cravings to an extent, patients also must modify their behaviors (e.g., limit exposure to high-risk foods) if they wish to achieve optimal control.

It is unclear why the reported cravings of those treated with sibutramine alone spiked from week 3 to week 6, as seen in Figure 3. One might argue that these subjects developed tolerance to the drug during these weeks. The prescribed dose of sibutramine

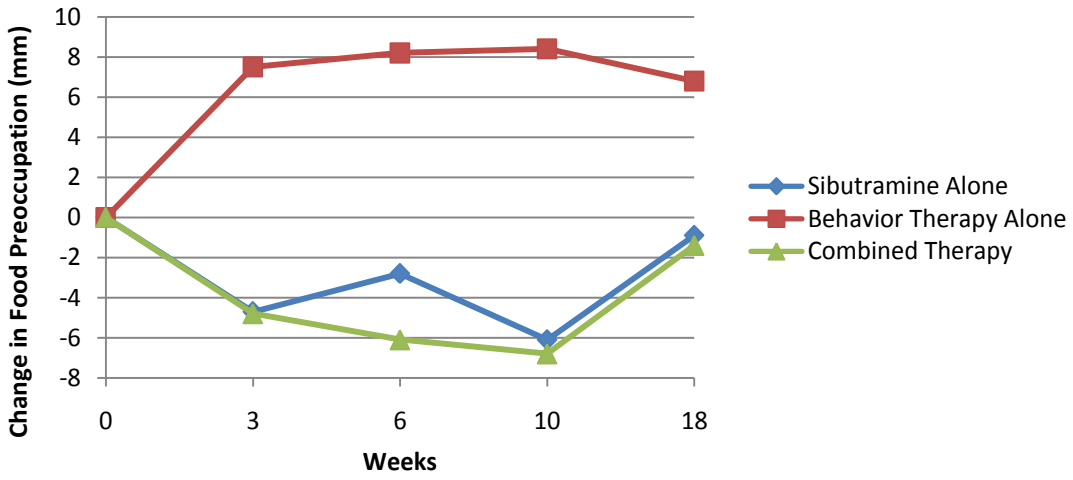

Figure 2. Mean changes (mm) in food preoccupation from baseline during 18 weeks of treatment in the three groups.

increased from 5 to 10 mg at week 3, and from 10 to 15 mg at week 6. Subjects may have developed tolerance to the lower doses of the medication, and thus experienced fewer effects from week 3 to week 6, before being prescribed the higher dose at week 6. Research in rats has suggested that tolerance can develop to sibutramine (Wellman, Jones, & Miller, 2003). If subjects treated with medication alone had developed tolerance to the drug, then we would have expected a similar response pattern from those treated with combined therapy (since these subjects were administered the same doses as those treated with medication alone). However, the response patterns of these groups were inconsistent, suggesting that their scores likely were not affected by the development of tolerance.

Ratings of satiation did not differ significantly among the groups, which was surprising in light of evidence that sibutramine precipitates the satiation process (e.g.,

