Clinical Management of Obesity

Apovian, Aronne & Powell

Clinical Management of Obesity

Caroline M. Apovian, MD
Louis Aronne, MD
Amanda G. Powell, MD

First Edition

Clinical Management of Obesity

First Edition

Caroline M. Apovian, MD
Professor of Medicine and Pediatrics,
Boston University School of Medicine
Director, Center for Nutrition and
Weight Management,
Section of Endocrinology, Diabetes, and Nutrition
Boston Medical Center

Louis Aronne, MD
Sanford I. Weill Professor of Metabolic Research,
Weill Cornell Medical College
Director of the Comprehensive
Weight Control Center,
New York Presbyterian/Weill Cornell Medical Center

Amanda G. Powell, MD
Assistant Professor of Medicine
Tufts University School of Medicine
Director of Medical Weight Loss
Lahey Hospital & Medical Center

PROFESSIONAL
COMMUNICATIONS, INC.

Caroline M. Apovian, MD
Louis Aronne, MD
Amanda G. Powell, MD

Professional Communications, Inc.
A Medical Publishing & Communications Company

400 Center Bay Drive
West Islip, NY 11795
(t) 631/661-2852
(f) 631/661-2167

1223 W. Main St, #1427
Durant, OK 74702-1427
(t) 580/745-9838
(f) 580/745-9837

For orders only, please call
1-800-337-9838
or visit our Web site at
www.pcibooks.com

ISBN: 978-1-932610-93-2
Printed in the United States of America

DISCLAIMER

The opinions expressed in this publication reflect those of the authors. However, the authors make no warranty regarding the contents of the publication. The protocols described herein are general and may not apply to a specific patient. Any product mentioned in this publication should be taken in accordance with the prescribing information provided by the manufacturer.

This text is printed on recycled paper.

DEDICATION

To the millions of patients suffering with their weight. We hope that this book helps providers find effective tools to manage the obesity epidemic.

ACKNOWLEDGMENT

We would like to thank Malcolm Beasley for assuring us that we could achieve the unachievable by writing an entire handbook on obesity in 9 months. We would like to thank Victor Runowicz for his assistance in the preparation of the manuscript.

TABLE OF CONTENTS

Prevalence of Obesity and Related Mortality	1
The Pathophysiology of Obesity	2
Obesity-Related Comorbidities	3
A Complications-Centric Approach to the Treatment of Obesity	4
Benefits of Weight Loss	5
Approach to the Obese Patient	6
Drug-Induced Weight Gain	7
Dietary Interventions, Physical Activity, and Behavioral Approaches to the Treatment of Obesity	8
Pharmacologic Treatment	9
Bariatric Surgery	10
Abbreviations/Acronyms	11
Index	12

TABLES

Table 1.1 Cause-Specific Mortality vs BMI in the Ranges of 15-25 kg/m^2 and 25-50 kg/m^2 18

Table 3.1 Associations Between Biomarker Levels and Obesity Class: NHANES 1999-2004 49

Table 3.2 CRP and Fibrinogen Levels According to Diabetes and Hypertension Status.....51

Table 3.3 Prevalence and Adjusted Odds Ratios of Comorbidities According to Body Weight 55

Table 3.4 Impact of BMI Category on Increasing Number of Concurrent Comorbidities 57

Table 4.1 Edmonton Obesity Staging System (EOSS) 81

Table 4.2 Risk Factors of Metabolic Syndrome.....85

Table 4.3 Cardiometabolic Disease Staging System (CMDS).....88

Table 4.4 BMI-Centric Guide to Choosing Treatments for Obesity.....92

Table 5.1 Incidence (Cases per 100 Person-Years) of Diabetes During DPP, Bridge Period, and DPPOS 99

Table 5.2 Risk Factors of Metabolic Syndrome.....104

Table 5.3 Look AHEAD Study: Mean Changes in Weight, Fitness, and CVD Risk Factors in ILI and DSE Groups and the Difference Between Groups Averaged Across 4 Years 107

Table 6.1 Classes of Medications Promoting Weight Gain.....130

Table 6.2 BMI 132

Table 6.3 Variations in Percentage of Body Fat for Blacks, Asians, and Whites 134

Table 7.1 List of Select Drugs That Are Weight Gaining, Weight Neutral, and Weight Reducing for Each Type of Treatment 148

Table 8.1 Sample Dietary Compositions.....163

Table 8.2 Comparison of Lifestyle Intervention Features of Diabetes Prevention Program and Look AHEAD Trial 174

Table 9.1 Obesity Medications Available Prior to 2012 184

Table 9.2 Summaries of Prescribing Information for Currently Available Obesity Medications 186

Table 9.3 Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Combination Treatment With Phentermine/Topiramate ER in Overweight/Obese Patients 200

Table 9.4 Summary of Mean Changes From Baseline in Metabolic and CV Risk Factors and Waist Circumference in Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Phentermine/Topiramate ER in Overweight/Obese Patients....206

Table 9.5 Summary of Adverse Events With Incidence ≥1% Leading to Treatment Discontinuation in the EQUIP and CONQUER Clinical Trials 209

Table 9.6 Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Lorcaserin in Overweight/Obese Patients.....214

Table 9.7 Mean Changes From Baseline in Metabolic and CV Risk Factors in Randomized, Placebo-Controlled Trials With Lorcaserin in Overweight/Obese Patients 220

Table 9.8 Summary of Adverse Events Reported by ≥2% of Lorcaserin Patients and More Commonly Than With Placebo in Patients Without Diabetes in the BLOSSOM, BLOOM, and BLOOM-DM Studies.....222

Table 9.9 Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Combination Treatment With Naltrexone ER/Bupropion ER in Overweight/Obese Patients.....226

Table 9.10 Summary of Mean Changes From Baseline in Metabolic and CV Risk Factors and Waist Circumference in 56-Week Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Naltrexone SR/Bupropion SR.....234

Table 9.11 Adverse Reactions Wth an Incidence of at Least 2% Among Patients Treated With Naltrexone SR/Bupropion SR and More Commonly Than Placebo 236

Table 9.12 Changes From Randomization to Week 56 in Measures of Glycemic Control, Lipids, and Cardiovascular Biomarkers....240
Table 9.13 Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Liraglutide and More Commonly Than Placebo....244
Table 10.1 RYGB: Potential Advantages and Disadvantages....256
Table 10.2 VSG: Potential Advantages and Disadvantages....258
Table 10.3 BPD/DS: Potential Advantages and Disadvantages....260
Table 10.4 AGB: Potential Advantages and Disadvantages....263
Table 10.5 Pooled Data From Systematic Review....266
Table 10.6 Estimated Rates (%) of Surgical Risks and Complications....270
Table 10.7 Short-Term and Long-Term Weight Loss With RYGB, AGB, or VSG....274
Table 10.8 Routine Postsurgical Laboratory Follow-Up of Individuals After Bariatric Surgery....279

FIGURES

Figure 1.1 Trends in the Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 and Over by Sex: 1960-1962 Through 2009-2010....14
Figure 1.2 Hazard Ratios for Death From Any Cause According to BMI for All Study Participants and for Healthy Subjects Who Never Smoked: Pooled Data From 19 Prospective Studies That Included 1.46 Million Caucasian Adults, 19 to 84 Years of Age....16
Figure 1.3 Relative Risks for Mortality From Cancer According to BMI Among US Men and Women: 1982 Through 1998....20
Figure 2.1 Two Major Opposing Pathways Affect Food Intake and Energy Expenditure in the Arcuate Nucleus of the Hypothalamus....25

Figure 2.2 Peptide Modulators of Food Intake and Energy Expenditure....27
Figure 2.3 Brain Sensing of Gut- and Adipocyte-Derived Hormones....29
Figure 2.4 CNS Regulates Food Intake, Energy Expenditure, and Reward in Response to Satiety Signals....32
Figure 2.5 Naltrexone Potentiates the Actions of Bupropion....34
Figure 2.6 Actions of Lorcaserin Enhance POMC....35
Figure 3.1 Comorbidities Associated With Obesity....48
Figure 3.2 Factors Secreted by Adipose Tissue....49
Figure 3.3 Relationships Between Body Weight and Diabetes....52
Figure 4.1 Complications-Centric Model for Care of the Overweight/Obese Patient....76
Figure 4.2 Prediction of All-Cause Mortality Using EOSS or BMI Criteria....82
Figure 4.3 Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort....90
Figure 4.4 Survival Probability as a Function of Increasing CMDS Risk Stage: NHANES....91
Figure 4.5 Intensification of Therapies to Achieve Weight Loss Goals....93
Figure 5.1 DPP Study: Cumulative Incidence of Diabetes at 3 Years in Overweight/Obese Individuals at High Risk for Diabetes....97
Figure 5.2 DPPOS Study: Cumulative Incidence of Diabetes at Over 10 Years Since Randomization in the DPP Study of Overweight/Obese Individuals at High Risk for Diabetes....99
Figure 5.3 DPPOS Study: Changes From DPP Baseline in CVD Risk Factors During 10 Years of Follow-Up....102
Figure 5.4 Look AHEAD Study: Changes in Weight and CVD Risk Factors During 4 Years in Patients in the ILI and DSE Groups....108

Figure 5.5 Look AHEAD Study: Prevalence of Any Remission (Partial or Complete) by Intervention Condition and Year in Overweight/Obese Diabetic Patients....113
Figure 5.6 Effect of Modest Weight Loss on Glycemic and CVD Risk Factors in Overweight/Obese Diabetic Patients....116
Figure 5.7 Look AHEAD Study: Changes in BDI Scores and Percent Weight Loss During 1 Year by Intervention and Baseline Depression Status....118
Figure 5.8 Long-Term Effect of Weight Loss on Obstructive Sleep Apnea Severity in Obese Patients With T2D....120
Figure 6.1 STOP BANG Questionnaire for Sleep Apnea....138
Figure 6.2 2013 AHA/ACC/TOS Treatment Algorithm for Patients With Overweight and Obesity....142
Figure 8.1 Simple Tips to Counsel Patients....168
Figure 8.2 Visual Aids Make "Portion Sense" 169
Figure 9.1 Weight Loss With Continuous or Intermittent Treatment With Phentermine....193
Figure 9.2 Effects of Orlistat as an Adjunct to Lifestyle Modification Diet on Weight Loss and Incidence of Diabetes in Obese At-Risk Patients....195
Figure 9.3 EQUIP Study: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Obese (BMI≥35 kg/m^2) Patients....202
Figure 9.4 CONQUER: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Overweight and Obese (BMI 27-45 kg/m^2) Patients With ≥2 Risk Factors....203
Figure 9.5 SEQUEL: Time Course of Weight Change During 108 Weeks of Treatment With Phentermine/Topiramate ER in Overweight/ Obese Patients....204
Figure 9.6 BLOSSOM: Changes From Baseline in Mean % Change From Baseline Body Weight....212

Figure 9.7 BLOOM: Changes From Baseline Body Weight (kg) During Year 1 and During Year 1 and Year 2 216
Figure 9.8 BLOOM-DM: Change From Baseline in Body Weight During 52 Weeks of Treatment 217
Figure 9.9 COR-I Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment....228
Figure 9.10 COR-II Trial: Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment 229
Figure 9.11 COR-BMOD Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment 231
Figure 9.12 COR-Diabetes Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment....232
Figure 9.13 Mean Percentage Change in Body Weight in the SCALE Maintenance Trial....242
Figure 9.14 Potential Therapeutic Targets for Development of Antibody Drugs 246
Figure 10.1 Number of Bariatric Procedures Performed in the United States From 1992 to 2009....252
Figure 10.2 Roux-en-Y Gastric Bypass....255
Figure 10.3 Vertical Sleeve Gastrectomy 257
Figure 10.4 Biliopancreatic Diversion With Duodenal Switch 259
Figure 10.5 Adjustable Gastric Band 261
Figure 10.6 Meta-analysis of Postoperative Change in BMI Over 5 Years 265

Introduction

Why did we write this handbook? Obesity is now considered a disease that should be treated as a chronic medical condition by providers. The prevalence of obesity continues to rise in certain populations while stabilizing in general; obesity is at epidemic levels nonetheless. Providers have been called upon to address this epidemic and need training and tools to effectively manage their patients.

There are a myriad of obesity-related diseases, and the new paradigm for providers is to treat the obesity in conjunction with a comorbid condition. The goal is to treat the obesity and obviate the need for additional medications for each specific comorbid condition. This is called the weight-centric approach to cardiometabolic and anatomic disease prevention or management. Special attention is paid to the role of drug-induced weight gain as a significant factor to consider in the primary care practice when faced with a patient with obesity.

The landscape for obesity treatment has changed over the last decade because of the research elucidating the neurohormonal pathways contributing to energy balance and body weight regulation with afferents coming from the gut, adipose tissue, and other organ systems. Information has revealed the powerful environmental and biological cues to overeat in this obesogenic environment. Behavioral techniques and dietary and exercise recommendations have become more sophisticated to respond to the need for better treatment options in this era of electronic medicine.

This handbook provides a guide to the assessment and treatment of obesity specifically for physicians, nurse practitioners, and other allied health providers. It is a step-by-step approach, which includes dietary recommendations, physical activity goals, lifestyle modification, pharmacotherapy and surgical options.

We hope this book provides a relief to those health care providers who feel at a loss when faced with a patient suffering with obesity.

1 Prevalence of Obesity and Related Mortality

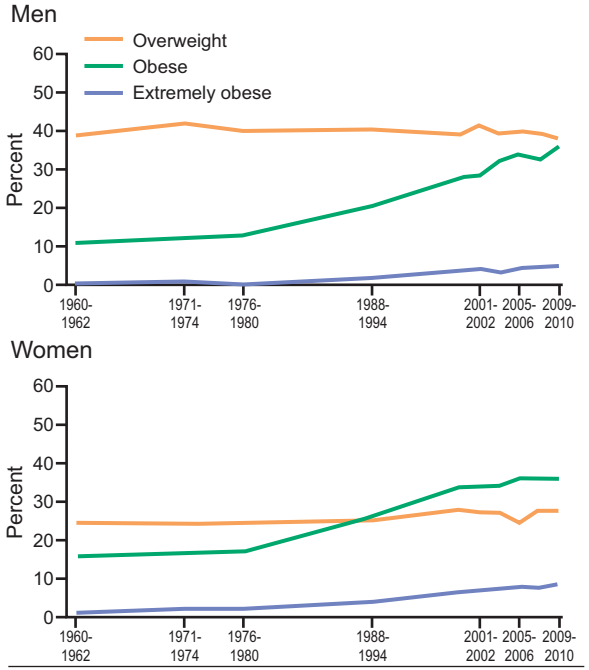
Prevalence

During the past 5 decades, there has been an increasing concern over a significant increase in the prevalence of obesity in the United States. Beginning in the early 1960s, the overall prevalence of overweight (body mass index [BMI] 25 to <30) adults aged 20 years and over increased only slightly from 31.5% to 32.7% by 2009-2010. However, in the same period, the prevalence of obesity (BMI ≥30) increased from 13.4% to 36.1%, and the prevalence of severe obesity (BMI ≥40) increased from 0.9% to 6.6%.[1]

However, the trends among adult men and women differed markedly during this period (**Figure 1.1**). While the prevalence of overweight among both men and women remained relatively stable during this period, the rate was higher among men (~40%) compared with women (~35%) and remained so through 2009-2010. However, the prevalence of obesity among men rose linearly from ~10% in 1960-1962 until it more than tripled to ~36% by 2009-2010. In adult women, the prevalence rate of obesity did not increase notably until the late 1970s and the subsequent increase was not as pronounced as in men. However, the obesity rate began to increase until more women were obese than women who were overweight.

These trends among men and women then converged until the prevalence of obesity in adult men and women was essentially the same by 2009-2010. At that point, 35.7% of US men and women were obese.[2] There was no significant difference in prevalence between men and women at any age. Overall, adults aged 60 and over were more likely to be obese than

FIGURE 1.1 — Trends in the Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 and Over by Sex: 1960-1962 Through 2009-2010



Fryar CD, et al. http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.pdf. Accessed June 10, 2014.

younger adults. Among men there was no significant difference in obesity prevalence by age. However, among women, 42.3% of those aged 60 and over were obese compared with 31.9% of women aged 20 to 39.

The prevalence of obesity among US children and adolescents also is a concern. In the past 30 years, the prevalence of obesity has more than doubled in children and tripled in adolescents.[3,4] In 1980, 7% of children aged 6 to 11 years were obese and 5% of adolescents aged 12 to 19 years were obese. By 2010,

18% of children aged 6 to 11 years were obese while the prevalence of obesity among adolescents aged 12 to 19 years also increased to 18%.[3,4] There was a significant increase in obesity among adolescent males aged 12 through 19 years but not among any other age group or among females.

Despite the recent slowing rates of obesity, the most recent (2009-2010) national data on obesity prevalence indicate that over 78 million US adults (41 million women and more than 37 million men) and about 12.5 million US children and adolescents (5 million girls and approximately 7 million boys) were obese.[3,4]

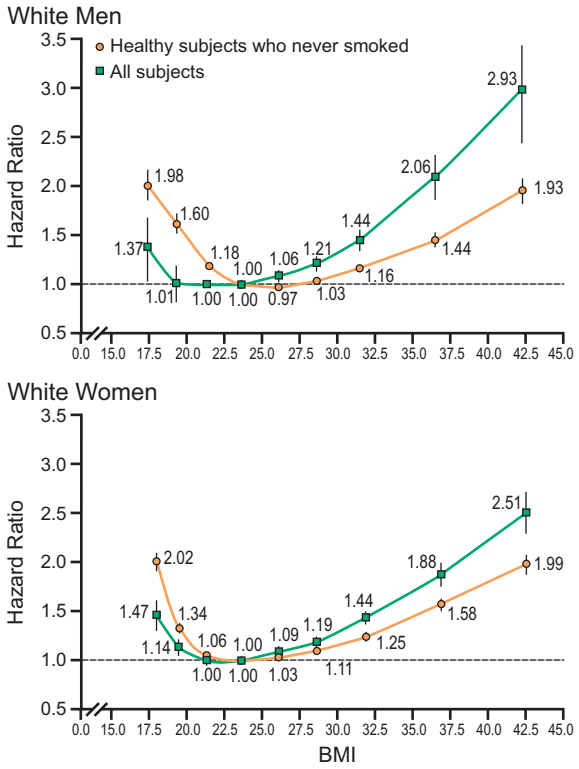
Obesity and Mortality

A considerable body of evidence has documented significant associations between obesity and a spectrum of comorbidities (see *Chapter 3*). Similarly, obesity is also associated with increased mortality, both all-cause and cause-specific.[5-8]

All-Cause Mortality

Berrington de Gonzalez and associates analyzed pooled data from 19 prospective studies that included 1.46 million white adults to assess the association between BMI and all-cause mortality.[5] A total of 160,087 deaths were identified during a median follow-up period of 10 years. To minimize the effects of potentially confounding conditions, the results were calculated for all subjects and then sequentially re-analyzed after exclusion of specific subpopulations (eg, healthy subjects who never smoked, those specific medical conditions, etc). The hazard ratios (HR) among healthy participants who never smoked (the population of interest) and all subjects formed a J-shaped relationship between BMI and all-cause mortality with a BMI of 22.5 to 24.9 as the reference category (**Figure 1.2**). In both men and women, the HRs increased in almost a linear fashion according to BMI to reach 2.51 among women and 2.93 among men at BMI 42.5. It is interest-

FIGURE 1.2 — Hazard Ratios for Death From Any Cause According to BMI for All Study Participants and for Healthy Subjects Who Never Smoked: Pooled Data From 19 Prospective Studies That Included 1.46 Million Caucasian Adults, 19 to 84 Years of Age



Subjects were considered healthy if they had no cancer of heart disease at baseline.

Berrington de Gonzalez A, et al. *N Engl J Med*. 2010;363:2211-2219.

ing to note that overweight (BMI 25 to <30) was also associated with small increases in HR.

Another review and meta-analysis estimated the all-cause mortality risks associated with normal weight, overweight, and obesity relative to normal weight based on data from 97 prospective studies with a combined sample size of more than 2.88 million individuals and more than 270,000 deaths.[6] The populations of these studies included those from United States, Canada, Europe, Australia, China or Taiwan, Japan, Brazil, Israel, India, and Mexico. Similar to the results of the previously discussed study, the HRs for all-cause mortality relative to normal weight (BMI = 18.5 to <25) increased according to incremental increases in BMI. The all-cause mortality HRs were 0.94 for overweight, 1.18 for obesity (all grades combined), 0.95 for grade 1 obesity, and 1.29 for grades 2 and 3 obesity. Thus, relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Whereas, grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality.