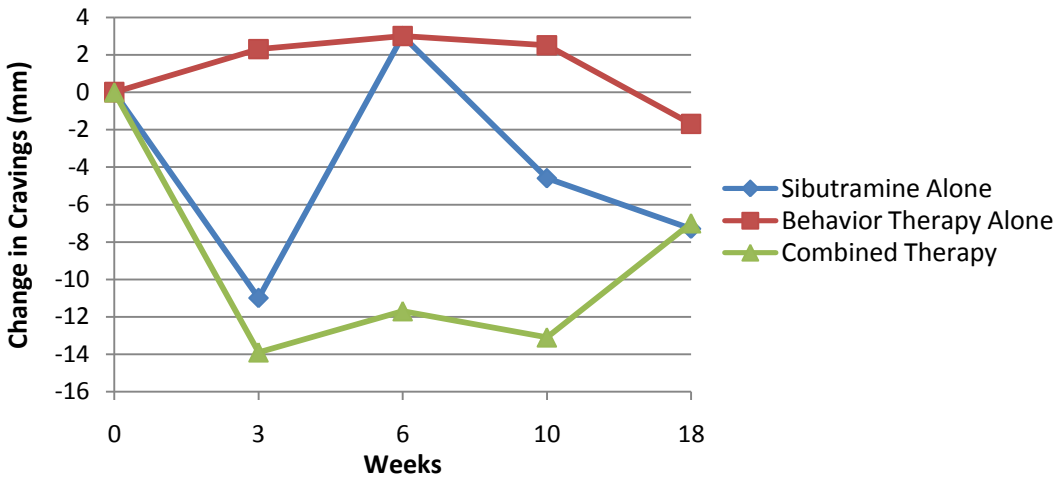

Figure 3. Mean changes (mm) in cravings from baseline during 18 weeks of treatment in the three groups.

meal size is reduced following administration of the drug) (Chapelot et al., 2000). There was, however, a significant difference in scores collapsed across the groups at week 3 compared with week 6, and at week 6 compared with week 18. As shown in Figure 4, satiation ratings decreased significantly (thus, appetite control worsened) from week 3 to week 6, and then increased significantly (thus, appetite control improved) from week 6 to week 18. This response pattern suggests that during 18 weeks of treatment, regardless of modality, patients may feel less satiated during the first few weeks of the intervention, before experiencing an increase in fullness thereafter.

Interestingly, satiation scores among subjects treated with combined therapy and behavior therapy alone remained slightly below their baseline levels at week 18, despite their improvements from week 6 (see Figure 4). By contrast, the ratings among those treated with sibutramine alone remained above baseline for the majority of treatment.

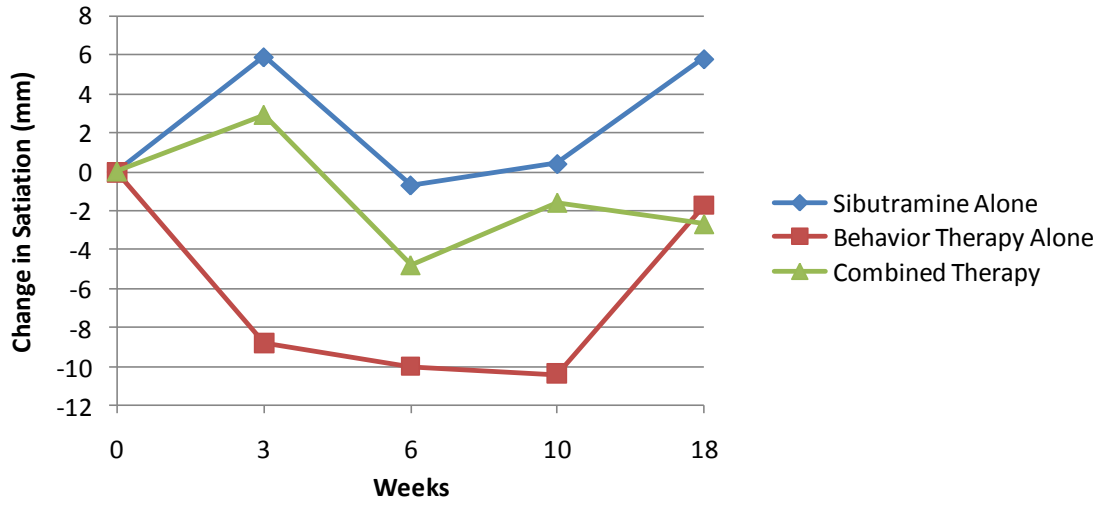

Figure 4. Mean changes (mm) in satiation from baseline during 18 weeks of treatment in the three groups.