■ Cause-Specific Mortality

Collaborative analyses of 57 prospective studies with 894,576 participants calculated the HRs of all-cause and cause-specific mortality vs baseline BMI.[7] Study participants were mostly (61%) from Western Europe and North America with a mean recruitment age 46, and a mean BMI of 25. To limit reverse causality, the first 5 years of follow-up were excluded, leaving 66,552 deaths of known cause during a mean of 8 further years of follow-up (mean age at death 67). The numbers of deaths according to specific cause were: 30,416 vascular; 2070 diabetic, renal or hepatic; 22,592 neoplastic; 3770 respiratory; 7704 other. Ischemic heart disease accounted for more than a quarter of all deaths of known cause. Overall, BMIs in the overweight/obese range (25-50) were associated with higher

mortality HRs compared with the normal/underweight BMI range (15-25) (**Table 1.1**). The highest HRs were associated with cardiovascular (CV) disease, diabetes, and non-neoplastic kidney and liver diseases. Overall, at a BMI of 30 to 35, median survival was reduced by 2 to 4 years and at a BMI of 40 to 45, it was reduced by 8 to 10 years.

Cancer-Related Mortality

An analysis of a prospectively studied population of more than 900,000 US adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982 examined the relation in men and women between the BMI in 1982 and the relative risk (RR) of death from all cancers and from cancers at individual sites during 16 years of follow-up.[8] The cancer-related

TABLE 1.1 — Cause-Specific Mortality vs BMI in the Ranges of 15-25 kg/m^2 and 25-50 kg/m^2

	Hazard Ratios	
	BMI 15-25 kg/m^2	**BMI 25-50 kg/m^2**
Ischemic heart disease	1.22	1.39
Stroke	0.92	1.39
Other vascular disease	0.84	1.47
Diabetes	0.96	2.16
Kidney disease[a]	1.14	1.59
Liver disease[a]	0.69	1.82
Lung cancer	0.71	0.98
Upper aerodigestive cancer	0.49	0.98
Other specified cancer	0.94	1.12
Respiratory disease	0.31	1.20
Other specified disease	0.62	1.20
External cause	0.82	1.19
Unknown cause	0.72	1.22

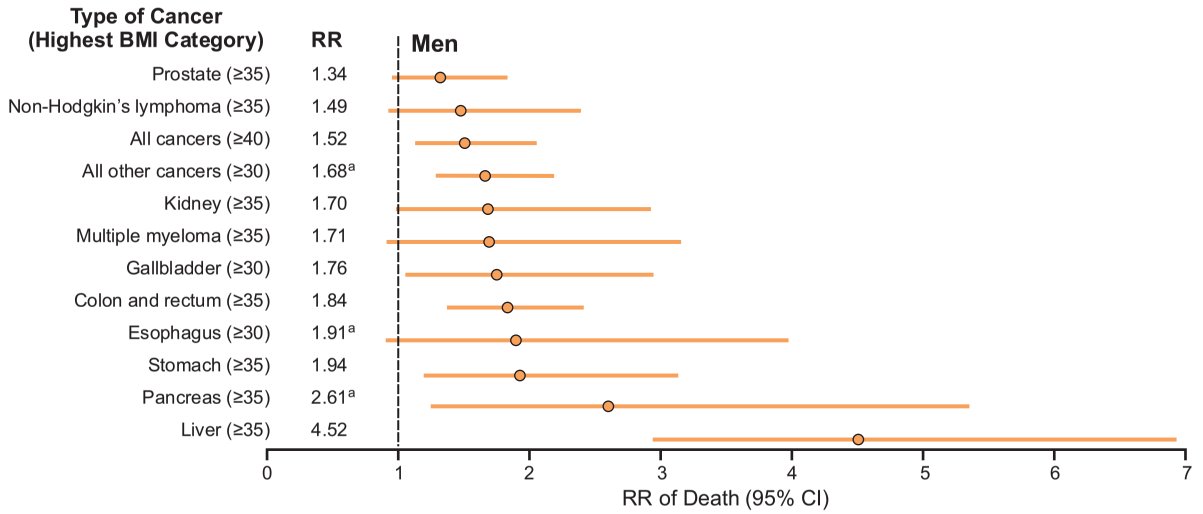
[a] Non-neoplastic.

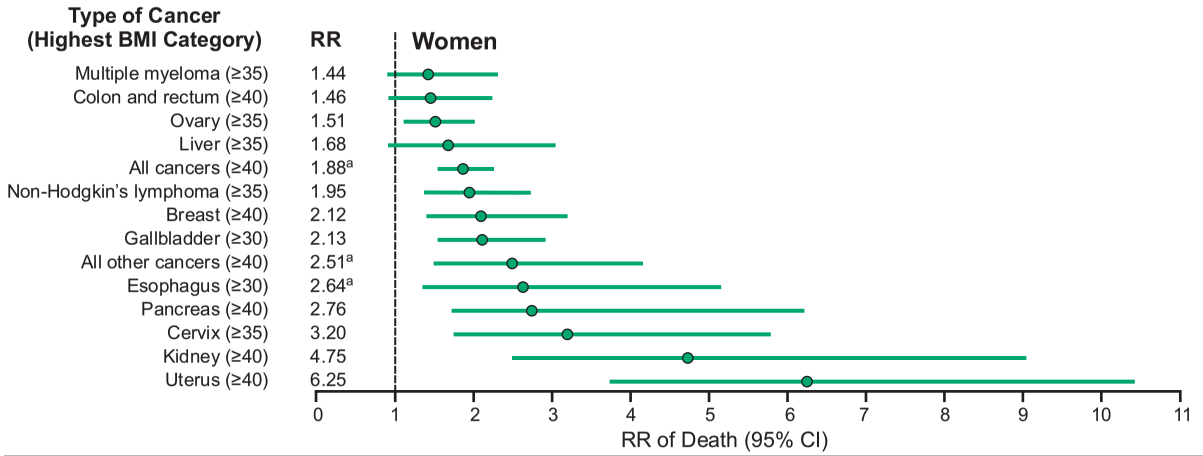
Prospective Studies Collaboration, et al. *Lancet*. 2009;373:1083-1096.

deaths rates among subjects with a BMI of ≥40 were 52% higher for men and 62% higher for women than the rates in men and women of normal weight. For men, the RR of death was 1.52 while the RR risk was 1.62 for women. On the basis of the associations observed in this study, the authors estimated that current patterns of overweight and obesity in the United States could account for 14% of all cancer-related deaths in men and 20% of all cancer-related deaths in women.[8]

The relationship between obesity and cancer mortality also holds for individual-site cancer mortality. The RRs for mortality from specific cancers among obese US men ranged from 1.34 for prostate cancer to 2.61 for pancreatic cancer and 4.52 for liver cancer (**Figure 1.3**, *top*). Among US women, the RRs tended generally to be higher than in men. For example, the most potentially deadly relationships were between obesity and pancreatic (RR 2.76), cervical (RR 3.20), kidney (RR 4.75), and uterine (RR 6.25) cancers (**Figure 1.3**, *bottom*).[8]

FIGURE 1.3 — Relative Risks for Mortality From Cancer According to BMI Among US Men and Women: 1982 Through 1998





For each RR, the comparison was between subjects in the highest BMI category (indicated in parentheses) and those in the reference category (BMI, 18.5-24.9). Results of the linear test for trend were significant ($P \leq 0.05$) for all cancer sites.

[a] Indicates RR for subjects who never smoked.

Calle EE, et al. *N Engl J Med*. 2003;348(17):1625-1638.

REFERENCES

1. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and extreme obesity among adults: United States, Trends 1960-1962 through 2009-2010. NCHS Health E-Stat. 2012. Centers for Disease Control Web site. http://www.cdc.gov/nchs/data/hestat/obesity_adult_09_10/obesity_adult_09_10.pdf. Accessed June 10, 2014.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS data brief, no 82, January 2012. Centers for Disease Control Web site. http://www.cdc.gov/nchs/data/databriefs/db82.pdf. Accessed June 10, 2014.
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA*. 2012;307:483-490.
4. National Center for Health Statistics. Health, United States, 2011: With Special Features on Socioeconomic Status and Health. Centers for Disease Control Web site. http://www.cdc.gov/nchs/data/hus/hus11.pdf. Accessed June 10, 2014.
5. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363:2211-2219.
6. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307:491-497.
7. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083-1096.
8. Calle EE, Rodriguez C, Walker-Thurmond, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625-1638.

2 The Pathophysiology of Obesity

Obesity is a disease manifested as excess adipose tissue. It is now considered a chronic disease with multiple etiologies including genetic, environmental, behavioral, and defects in neurohormonal signaling.

Energy Balance/Homeostatic Regulation of Food Intake

Energy homeostasis is the steady state balance between energy intake vs energy expenditure, and humans have evolved multiple mechanisms to maintain energy homeostasis. Homeostatic control of food intake involves complex communication between the central nervous system (CNS) (hypothalamus) and the periphery. Intake involves the process of obtaining and digesting nutrients, as well as the regulation of feeding behavior. Energy expenditure involves basal metabolic rate, non-shivering thermogenesis, diet-induced thermogenesis, and physical activity. Basal metabolic rate accounts for approximately 60% to 70% of total energy expenditure (TEE) and increases with overall body weight as the demand increases with the increased body mass.[1] Thermogenesis contributes to energy expenditure, including the regulation of brown adipose tissue for heat generation. Further, after eating, the body utilizes energy for digestion and absorption in a process called diet-induced thermogenesis. Lastly, physical activity is responsible for approximately 20% to 30% of total energy expenditure and is one of the most modifiable components of energy expenditure.

In order to maintain balance, a neural regulator (the hypothalamus) senses fuel availability and generates appropriate signals to the neural circuits control-

ling food intake and energy expenditure, referred to as the homeostatic regulation of adiposity and body weight.[2] Under steady-state conditions, all energy consumed is normally metabolized to maintain basic metabolic rate, thermogenesis, and energy expenditure. Excess fuel is stored to be used later and is required for human survival during times of starvation. However, these pathways are now operating under a condition of sustained positive energy balance and the body's efficient storage of fat can lead to obesity. Ultimately, obesity is a result of a disruption in energy homeostasis.