Caution must be used when interpreting these results because of the absence of significant differences in satiation scores among the groups. However, these data suggest that those treated with medication alone experienced a greater sensation of fullness, and thus better appetite control, than those treated with either combined therapy or behavior therapy alone. The discrepancy in scores between the sibutramine alone and combined therapy groups is puzzling, as we would expect satiation ratings to increase in both conditions as a result of the medication. Patients who received combined therapy lost significantly more weight than those who received sibutramine alone in the original trial (see Figure 1). It is possible that greater compensatory metabolic and hormonal changes (Brownell, 2010), resulting from the greater weight loss achieved with combined therapy, attenuated the effects of the medication and, thus, led to a lesser sensation of fullness among these subjects. By comparison, these biological forces may have exerted less

influence on the satiation levels of those treated with medication alone because of their smaller weight losses.

Although hunger ratings among the three groups were in the expected directions, the differences in scores were not statistically significant (see Figure 5). This outcome is surprising since we expected a greater suppression of hunger among those treated with sibutramine than with behavior therapy. Perhaps the effects of the medication on hunger levels were not sufficiently robust for subjects to notice. Two controlled laboratory studies have suggested that the subjective effects of sibutramine may be subtle. Chapelot et al. (2000) found that acute sibutramine (15 mg) treatment decreased total daily energy intake by approximately 14% in a group of lean men. Rolls, Shide, Thorwart, and Ulbrecht (1998) found that maintenance on 10 and 30 mg of sibutramine decreased total daily energy intake by up to 23% in a group of obese women. In both studies, sibutramine produced only minimal effects on subjective ratings of hunger, despite the observed reductions in energy intake.

Another potential explanation for the lack of group differences in hunger scores relates to the pharmacokinetics of sibutramine. Peak plasma concentrations of the active sibutramine metabolites (i.e., active metabolites 1 and 2) are reached 3 to 4 hours after a single dose of sibutramine (15 mg) (Garratt, Hind, & Haddock, 1995). Findings show that hunger ratings begin to decrease 240 minutes (or 4 hours) after administration of the drug and that the medication exerts its most potent action on energy intake at lunchtime (following morning administration) (Chapelot et al., 2000). Patients treated with sibutramine in the current study were required to take the medication in the morning

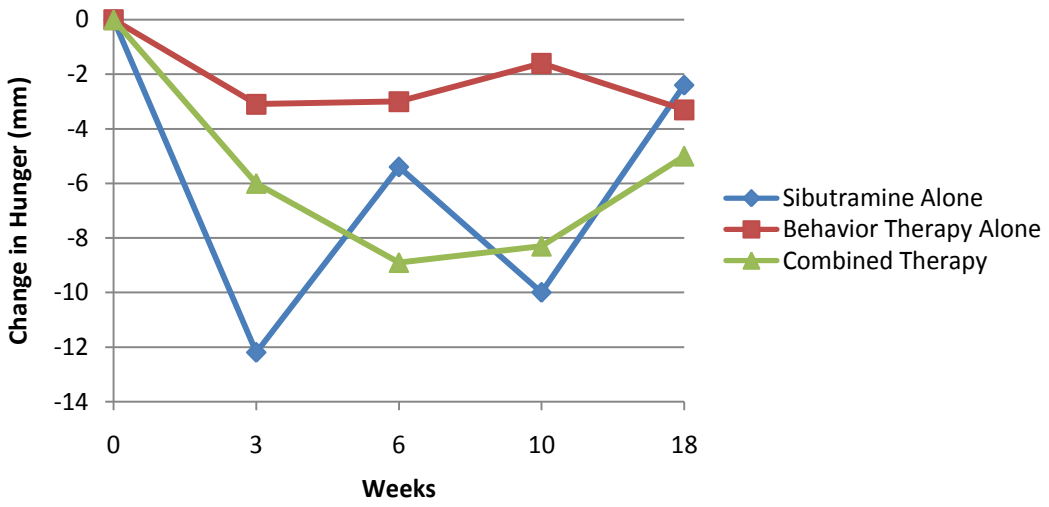

Figure 5. Mean changes (mm) in hunger from baseline during 18 weeks of treatment in the three groups.

and to complete the visual analogue scales, like all subjects, on-site in the evening. It is possible that their hunger scores corresponded with the lower plasma concentrations of the medication at the time they completed the scales and, therefore, captured subjects while their hunger was being less suppressed by the drug. Had these subjects completed the scales at lunchtime, concomitant with the estimated plasma peak of active metabolites 1 and 2, we may have found a significant difference in hunger scores compared with those of subjects who did not receive the drug.

The lack of group differences in hunger scores also may be attributable to the effects of exercise. Although the impact of exercise on appetite remains unclear (Martins, Morgan, & Truby, 2008), research has shown a reduction in hunger and a decrease in energy intake after moderate exercise in both obese and nonobese men (Westerterp-Plantenga, Verwegen, Ijedema, Wijckmans, & Saris, 1997). Vigorous exercise (high-

intensity cycling or running) also has been shown to reduce hunger significantly (King, Burley, & Blundell, 1994). Patients who received behavior therapy in the current study were prescribed specific exercise goals (e.g., walk for 30 minutes per day, most days of the week), which were closely monitored and reviewed during group sessions. As shown in Figure 5, patients treated with behavior therapy alone reported feeling less hungry throughout treatment, which may be attributable in part to their having increased their physical activity as prescribed. Their reductions in hunger may have reduced our power of detecting significant differences in hunger scores among the groups.

Finally, subjects may have become tolerant to the suppressive effects of sibutramine on hunger during the course of the trial, which also would have reduced our power of detecting group differences in hunger scores. As shown in Figure 5, subjects who received sibutramine alone reported an increase in hunger from week 3 to week 6, after which their hunger subsided in accordance with being prescribed 15 mg of the drug (at week 6). However, hunger ratings increased again from week 10 to week 18. One might argue that these subjects became tolerant to each dose of the medication over time, which potentially could explain their progression of scores and their failure to achieve better hunger control than those treated with behavior therapy alone. However, because those who received combined therapy failed to display a similar response pattern to that of those who received medication alone, it appears unlikely that the subjects' ratings were affected by the development of tolerance.

In total, although we failed to find significant differences across all measures of appetite, most of our findings were in the expected direction and corresponded with our

original hypotheses. Patients who received sibutramine alone reported more fullness and less food preoccupation, fewer cravings, and reduced hunger. They did not display a significant increase in weight control behaviors. By contrast, those who received behavior therapy alone reported less fullness and more food preoccupation and cravings. However, these patients did show a significant increase in weight control behaviors. Patients treated with combined therapy reported improvements in both appetite control and eating behavior. They reported reductions in food preoccupation, cravings, and hunger, along with a significant increase in weight control behaviors. Thus, the greater weight loss achieved with combined therapy in the original trial may be attributed to the complementary mechanisms of action of each approach, as suggested by Wadden, Berkowitz, et al. (2005). Sibutramine appeared to modify subjects' internal environment related to appetite, while behavior therapy appeared to modify their external environment related to food. Used together, these therapies appeared to address a greater number of variables than when used separately, which consequently led to greater weight loss. Our results are significant in that they provide evidence for the additive effects of sibutramine and behavior therapy.