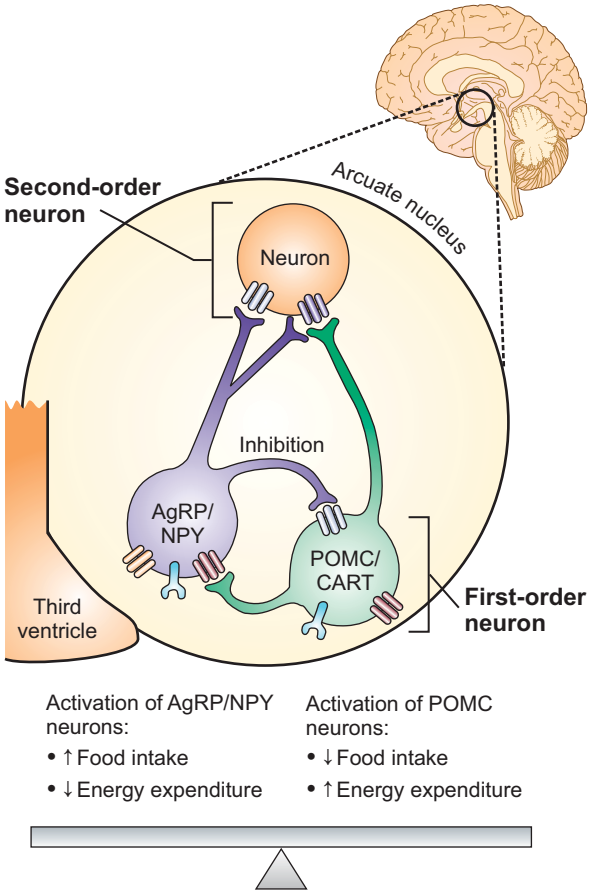
Hypothalamus as Key Regulator

The hypothalamus is the regulation center of appetite and energy expenditure, integrating both CNS and peripheral signals that subsequently modulate feeding behavior and energy balance.[3] The hypothalamus consists of several interconnecting nuclei, including the arcuate nucleus (ARC), which is considered to be the primary region sensing the peripheral metabolic signals leading to feeding behavior and appetite regulation. Within the ARC, there are two distinct neuronal populations: one which expresses orexigenic peptides including neuropeptide Y (NPY) and agouti-related peptide (AgRP) which functions to reduce energy expenditure and increase appetite (**Figure 2.1**).[4]

NPY is a 36 amino acid neural transmitter that is widely distributed throughout the CNS with the highest concentration found in the ARC of the hypothalamus. The appetite-stimulating effects of NPY are mediated by several subtypes of NPY receptors on the orexigenic neuron. The production of NPY from the NPY/AgRP neuron is stimulated by the gut "hunger signal" ghrelin and inhibited by leptin, amylin, insulin, and serotonin (5-HT).

AgRP is a 132 amino acid peptide signaling molecule co-expressed with NPY in the NPY/AgRP neuron. The production of AgRP from the NPY/AgRP neuron is stimulated by ghrelin and inhibited by

FIGURE 2.1 — Two Major Opposing Pathways Affect Food Intake and Energy Expenditure in the Arcuate Nucleus of the Hypothalamus



Key: AgRP, agouti-related protein; CART, cocaine and amphetamine-regulated transcript; NPY, neuropeptide Y; POMC, propiomelanocortin.

Modified from Vetter ML, et al. *Nat Rev Endocrinol*. 2010;6:578-588; and Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

leptin, amylin, insulin, and 5-HT. AgRP is also highly expressed in the adrenal gland. As an antagonist of α-MSH (melanocyte-stimulating hormone), AgRP completes the binding of MC4R by α-MSH, leading to lowered satiety and overeating.

The other neuronal population is the anorexigenic peptides, including proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). POMC is a prohormone synthesized in the POMC/CART neuron in the ARC of the hypothalamus. Activation of POMC neurons leads to release of α-MSH which binds to MC4R, leading to a reduction in appetite and increased energy expenditure. CART is an approximately 50 amino acid long peptide derived in the POMC/CART neuron. Its main function in the hypothalamus is to stimulate anorexigenic neurons to suppress appetite. First discovered as a respondent to cocaine and amphetamine administration, CART is believed to play roles in reward and addiction regulations. Both NPY/AgrP and POMC neurons project from the arcuate nucleus to the hypothalamus (as well as other brain regions), which contains a dense neuronal population that expresses the melanocortin receptor 4 (MC4R). Activation of MC4R by αMSH relays a satiety signal, resulting in a reduction in food intake. This neuronal regulatory system is regulated by modulators such as leptin and insulin (**Figure 2.2**).[4]

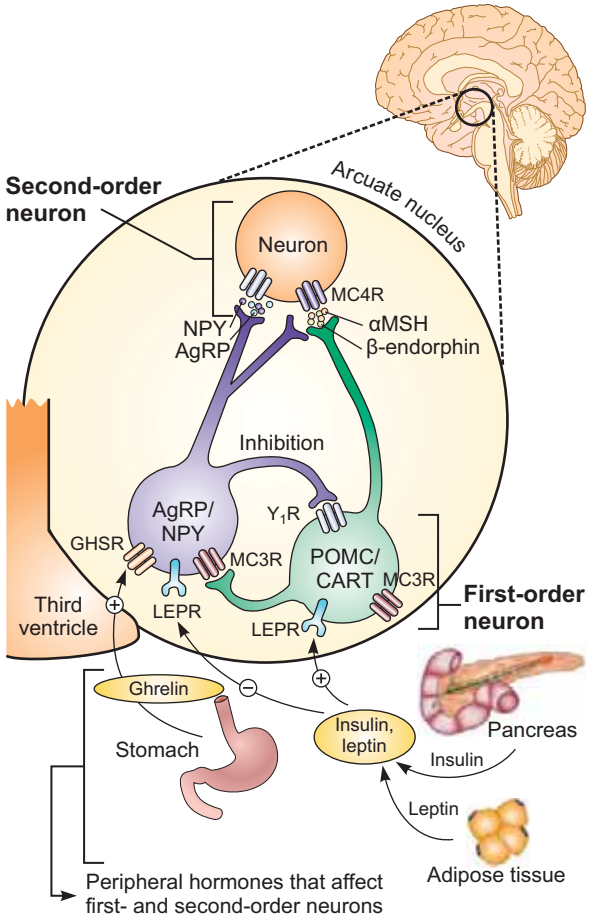
Peripheral Signaling

Peripheral signals send signals to the CNS via three routes:

- Humoral
- Metabolic
- Neural.

Humoral factors include hormones secreted by the gastrointestinal (GI) system, adipose tissue, and pancreas. These signals include peptides, ghrelin, leptin, insulin, cholecystokinin (CCK), and tumor necrosis

FIGURE 2.2 — Peptide Modulators of Food Intake and Energy Expenditure



Key: AgrP, agouti-related peptide; CART, cocaine and amphetamine-regulated transcript; GHSR, growth hormone secretagogue receptor; LEPR, leptin receptor; MC3R, melanocortin receptor 3; NPY, neuropeptide Y; POMC, proopiomelanocortin; Y_1R, neuropeptide Y_1 receptor.

Modified from Vetter ML, et al. *Nat Rev Endocrinol*. 2010;6:578-588; and Saper CB, et al. *Nature*. 2005;437(7063):1257-1263.

factor alpha (TNF-α). Metabolic factors include carbohydrates, lipids ketones, and other metabolites. Finally, the autonomic nervous system sends signals from the peripheral organs to the CNS. Subsequently, all of these signals are integrated and regulate both short-term energy intake as well as long-term energy stores to modulate energy intake and energy expenditure.[5] These multiple signaling pathways ensure that food is consumed when needed. However, ongoing access to highly palatable foods may override the inhibitory processes that signal satiety and one may begin to overconsume large amounts of food despite nutrient overload.[6]

Humoral Signaling

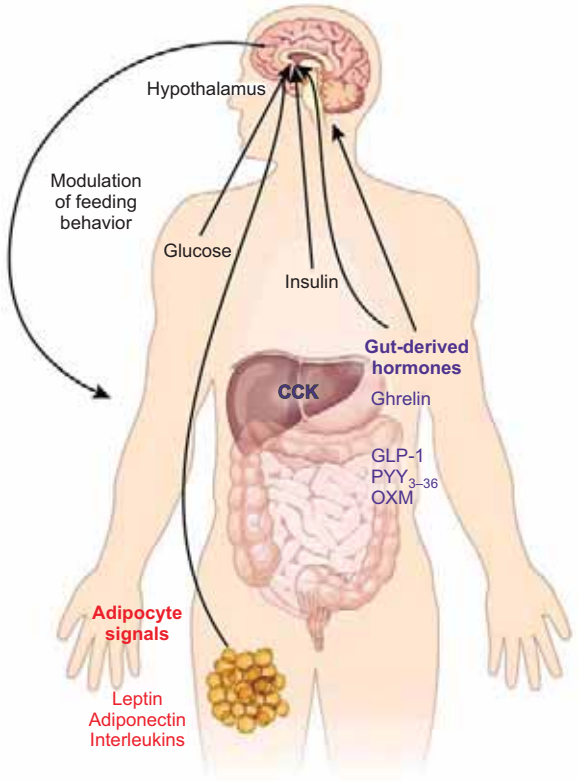
Gastrointestinal Signals

The primary role of the GI tract is to digest and absorb nutrients. However, it also plays a role in energy homeostasis via mechanoreceptors and chemo sensors which detect the amount and quality of food intake. Gastric distension leads to vagal stimulation due to secretion of serotonin from gastric enterochromaffin cells or from direct stimulation of stretch receptors. The small intestine secretes satiety signals including CCK, peptide YY (PYY), serotonin, and glucagon-like peptide-1 (GLP-1) (**Figure 2.3**).[7]

CCK is released via duodenum and small intestine in response to fat and protein intake and signals satiety. PYY (and GLP-1 are both released in the small intestine in response to luminal nutrient stimulation). PYY binds to and inactivates NPY/AgRP leading to anorexia. GLP-1 delays gastric emptying leading to improved satiety.

Ghrelin, secreted from stomach, exerts an orexigenic effect. Ghrelin levels are elevated during the fasting state and thus is considered the physiologic "hunger" hormone. Ghrelin levels rise before each meal and rapidly fall after eating. Further, diet-induced weight loss in obese individuals show increased plasma

FIGURE 2.3 — Brain Sensing of Gut- and Adipocyte-Derived Hormones



Key: GLP-1, glucagon-like peptide 1; $PYY_{3–36}$, peptide YY residues 3–36; OXM, oxyntomodulin; CCK, cholecystokinin.

The brain is responsive to signals from adipose, gut and pancreatic hormones, brain-derived energy balance–associated neurotransmitters and neuropeptides, and dietary nutrients. Gut- and adipocyte-derived hormones, reflecting short- and long-term nutritional status, respectively, circulate in the periphery and signal to specific receptors in the brain.