After the current study was completed, the FDA requested that Abbott Laboratories – the manufacturer of sibutramine (branded as Meridia in the United States) – voluntarily withdraw the drug from the market, based on data from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) (James et al., 2010). The SCOUT study was a randomized, placebo-controlled, multicenter trial, conducted between January 2003 and March 2009, which sought to demonstrate the long-term health benefits of weight

management with sibutramine plus lifestyle modification. The sample consisted of approximately 10,000 subjects, aged 55 years or above, with a BMI between 27 and 45 kg/m^2, or between 25 and 27 kg/m^2 with an increased waist circumference. Subjects were required to have a history of cardiovascular disease (i.e., coronary artery disease, stroke, or occlusive peripheral arterial disease) and/or type 2 diabetes with at least one other cardiovascular risk factor (i.e., hypertension, dyslipidemia, current smoking, or diabetic nephropathy). Results showed a 16% increase in risk of major adverse cardiovascular events (which were a composite of nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, and cardiovascular death) in patients treated with Meridia compared with those treated with placebo. At the end of the trial (60 months), the difference in mean percent change in body weight between the Meridia and placebo groups was only 2.5%. Based on these results, the FDA concluded that the risk of an adverse cardiovascular event from Meridia outweighed any benefit from the modest weight loss observed with the drug. Abbott Laboratories agreed to remove Meridia from the market in October 2010.

The results of the current study still have significant implications on clinical practice, in spite of the recent withdrawal of sibutramine. A number of medications remain on the market for the short-term treatment of obesity, such as phentermine, diethylpropion, and phendimetrazine. These agents generally affect the availability of serotonin, norepinephrine, and/or dopamine in the central nervous system, which in turn suppresses appetite (Huizinga, 2007). Orlistat, a gastric and pancreatic lipase inhibitor that reduces the absorption of dietary fat, also remains approved for the long-term

management of obesity. Current guidelines recommend that weight loss medications be used as an adjunct to a comprehensive program of diet, exercise, and behavior therapy (NHLBI, 1998). The results of the original trial confirm that significant weight loss occurs with this approach (Wadden, Berkowitz, et al., 2005), and we have shown this outcome to be attributable to the complementary mechanisms of action of pharmacotherapy and behavior therapy. Unfortunately, weight loss medications often are prescribed by physicians in the absence of lifestyle counseling (Blanck, Kahn, & Serdula, 2004; Phelan & Wadden, 2002).

In fact, surveys indicate that fewer than one half of obese patients are counseled by their physicians about losing weight and that these rates are actually declining (Jackson, Doescher, Saver, & Hart, 2005; McAlpine & Wilson, 2007). Data from the 1995 to 2004 National Ambulatory Medical Care Survey (NAMCS) – an annual national survey of visits to office-based physicians – show that obesity-related counseling occurred in only 25.3% of office visits in 1995-1996 and dropped to 24% in 2003-2004 (McAlpine & Wilson, 2007). Findings from the Behavioral Risk Factor Surveillance System (BRFSS) – an annual telephone survey conducted by all states, the District of Columbia, and Puerto Rico – indicate that 44% of patients received weight loss advice from their physicians in 1994, compared with only 40% in 2000 (Jackson et al., 2005).

Numerous barriers appear to exist in the provision of lifestyle counseling by physicians. In a national survey of physicians' attitudes towards obesity and its treatment, Foster et al. (2003) found that more than one half of the 620 respondents reported that they would spend more time providing weight management services if their time were

reimbursed appropriately. Lack of reimbursement, therefore, appears to be a key obstacle to providing obesity-related counseling. Physicians also rated lack of physical activity as being significantly more important than any other cause of obesity, followed by overeating and the consumption of a high-fat diet. Nearly one half of respondents rated psychological problems as very or extremely important causes of obesity. These data suggest that physicians may view obesity primarily as a behavioral as opposed to a biological or genetic problem. Given that their training traditionally has emphasized the biological management of disease, physicians may feel ill-equipped to manage obesity effectively. Indeed, only 14% of respondents believed that they were usually successful in helping patients lose weight.

Foster et al. (2003) also found that physicians tend to view obesity treatment as ineffective. Less than 50% of respondents felt that it was possible for obese patients to lose a significant amount of weight, and only 22% believed that maintaining weight loss was possible in the long term. Moreover, physicians rated the treatment of 9 out of 10 chronic conditions (including but not limited to hypertension, diabetes, and coronary artery disease) as significantly more effective than the treatment of obesity. Leverence et al. (2007) recently substantiated these findings, indicating that the perceived ineffectiveness of treatment contributes to physicians' reluctance to provide weight loss counseling.