Yeo GS, Heisler LK. *Nat Neurosci*. 2012;15(10):1343-1349.

ghrelin levels, suggesting that ghrelin may represent a compensatory response to altered energy metabolism.[8]

■ Adipose Signals

Adipose tissue has been recognized as more than just a depot of excess fat. Adipose tissue is recognized as an active organ that secretes a variety of hormones and adipokines, all of which act on a variety of metabolic processes and influence energy homeostasis.[9] Key signaling molecules include leptin, insulin, TNF-α, IL-6, and resistin (**Figure 2.3**).[7]

Leptin is a hormone discovered in 1994 which is secreted by adipose tissue and in normal individuals, leptin levels correlate with adipose tissue mass. Leptin receptors are highly expressed in the ARC of the hypothalamus. Binding of the leptin receptors induces an increase in anorexigenic POMC/CART signaling and decreased activity of the orexigenic signals NPY/AgRP, resulting in reduced food intake and increased energy expenditure.[10,11] Studies have shown that leptin acts as a satiety factor that signals the CNS that adipose tissue stores are adequate.[12] The absence of leptin acts as a signal of starvation, thus leptin deficient individuals develop severe obesity and hyperphagia. Leptin has successfully treated hyperphagia in leptin deficient individuals; however, most obese humans have elevated leptin levels, implying leptin resistance and treatment in these patients has been ineffective.

■ Pancreatic Signals

Insulin is secreted from the pancreatic B cells following a meal and transported to the brain (**Figure 2.2**).[4] Fasting insulin levels positively correlate with body fat mass and insulin has been considered a surrogate marker for adiposity.[3] Insulin receptors are expressed in the hypothalamic nuclei including the ARC. Insulin, similar to leptin, binds to the ARC neurons and results in POMC activation and NPY/AgRP inhibition, leading to reduced food intake.

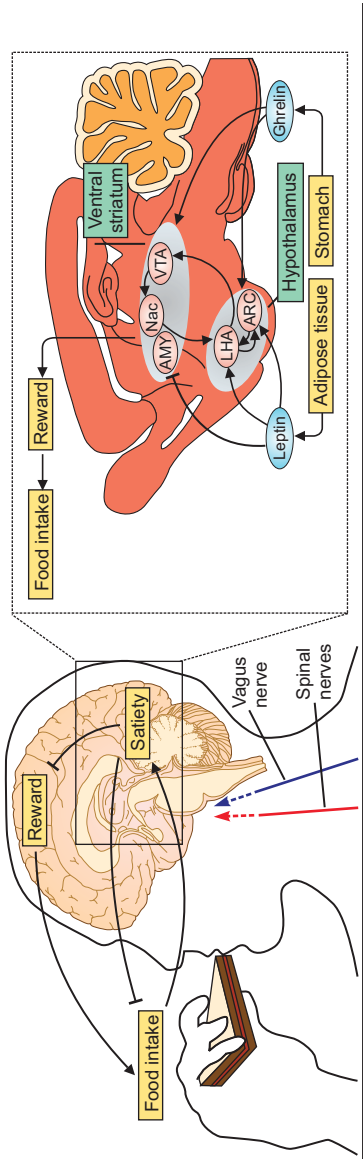
Reward or "Hedonic" Pathway

Certain forms of obesity may be driven by excessive motivational drive for food and mediated by reward "hedonic" circuitry. Certain foods, particularly those containing sugar and fat, are potently rewarding. In animal models, this can trigger addictive-like behaviors; however, the response to food by humans is more complex. In humans, the rewarding property of food is influenced by many other factors including palatability, availability, economics, and incentives ("supersizing"), and social routines.[13] During periods of energy abundance, the reward system regulation can override the homeostatic pathway (by increasing the desire to consume foods that are highly palatable), leading to obesity.

Several neurotransmitters have been implicated in the rewarding effect of food; however, dopamine has been the most thoroughly investigated and is best characterized.[6] Upon exposure to a food reward, dopamine neurons fire, leading to an increase in dopamine release in the nucleus accumbens (NAc). Disruption of the dopamine reward pathway has been implicated in the loss of control seen in obesity (**Figure 2.4**).[14]

In addition, obese individuals may respond to food differently than their lean counterparts. Data using functional magnetic resonance imaging (MRI) have demonstrated that high glycemic index meals (highly palatable foods) increase activity in the NAc.[15] Furthermore, functional MRI shows significantly greater activation of the NAc in obese women compared with normal-weight women. This greater activation was observed in response to pictures of high-calorie (eg, cheesecake, ribs) vs low-calorie foods (eg, steamed vegetables, broiled fish). Exaggerated reactivity to food cues, especially those associated with high-calorie foods, may be a factor underlying obesity. This increased motivational potency of foods in obese individuals appears to be mediated in part by a hyperactive reward system.[16]

FIGURE 2.4 — CNS Regulates Food Intake, Energy Expenditure, and Reward in Response to Satiety Signals



The CNS integrates input from long-term energy stores and short-term meal-related signals (reward system) to regulate food intake and energy expenditure in a manner that maintains homeostasis over time. In response to energy deprivation, the rewarding properties of food are increased (via projection of dopaminergic neurons in the VTA to the NAc), and the response to satiety signals are reduced, resulting in increased food consumption. Conversely, positive energy balance induced by overfeeding inhibits the reward response, and enhances satiety. However, neurocircuits exist that can override the homeostatic control of energy balance. For example, the increased desire to consume foods that are highly palatable can trigger eating at times when food would not otherwise be consumed.

Morton GJ, et al. *Nat Rev Neurosci.* 2014;15(6):367-378; and Saper CB, et al. *Nature.* 2005;437(7063):1257-1263.

Role of Obesity Pharmacotherapy

The current approved obesity pharmacotherapy targets the above pathways in an effort to manage appetite and reduce weight (see further details in *Chapter 9*). Phentermine increases dopamine and norepinephrine in the hypothalamus enhancing POMC neuron pathways to increase alpha-MSH, which binds to MC4R to partially suppress appetite. Bupropion SR plus naltrexone SR (Contrave) targets the POMC pathway. Bupropion may enhance POMC-mediated appetite suppression; however, it also activates the B-endorphin/opioid-mediated negative feedback loop which mitigates how much bupropion can activate POMC. Thus naltrexone removes this negative feedback and can potentiate bupropion's ability to increase POMC firing, leading to stronger appetite suppression. Finally, lorcaserin, a serotonin 5HT2c receptor agonist, may work in part by activating POMC appetite-suppressing pathway (**Figure 2.5** and **Figure 2.6**).

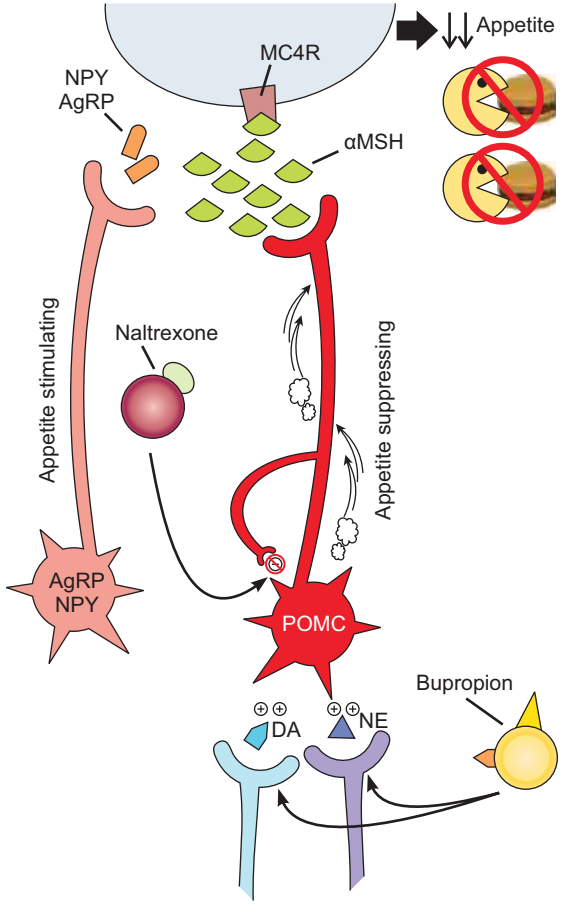
Genetic and Environmental Factors

Genetics

Genetic causes of obesity may derive from monogenic or polygenic hypothalamic defects resulting in impairment in the ability of the hypothalamic circuitry to regulate body weight by controlling energy expenditure, food intake, and some peripheral metabolic actions. The latest version of the human obesity gene map reported 11 human genes that cause monogenic obesity and 52 genomic regions harboring a trait loci associated with obesity.[17] Single gene mutations can result in syndromes in which obesity is a symptom; including Leptin Deficiency, Prader-Willi Syndrome, and Bardet-Biedl syndrome and mutations in the FTO and POMC genes.

Leptin deficiency is a mutation of the Ob gene which encodes for leptin. It is associated with severe, early-onset obesity and was the first monogenic form

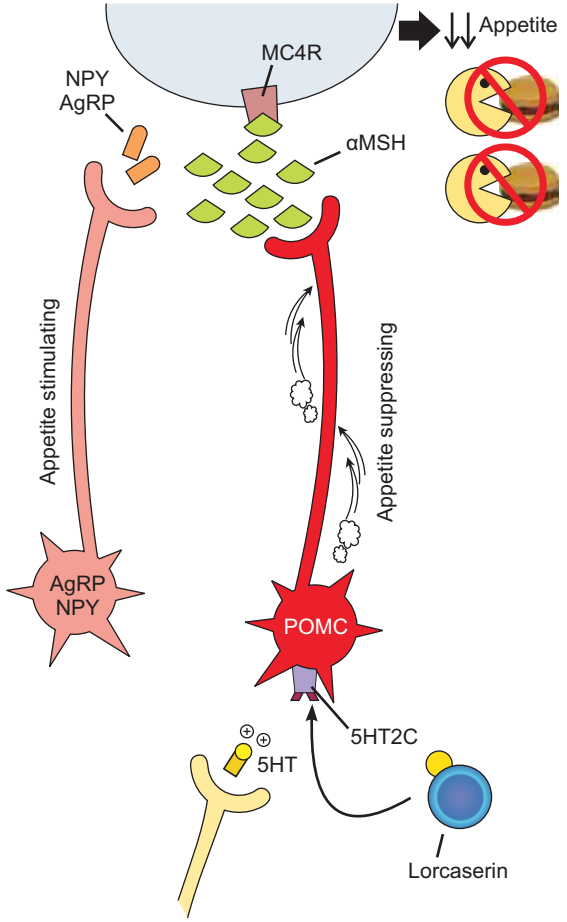
FIGURE 2.5 — Naltrexone Potentiates the Actions of Bupropion



Key: AgRP, agouti-related protein; αMSH, α-melanocyte–stimulating hormone; DA, dopamine; MC4R, melanocortin 4 receptor; NE, norepinephrine; NPY, neuropeptide Y; POMC, proopiomelanocortin.