Furthermore, Foster et al. (2003) found that physicians, much like the general population (Grilo, 2006), tend to hold critical views of obese patients. More than one half of respondents viewed these patients as awkward, unattractive, ugly, and noncompliant,

and approximately one third characterized them as weak willed, sloppy, or lazy. Prior studies have shown that the heavier the patient, the more negative the attitudes and distancing behaviors are of physicians (Harvey & Hill, 2001; Hebl & Xu, 2001). Therefore, in addition to the lack of reimbursement, the perception of obesity as a behavioral or psychological problem, and the belief that obesity treatment is ineffective, it is possible that physicians are reluctant to provide lifestyle counseling to obese patients as a result of their negative attitudes toward these individuals. Such attitudes were discovered decades ago (Maddox & Liederman, 1969) and, unfortunately, appear to persist today.

The challenges that physicians face when treating obese patients potentially can be overcome through the integration of behavioral health providers (BHPs) within primary-care settings (Hunter, Goodie, Oordt, & Dobmeyer, 2009; Tsai, Carvajal, Egner, & Wadden, 2010). Many common medical conditions, such as obesity, involve maladaptive behaviors that initiate, exacerbate, or maintain symptoms. Modifiable behavioral factors (e.g., poor diet, lack of physical activity) are found to be the leading causes of chronic health problems and mortality in the United States (APA, 2009). Currently, physicians, physician assistants, and nurse practitioners provide the majority of behavioral health services in primary care (Hunter et al., 2009). The aforementioned obstacles to the delivery of these services, however, may compromise the standard of care provided to patients. In addition, these providers, while qualified to deliver physical medicine, often lack the appropriate training in lifestyle counseling (Hunter et al., 2009). Evidence shows that while low- to moderate-intensity physician counseling for obesity

(i.e., fewer than two visits per month), without pharmacotherapy, fails to yield clinically significant weight loss, more intensive counseling provided by nonphysician personnel may help patients achieve this goal (Tsai & Wadden, 2009). BHPs who specialize in lifestyle modification, therefore, can be used to provide these services in place of medical personnel. The integration of BHPs within primary care would reduce the burden on physicians to provide all acute, chronic, and preventive services for their patients (Frank, 1998; Yarnall, Pollak, Ostbye, Krause, & Michener, 2003) and would enable physicians to focus primarily on the biological management of obesity while allocating the behavioral management to BHPs located within the practice.

From a broader perspective, the APA recently has advocated for the integration of psychologists and other mental health providers within primary care and other health care settings, including specialized medical centers, long-term care settings, and community-based health and social service organizations (APA, 2008, 2009; Clay, 2010). Integrated health care (also known as interdisciplinary health care) is an approach to clinical practice that is characterized by a high degree of collaboration and communication among a diverse team of health care professionals (APA, 2008). Members of the team may include physicians, psychologists, social workers, occupational and physical therapists, and other specialists, depending on the needs of the patient. Information related to patient care is shared among members in an effort to develop a comprehensive treatment plan that addresses the complete biological, psychological, environmental, and sociocultural needs of the patient, thereby improving the standard of care of patients. Findings show that integrated health care enhances access to services, improves quality

of care, and lowers overall health care expenditures, and the APA considers its delivery a top priority for national health care reform (APA, 2008, 2009; Clay, 2010).

In accordance, Hunter et al. (2009) recently developed a five-step, patient-centered model of obesity counseling for BHPs who are integrated within primary-care settings. The five steps, known as the 5A's, are Assess, Advise, Agree, Assist, and Arrange. The 5A's format has been strongly recommended for assessing and treating a variety of behavioral health concerns in primary care, including obesity (Goldstein, Whitlock, & DePue, 2004; Simkin-Silverman & Wing, 1997). The specific interventions at each stage are based on treatment guidelines issued by the NHLBI (1998) and are designed to help patients develop a self-manageable weight loss plan, with the assistance of the primary-care team. We conclude this discussion by presenting an overview of the model in order to provide BHPs with an empirically based option for treating obesity in primary care. More information about the model can be found in Hunter et al. (2009).

In the first stage – Assess – the BHP measures patients' BMI and collects information about their weight history, including patterns of weight loss and weight gain. Information from their weight history is used to establish their learning history related to weight, which the BHP can later use to develop personalized recommendations for weight loss. This stage also includes an assessment of patients' thoughts associated with weight loss, which can help the BHP to determine patients' self-efficacy with respect to losing weight. Patients' thoughts about losing weight also can provide a measure of their motivation and readiness to change, areas that can have significant implications on treatment (Hawkins, Hornsby, & Schorling, 2001; Simkin-Silverman & Wing, 1997;

Smith, Heckemeyer, Kratt, & Mason, 1997). Finally, the BHP assesses patients' eating behaviors, such as their food and beverage choices, speed and frequency of eating, and times and places associated with eating. Patients who display symptoms of an eating disorder, such as binge-eating and/or purging, may be referred to specialty care.

During the Advise stage, the BHP informs patients about the medical benefits of losing weight and highlights the benefits associated with a modest weight loss (i.e., 5 to 10% of initial weight). Patients also are educated on the importance of losing weight slowly (e.g., 1 to 2 pounds per week) as a means of producing a safe, sustainable weight loss. Those who are prescribed weight loss medications or who are attending commercial weight loss programs are encouraged to continue these treatments if they find them helpful. However, they are informed that regular follow-up appointments with the BHP may help to maximize their success.

Hunter et al. (2009) conceptualize the Agree stage as a bridge between the Assess and the Assist stages, wherein the BHP determines if patients are interested in losing weight and in developing a weight loss plan. While many patients have a strong desire to lose weight, they tend to be ambivalent about modifying their lifestyle as a result of their past difficulties or relapse experiences (Simkin-Silverman & Wing, 1997). Therefore, the BHP uses motivational interviewing techniques, such as open-ended questions, reflective listening, and affirmation, in order to increase patients' motivation for change. The BHP explores patients' ambivalence in a nonconfrontational manner, encourages them to express their arguments for change, and helps them resolve their ambivalence through the development of self-motivational statements (Miller & Rollnick, 2002). Such techniques

have been shown to improve adherence to weight loss programs (Simkin-Silverman & Wing, 1997; Smith et al., 1997).

Formal intervention occurs during the Assist stage, wherein the BHP helps patients reduce their energy intake and increase their physical activity in order to lose weight. Principal interventions include goal setting, calorie education, and behavior-change planning. Consistent with recommendations of the NHLBI (1998), patients are encouraged to lose 1 to 2 pounds per week, with the goal of losing and maintaining 10% of their initial body weight. They are encouraged to reduce their intake of calorie-dense foods and increase their intake of fruits, vegetables, and whole grains. Patients also are instructed to monitor their food intake through the completion of food records. Finally, they are encouraged to make healthful changes to their eating and physical activity, such as reducing portion sizes, eating on a schedule, storing high-calorie foods out of sight, and gradually increasing the amount of walking.

In the final stage – Arrange – the BHP develops a follow-up plan with patients, including when and how often future sessions will take place. These sessions are used to assess progress, address any lapses in weight, and reinforce healthful behaviors and/or introduce new skills related to weight control. Typically, the BHP meets with patients on a weekly basis in order to monitor progress and resolve any barriers to adherence. Sessions are then tapered down (e.g., from weekly to monthly) when patients display adequate control of their weight. The BHP aims to help patients follow a plan that they can self-manage in the long term, with the assistance of the primary-care team. Patients

who fail to lose weight with primary-care intervention may be referred to specialty care, such as a comprehensive behavioral weight loss program.