Stahl SM. In: *Stahl's Essential Psychopharmacology*. 4th ed. New York, NY: Cambridge University Press; 2013:537-575.

FIGURE 2.6 — Actions of Lorcaserin Enhance POMC



Key: 5HT, 3-hydroxytryptamine (serotonin); 5HT2C, 3-hydroxytryptamine 2C; AgRP, agouti-related protein; αMSH, α-melanocyte–stimulating hormone; MC4R, melanocortin 4 receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin.

Stahl SM. In: *Stahl's Essential Psychopharmacology*. 4th ed. New York, NY: Cambridge University Press; 2013:537-575.

of obesity discovered. Carriers of leptin gene mutations are able to normalize their body weight after daily subcutaneous leptin administration. The Prader-Willi syndrome is a neurodegenerative disorder that is caused by genetic abnormalities of the long arm of chromosome 15 (q11-13). Affected infants have poor muscle tone and feed poorly at birth. Later their appetite becomes voracious and they become obese, have behavior problems (irritability, tantrums), delayed development, short stature, and, later, hypogonadotropic hypogonadism. Bardet-Biedl syndrome occurs from mutations to the primary cilium altering cellular signaling and is a disorder characterized by obesity and several other abnormalities, including microorchidism in men, intellectual disability (mental retardation), retinal dystrophy, polydactyly, renal malformations (particularly calyceal abnormalities), and polyuria and polydipsia.

Humans with the two copies of the FTO gene (fat mass and obesity associated gene) have been found on average to weight 3 to 4 kg more and have a 1.67-fold greater risk of obesity compared with those without the risk allele. In addition, human studies have found that both adults and children with at least one FTO risk allele report greater food intake, impaired satiety responsiveness, and more frequent eating loss of control. The increased consumed energy was due to an increased preference for energy dense foods, specifically those with a higher fat content.[18] Furthermore, FTO is strongly expressed in the hypothalamus, particularly the arcuate, paraventricular (PVN), dorsomedial, and ventromedial nuclei, all key regions crucial to energy intake.

POMC deficiency is characterized by severe, early-onset hyperphagic obesity and congenital adrenal insufficiency. In the first months of life, most children with POMC deficiency experience exponential weight gain, hyperphagia, cholestasis, and adrenal insufficiency. Weight gain continues rapidly so that by the end of the first year of life, obesity is severe.

■ Epigenetics

Among the different mechanisms that can lead to interindividual differences in obesity, the epigenetic regulation of gene expression has emerged in the past few years as a potentially important contributor. Epigenetics are heritable changes in gene activity which are not caused by changes in the DNA sequence itself. Epigenetic mechanisms are intrinsically malleable and can be influenced by factors including diet, pharmacologic agents, and environmental toxins.[19]

As an example, the fetus or neonate is extremely sensitive to perturbation by chemicals with hormone-like activity. Environmental chemicals can disrupt the programming of endocrine signaling pathways that are established during perinatal life and result in adverse consequences into adulthood. These endocrine disruptors include pesticides, bisphenol A, organophosphates, polychlorinated biphenyls, polybrominated biphenyls, phthalates, and heavy metals. As an example, in utero or neonatal exposure to Bisphenol A may interact with other factors that influence fetal and postnatal growth in contributing to the obesity epidemic.

Furthermore, studies have examined the intrauterine environment of obese women to understand whether it induces developmental adaptations in the developing fetus that then predispose that fetus to obesity. This has been demonstrated in data from obese women who underwent bariatric surgery. The children born after maternal weight loss have a lower risk for obesity than do their siblings born before maternal weight loss.[20] Such “metabolic imprinting” of body weight regulation could occur via epigenetic mechanisms.[21]

■ Environmental Factors

Environmental influences, including the physical, social, and economic environment, have likely all contributed to the obesity epidemic. The physical environment includes easy access/use of automobiles, as well as exposure to pollutants and “obesogens.” The social environment includes recreational eating (social

eating influences meal duration and consumption norms), ongoing advertisements of unhealthy foods, and availability of larger portion sizes.

■ **Genetics vs Environment**

The contribution of genetics and environment to the etiology of obesity has been evaluated by multiple studies. Twin studies have shown that genetics explain 50% to 90% of the variation in BMI. In a study of same-age, unrelated siblings reared together since infancy, 61% of the variance was genetic, 25% due to the common or shared environment, and 14% due to the unique environment. Thus genetics likely accounts for 60% to 70% of BMI, whereas environmental factors may explain the remaining 30% to 40%.[22]

In a given population, a person may be genetically susceptible to obesity but only unless exposed to certain environmental conditions, such as a readily available, highly-caloric, high-fat diet and sedentary lifestyle, would it be expressed. Environmental conditions in developing countries favor the genetically susceptible towards obesity. Evidence of this comes from immigrants who move to the United States who show marked differences in the incidence of obesity compared with their counterparts who remain in their native countries. In addition, studies of the Pima Indians have shown that those residing in Arizona have highest prevalence of obesity vs those living in a traditional lifestyle in remote area of Mexico—(BMI was 24.9 vs 33.4). The groups differ in diet and energy expenditure based on location in which they live and affluence. Those living in Mexico have a diet with lower animal fat and reduced caloric intake vs those in Arizona have higher fat and more calorically dense food with more complex carbohydrates.[23]

Gut Microbes

The human gut is populated with both symbiotic and commensal microbes, and there is increasing

evidence that the gut microbiota may play a role in the development of obesity. Studies in mice have shown that obesity can be induced in lean individuals via fecal transplants from obese individuals.[24]

The exact mechanism of how gut microbes influence BMI is unknown; however, animal models suggest that obesity is associated with alterations in the composition and functional properties of the gut microbiota. Although the data is conflicting, some data suggest a shift in the abundance of two dominating divisions of the bacteria, Bacteroidetes and Firmicutes. Compared with lean individuals, obese individuals have a lower ratio from the phylum Bacteroidetes to that of the phylum Firmicutes.[25] Host bacteria may affect energy balance through several mechanisms, including increased fermentation of undigested polysaccharides and obtaining extra energy from the portion of food, reduced expression of fasting-induced adipocyte factor with inhibitory activity towards lipoprotein lipase and increased release of peptide YY which slows intestinal motility.

Furthermore, the key importance of antibiotic use and dietary nutrient composition are increasingly recognized. The role of the Western diet in promoting an obesogenic gut microbiota has been evaluated and shown that it may increase the abundance of Firmicutes at the expense of Bacteroidetes, inducing enrichment in genes enabling energy harvest from the diet. Further, the changes in the microbial composition were completely reversed after a shift back to the original diet.[26]

Medical Conditions

Medical conditions linked to obesity including Cushing's syndrome, hypothyroidism, PCOS, and growth hormone deficiency. Psychiatric conditions may also play a role including binge-eating and night-eating disorders. Finally, multiple medications may contribute to obesity (see *Chapter 7* regarding medication-induced weight gain).

■ **Cushing's Syndrome**

Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the hormone cortisol. This can be caused by taking glucocorticoid drugs, or diseases that result in excess cortisol, adrenocorticotropic hormone (ACTH), or corticotropin-releasing hormone (CRH) levels. Progressive weight gain is the most common symptom of Cushing's syndrome. This weight gain usually affects the face, neck, trunk, and abdomen more than the limbs, which may be thin. People with Cushing's syndrome often develop a rounded face and collections of fat on the upper back and at the base of the neck.

■ **Hypothyroidism**

The relationship between thyroid dysfunction and obesity is complex and bidirectional. Patients with hypothyroidism often gain weight due to slowing of metabolic activity. The weight gain is usually modest, and marked obesity is uncommon. Increasing serum thyroid-stimulating hormone (TSH) concentrations within the normal range have also been associated with a modest increase in body weight in adults but treatment of subclinical hypothyroidism does not appear to be associated with weight loss.

■ **PCOS**

PCOS is clinically characterized by oligomenorrhea and hyperandrogenism, as well as the frequent presence of obesity, glucose intolerance, and dyslipidemia. At least half of all women with PCOS are obese; however, the relationship between obesity and PCOS is not causal.

■ **Growth Hormone Deficiency**

Growth hormone deficiency is associated with weight gain and alterations in body composition, specifically central adiposity and a reduction in lean body mass.[27]

■ **Binge-Eating Disorder**

Binge-eating disorder is a psychiatric illness characterized by uncontrolled episodes of eating that usually occur in the evening. During such binges, a person rapidly consumes an excessive amount of food. Most people who have eating binges try to hide this behavior from others and often feel ashamed about being overweight or depressed about their overeating.

■ **Night-Eating Syndrome**

Night-eating syndrome is defined as consumption of at least 25% (and usually more than 50%) of energy between the evening meal and the next morning. It is a well-known pattern of disturbed eating in the obese, affecting approximately 10% of obese individuals.[28]

■ **Sleep**

Sleep deprivation has been linked to obesity. Sleep is an important modulator of neuroendocrine function and glucose metabolism. Sleep loss has been shown to result in metabolic and endocrine alterations, including decreased glucose tolerance, decreased insulin sensitivity, increased evening concentrations of cortisol, increased levels of ghrelin, decreased levels of leptin, and increased hunger and appetite.[29] Recent studies have shown a correlation between chronic short sleep (6 hours or less) and elevated BMI and waist circumference.[30] Short sleepers were as much as 1.7 kg/m^2 heavier and waist 3.4 cm greater than long sleepers (>10 hours).

Hypothalamic Obesity

Hypothalamic obesity (HO) comprises a series of genetic or acquired pathologic processes damaging the hypothalamic centers of body weight and energy expenditure leading to obesity. Specifically, HO is generally associated with damage to the ventromedial hypothalamus leading to hyperphagia, autonomic dysfunction, and decreased energy expenditure. One of the first hypothalamic syndromes described was

Babinski-Frohlich syndrome or hypothalamic infantilism obesity whereby a pituitary tumor led to a disorder characterized by headaches, visual changes, obesity, and hypogonadism, which is now known to be due to hypopituitarism. It is now understood that structural damage to the hypothalamus can lead to obesity including neoplasms, (eg, craniopharyngiomas), vascular malformations, and inflammatory or infiltrative diseases.

Adaptive Responses and Hormonal Changes to Weight Loss

Weight loss itself is difficult for most patients; however, maintaining the weight loss can be even more challenging. There are compensatory changes that occur with weight loss which may promote weight regain due to decreased daily resting energy expenditure (REE) and changes in peripheral signals that affect appetite stimulation and suppression.

Weight loss is associated with a reduction in TEE that is out of proportion to changes in lean body mass, the primary determinant of resting energy expenditure. Liebel and colleagues evaluated 18 obese subjects vs 23 subjects who had never been obese. They were studied at their usual body weight and after losing 10% to 20% of their weight by underfeeding.[31] The 24-hour energy expenditure, resting and nonresting, were evaluated. Results demonstrated that maintenance of a body weight at a level 10% or more below the initial weight was associated with a mean reduction in TEE of 6 ± 3 kcal per kilogram of fat-free mass per day in the subjects who had never been obese ($P < 0.001$) and 8 ± 5 kcal per kilogram per day in the obese subjects ($P < 0.001$). REE and non-REE each decreased 3 to 4 kcal per kilogram of fat-free mass per day in both groups of subjects. The thermic effect of feeding and non-REE increased by approximately 1 to 2 and 8 to 9 kcal per kilogram of fat-free mass per day, respectively, after weight gain. Thus maintenance of a reduced

weight was associated with compensatory changes in energy expenditure which oppose the maintenance of a body weight that is different from the usual weight.

These compensatory changes may account for the challenges in achieving long-term weight loss success. This reduction in TEE appears to persist indefinitely as long as the reduced weight is maintained. The lower TEE is important in that it means that the individual will need to restrict energy intake indefinitely or regain the lost weight.[32]

Furthermore, weight loss is also associated with an increase in the drive to eat and a reduction in satiety. Increased hunger and decreased satiety following weight loss are associated with increases in the 24-hour profile of circulating levels of the orexigenic hormone ghrelin, and reductions in the levels of the anorexigenic hormones PYY, CCK, leptin, and insulin.[33] These changes in appetite-related hormones appear to persist for at least 1 year following weight reduction and may remain altered indefinitely in a manner that promotes weight regain.[34]

Summary

Obesity is a disease with a complex etiology. Food intake is regulated by two complementary drives, the homeostatic and hedonic pathways. The homeostatic pathway controls energy balance by increasing the motivation to eat following depletion of energy stores. In contrast, hedonic or reward-based regulation can override the homeostatic pathway during periods of relative energy abundance by increasing the desire to consume foods that are highly palatable, subsequently leading to obesity. In addition, there are multiple factors which may contribute to a person's specific risk for obesity, including genetic and environmental factors.

REFERENCES

1. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest*. 1986;78(6):1568-1578.
2. Lenard NR, Berthoud HR. Central and peripheral regulation of food intake and physical activity: pathways and genes. *Obesity (Silver Spring)*. 2008;16(suppl 3):S11-S22.
3. Yu JH, Kim MS. Molecular mechanisms of appetite regulation. *Diabetes Metab J*. 2012;36(6):391-398.
4. Vetter ML, Faulconbridge LF, Webb VL, Wadden TA. Behavioral and pharmacologic therapies for obesity. *Nat Rev Endocrinol*. 2010;6(10):578-588.
5. Lee EB, Ahima RS. Central regulation of appetite and satiety behavior. In: Preedy VR, Watson RR, Martin CR, eds. *Handbook of Behavior, Food and Nutrition*. New York, NY: Springer; 2011:1023-1034.
6. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev*. 2013;14(1):2-18.
7. Yeo GS, Heisler LK. Unraveling the brain regulation of appetite: lessons from genetics. *Nat Neurosci*. 2012;15(10):1343-1349
8. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med*. 2002;346(21):1623-1630.
9. Rondinone CM. Adipocyte-derived hormones, cytokines, and mediators. *Endocrine*. 2006;29(1):81-90.
10. Minokoshi Y, Alquier T, Furukawa N, et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*. 2004;428(6982):569-574.
11. Sahu A. Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. *Front Neuroendocrinol*. 2003;24(4):225-253.
12. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002;110(8):1093-1103.
13. Garber AK, Lustig RH. Is fast food addictive? *Curr Drug Abuse Rev*. 2011;4(3):146-162.

14. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. *Nat Rev Neurosci*. 2014;15(6):367-378.
15. Lennerz BS, Alsop DC, Holsen LM, et al. Effects of dietary glycemic index on brain regions related to reward and craving in men. *Am J Clin Nutr*. 2013;98(3):641-647.
16. Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage*. 2008;41(2):636-647.
17. Rankinen T, Bouchard C. Genetics of food intake and eating behavior phenotypes in humans. *Annu Rev Nutr*. 2006;26:413-434.
18. Timpson NJ, Emmett PM, Frayling TM, et al. The fat mass- and obesity-associated locus and dietary intake in children. *Am J Clin Nutr*. 2008;88(4):971-978.
19. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet*. 2007;8(4):253-262.
20. Kral JG, Biron S, Simard S, et al. Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics*. 2006;118(6):e1644-e1649.
21. Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am J Clin Nutr*. 1999; 69(2):179-197.
22. Segal NL, Allison DB. Twins and virtual twins: bases of relative body weight revisited. *Int J Obes Relat Metab Disord*. 2002;26(4):437-441.
23. Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO. Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care*. 1994;17(9):1067-1074.
24. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006; 444(1722):1027-1031.
25. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial etiology. *Proc Natl Acad Sci USA*. 2005;102(31):11070-11075.
26. Musso, G, Gambino, R, Cassader M. Obesity, diabetes and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care*. 2010;33(10):2277-2284.

27. Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency - benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne)*. 2013;4:64.

28. Stunkard A, Berkowitz R, Wadden T, Tanrikut C, Reiss E, Young L. Binge eating disorder and the night-eating syndrome. *Int J Obes Relat Metab Disord*. 1996;20(1):1-6.

29. Beccuti G, Pannain S. Sleep and obesity. *Curr Opin Clin Nutr Metab Care*. 2011;14(4):402-412.

30. Ford ES, Li C, Wheaton AG, Chapman DP, Perry GS, Croft JB. Sleep duration and body mass index and waist circumference among US adults. *Obesity (Silver Spring)*. 2014;22(2):598-607.

31. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med*. 1995;332(10):621-628.

32. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. *Am J Clin Nutr*. 2008; 88(4):906-912.

33. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604.

34. Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. *Clin Sci (Lond)*. 2013;124(4):231-241.

3 Obesity-Related Comorbidities

Introduction

A vast body of data unequivocally documents the direct and indirect links between excessive body weight and a wide spectrum of comorbidities (**Figure 3.1**). Although the underlying pathophysiologic mechanisms are not yet fully elucidated, many of these mechanisms involve an array of factors secreted by metabolically dysfunctional adipose tissue (**Figure 3.2**) (see *Chapter 2*).

Obesity and Inflammation

Obesity has been linked to a chronic state of inflammation which may be involved in the development of comorbidities such as metabolic syndrome, CV disease, non-alcoholic steatohepatitis, and even cancer.[1] The association of obesity and levels of inflammatory biomarkers has been demonstrated in an analysis of data from the 1999-2004 National Health and Nutrition Examination Study (NHANES). Serum concentrations of C-reactive protein (CRP) and fibrinogen were compared across different weight classes. With CRP levels for normal weight individuals as a reference, CRP levels nearly doubled with each increase in weight class from +0.11 mg/dL for overweight to +0.73 mg/dL for obesity class III (**Table 3.1**). Similarly, with normal weight individuals as a reference, fibrinogen levels also increased with increasing weight class and were highest for obesity class III individuals (+93.5 mg/dL). Furthermore, individuals with hypertension or diabetes have higher levels of CRP and fibrinogen levels compared with individuals without hypertension

FIGURE 3.1 — Comorbidities Associated With Obesity

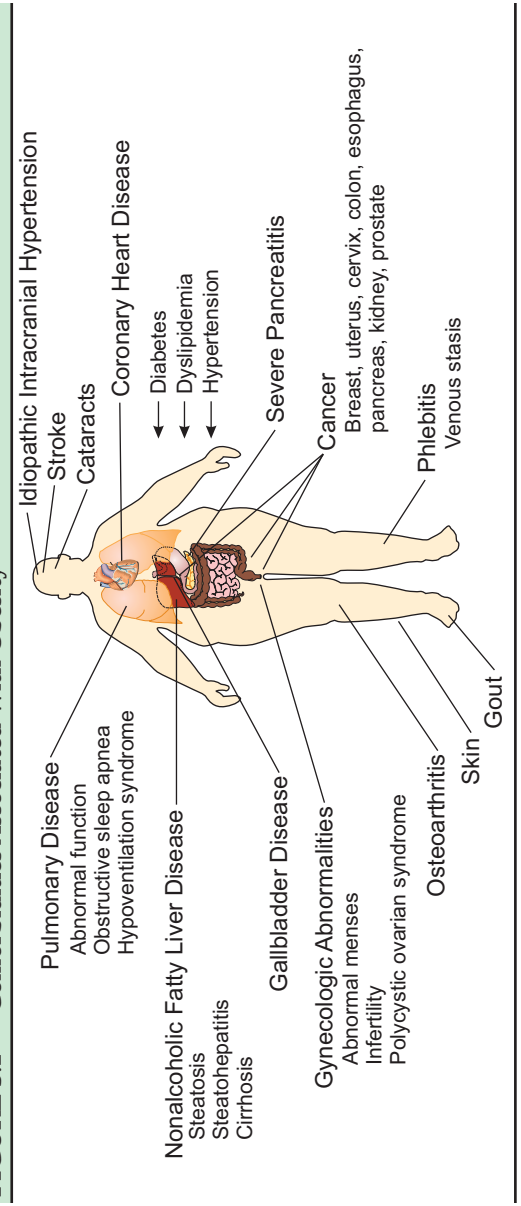


FIGURE 3.2 — Factors Secreted by Adipose Tissue

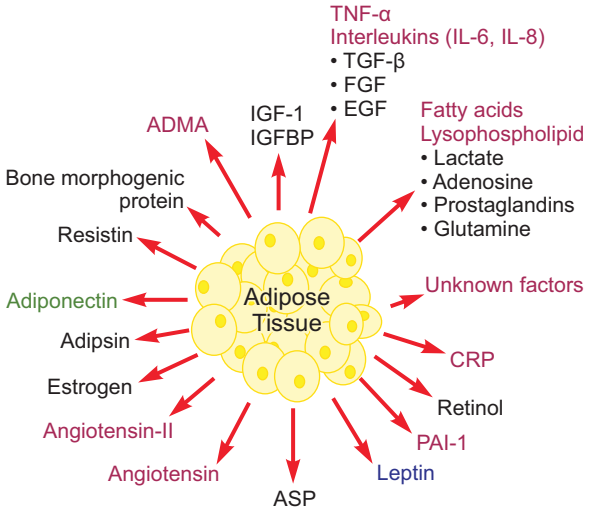


TABLE 3.1 — Associations Between Biomarker Levels and Obesity Class: NHANES 1999-2004

		Change From Reference Value (mg/dL)	
Obesity Class	**BMI**	**CRP**	**Fibrinogen**
Normal weight	<25.0	0.05[a]	287[a]
Overweight	25-29.9	0.11 ± 0.03	11.5 ± 0.39
Class:			
I	30-34.9	0.21 ± 0.03	25.6 ± 5.0
II	35-39.9	0.43 ± 0.09	40.0 ± 7.6
III	≥40	0.73 ± 0.09	9.35 ± 10.1

All *P* values <0.01 compared with reference value.