The current study has allowed us to identify the mechanisms of action responsible for the greater weight loss associated with combined therapy than with either therapy alone. However, our study is not without limitations. First, appetite ratings were made in retrospect (e.g., "How hungry have you felt over the past 24 hours?") and, as such, may have been subject to retrospective distortion. These ratings also provided a measure of subjective appetite, which can be influenced by a variety of factors. Appetite, for example, tends to vary in response to variations in patients' work or social activities (Womble et al., 2003). External factors, such as prior meals, physical activity, temperature, and weather, also may affect appetite (Flint et al., 2000). These events may afford or eliminate opportunities to eat, including what and how much food is eaten. Therefore, while some patients may view appetite as a trait characteristic, appetite is very much state dependent and changes in response to social and environmental cues (Womble et al., 2003). The design of our study did not allow us to control for these factors. Our study also included a relatively high ratio of female to male subjects. Studies with nonhuman primates (Foltin, 2006) and with rats (LeBlanc & Thibault, 2003) found that females were more responsive to the anorectic effects of sibutramine. Owing to the gender composition of our sample, our findings may not generalize adequately to the male population. More broadly, the original trial was conducted at an academic medical center and may well have included patients who were not representative of the general population. This is a common limitation among studies on obesity treatment (Wadden &

Butryn, 2003). Study volunteers often are more motivated to lose weight, as evidenced by their willingness to participate in clinical research trials. Our ability to generalize our results to the population at large thus may be compromised by this sample restriction.

Future investigations should examine the short- and long-term efficacy of combining behavior therapy with medications that are approved at present for the management of obesity. A number of new agents are currently under development, including combination drugs such as phentermine-topiramate and naltrexone-bupropion (Tsai et al., 2010). If approved, the efficacy of these drugs ought to be examined in combination with behavior therapy as well. Studies should also explore, in humans, the potential role of sex in moderating the effects of anorectic medications. The results of these studies would allow investigators to better match patients to particular drugs, whether used singularly or combined with behavior therapy, as to produce the best outcomes (Phelan & Wadden, 2002). Research also should focus on developing behavioral techniques that better address the elevations in food preoccupation and cravings that appear to accompany behavior therapy, as was shown in the current study. Findings have suggested that poor control of food preoccupation (Timmerman & Gregg, 2003) and cravings (Ferguson, Brink, Wood, & Koop, 1992) can impair weight control. Thus, patients likely would benefit from learning more effective ways to manage these events. Finally, future investigations on the additive effects of pharmacotherapy and behavior therapy should assess changes in appetite under a set of standardized conditions, similar to that utilized in prior studies of appetite (Chapelot et al., 2000; Flint et al., 2000; Rolls et al., 1998). For example, patients might be asked to rate their appetite before

consuming a fixed-calorie test meal and then every 30 minutes during a scheduled postprandial period under the same conditions, while their energy intake is covertly measured by investigators (e.g., via weighing food items before and after consumption). Such a design would allow for a more controlled comparison of appetite between different treatment conditions.

Obesity has reached epidemic proportions in the United States. Interventions that make the management of weight easier and more sustainable clearly are needed in order to improve the health of millions. Recently, the combination of sibutramine and behavior therapy has been found to produce greater weight loss than either therapy alone. We have expanded on this finding by providing evidence that sibutramine and behavior therapy, through their complementary mechanisms of action, work additively to produce this loss. Our findings underscore the importance of prescribing weight loss medications in conjunction with lifestyle modification. Unfortunately, physicians face many obstacles in providing lifestyle counseling to obese patients. The integration of BHPs within primary-care settings would reduce this burden on physicians and afford patients access to obesity counseling within the practice. Such an integrated approach to obesity management likely would improve the quality of care and subsequent health of obese patients.

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Appendix A

Appendix B