[a] Reference values.

Nguyen XM, et al. *J Gastrointest Surg*. 2009;13(7):1205-1212.

or diabetes, even when stratified according to BMI (**Table 3.2**).

Prevalence of Major Comorbidities

The associations between obesity and its common comorbidities, diabetes, hypertension, and dyslipidemia, have been reported by a considerable number of epidemiologic studies. The results from a selected sample of such studies are summarized below. Overall, the results from these studies indicate that the prevalence of the major comorbidities of obesity tend to increase with increases in body weight.

■ Diabetes

Obesity, and particularly central adiposity, is the dominant risk factor for the development of type 2 diabetes (T2D). It is also one of the most important modifiable risk factors for the prevention of T2D.[2]

In an analysis of data from adults with diabetes who participated in NHANES 1999-2006, the prevalence of diabetes increased with increasing weight classes, from 8% for normal weight individuals to 43% for individuals with obesity class III.[3]

A considerable body of evidence demonstrates that the long-term risk of T2D increases significantly with increasing body weight.[4] For example, according to data from the Behavioral Risk Factor Surveillance System, the prevalence of diabetes and mean body weight both increased by 49% from 1990 to 2000 (**Figure 3.3-A**). The effect of long-term weight change on the risk for clinical diabetes was evaluated in 114,281 women enrolled in the Nurses' Health Study. As shown in **Figure 3.3-B**, after adjusting for age, body weight was the major risk factor for diabetes during 14-year follow-up. Among women with a 5- to 7.9-kg weight gain, the relative risk for diabetes was 1.9 and for those with an 8.2- to 10.9-kg weight gain, the relative risk was 2.7.

Consistent with these observations, several studies have shown that weight loss is associated with a

TABLE 3.2 — CRP and Fibrinogen Levels According to Diabetes and Hypertension Status

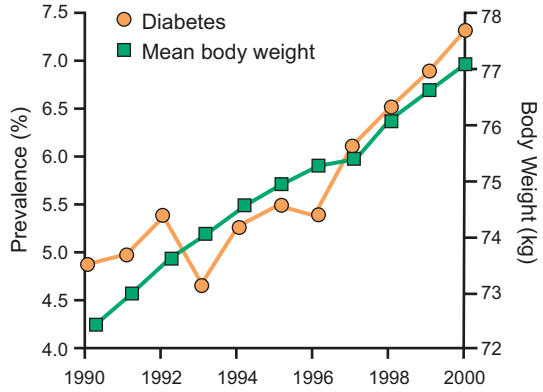
		Mean CRP Levels (mm/dL)				Mean Fibrinogen Levels (mm/dL)			
Obesity Class	**BMI**	**No DM**	**DM**	**No HTN**	**HTN**	**No DM**	**DM**	**No HTN**	**HTN**
Normal weight	<25	0.30	0.63	0.26	0.48	376	413	344	381
Overweight	25-29.9	0.36	0.46	0.35	0.45	364	381	353	376
Class:									
I	30-34.9	0.49	0.55	0.48	0.54	375	402	373	381
II	35-39.9	0.70	0.95	0.68	0.75	401	411	381	392
III	≥40	1.01	1.05	0.99	1.20	442	444	439	436

Key: DM, diabetes mellitus; HTN, hypertension.
$P = 0.02$.

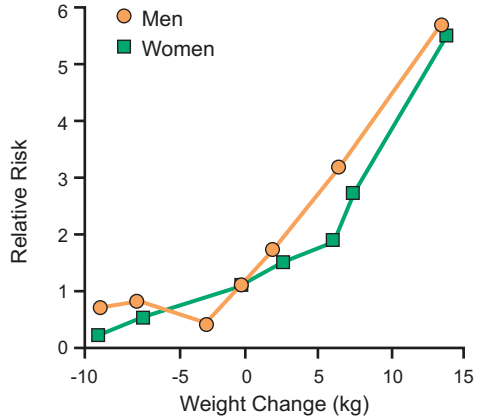
Nguyen XM, et al. *J Gastrointest Surg*. 2009;13(7):1205-1212.

FIGURE 3.3 — Relationships Between Body Weight and Diabetes

A. Relationship Between Increasing Body Weight and Diabetes Prevalence: 1990-2000



B. Relationship Between Weight Gain in Adulthood and the Risk of T2D in Men and Women



Haffner SM. *Obesity (Silver Spring)*. 2006;14(suppl 3):121S-127S.

significant reduction in the risk of diabetes. In a prospective, 20-year study of 7176 British men, the rate of new diabetes was 11.4 per 1000 person-years among obese subjects vs 1.6 among normal-weight subjects (P <0.0001), but the effect of weight change during a 5-year follow-up on the development of diabetes found a relative risk of 0.62 among those losing weight compared with 1.0 for stable weight and 1.76 among those gaining >10% body weight (P <0.0001).[5]

■ Hypertension

Greater body weight is one of the major risk factors for high blood pressure (BP). According to a recent American Heart Association (AHA) estimate, at least 75% of the incidence of hypertension is related directly to obesity.[6] The results of many studies indicate that the prevalence of hypertension increases with increasing body weight class.[7] Although reported prevalence rates have varied somewhat between studies likely due to differences in study populations, the relationship of hypertension prevalence and increasing body weight remains. In one study, the prevalence of hypertension increased from 18.1% in normal weight individuals to 52.3% in those with class III obesity.[8] Thus, individuals with class III obesity had a nearly five times higher risk (adjusted odds ratio [OR] 4.8) for hypertension.

■ Other Coronary Heart Disease Risk Factors

Obesity is a well-documented risk factor for the development of coronary heart disease (CHD) and stroke, especially when coincident with hyperglycemia, hypertension, and/or dyslipidemia.[7] Changes in 10-year CHD risk associated with levels of obesity and the prevalences of hypertension and abnormal total cholesterol level (>200 mg/dL) were assessed using data from 12,500 participants in the 1999-2006 NHANES.[9] The prevalence of hypertension increased according to increases in BMI, from 24% for BMI <25 to 54% for BMI ≥35. The prevalence of abnormal total cholesterol level (>200 mg/dL) increased from 40% for BMI <25 to 48% for a BMI ≥35. Among men, these changes

resulted in an increase in 10-year CHD risk of 3.1% with a BMI <25 to a peak of 5.6% for a BMI of 30 to 34.9. The 10-year CHD risk for women increased from 0.8% with BMI <25 to a peak of 1.5% for BMI ≥35.

A recent study quantified how much of the effects of BMI on CHD and stroke are mediated through BP, cholesterol, and glucose, and how much is independent of these factors.[10] Using data from 97 prospective cohort studies that collectively enrolled 1.8 million participants between 1948 and 2005, and included 57,161 CHD and 31,093 stroke events, HRs of BMI on CHD and stroke with and without adjustment for all possible combinations of BP, cholesterol, and glucose were estimated. For each cohort, the authors excluded participants who were younger than 18 years, had a BMI lower than 20, or who had a history of CHD or stroke. The HR of BMI on CHD and stroke with and without adjustment for all possible combinations of BP, cholesterol, and glucose was estimated. The HR for each 5 kg/m^2 higher BMI was 1.27 for CHD and 1.18 for stroke after adjustment for confounders. These findings suggest that 46% of the excess risk of BMI for CHD and 76% the excess risk for stroke is mediated by these factors. BP was the most important mediator, accounting for 31% of the excess risk for CHD and 65% for stroke. Both overweight (BMI ≥25 to <30) and obesity (BMI ≥30) were associated with a significantly increased risk of CHD and stroke compared with normal weight (BMI ≥20 to <25).

Since obesity, hypertension, diabetes, and dyslipidemia are clinical markers of the metabolic syndrome, an analysis of data from 13,745 adults who participated in NHANES 1999-2004 assessed the relationship of body weight and changes in the prevalences of these comorbidities and the metabolic syndrome itself.[8] With increasing overweight and obesity class, there were increases in the prevalences of hypertension, diabetes, dyslipidemia, and the metabolic syndrome (**Table 3.3**). The adjusted ORs of these comorbidities in individuals with class III obesity were also significantly greater compared with normal weight individuals (**Table 3.3**).

TABLE 3.3 — Prevalence and Adjusted Odds Ratios of Comorbidities According to Body Weight

	Prevalence		
	BMI <25 (%)	**BMI ≥40 (%)**	**Adjusted Odds Ratio for BMI ≥40[a]**
Hypertension	18.1	52.3	4.8
Diabetes	2.4	14.2	5.1
Dyslipidemia	8.9	19.0	2.2
Metabolic syndrome	13.6	39.2	2.0

[a] Normal-weight individuals as the reference.

Nguyen NT, et al. *J Am Coll Surg.* 2008;207(6):928-934.

Concurrent Comorbidities

Since many obese individuals may have multiple concurrent comorbidities, a recent study analyzed the primary care electronic health records of 223,089 adults aged ≥30 years to assess the prevalence and impact of BMI category on the probabilities of concurrent comorbidities.[11]

The presence of concurrent comorbidities was found to be strongly associated with levels of obesity. In normal weight men, the prevalence of multiple comorbidities was 23%, with increases to 27% in overweight, 33% in category I obesity, 38% in category II, and 44% in category III obesity. In women, the pattern was similar except the increases with each stage were higher than those in men (28%, 34%, 41%, 45%, and 51%, respectively). The odds of multiple comorbidities increased successively with each BMI category (**Table 3.4**). For overweight participants, the odds of one disease, compared with none, were 25% higher than for normal weight patients. In category I obese patients, the relative odds were 54% higher, and higher by 81% with category II obesity, and 124% with category III obesity. The effect of increasing BMI category on concurrent comorbidities was similar to that of ageing, with obese patients having a prevalence of concurrent comorbidities similar to that of normal weight patients several decades older.

■ Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a syndrome characterized by repetitive episodes of upper airway obstruction that occur during sleep.[12-14] Associated features include loud snoring, fragmented sleep, repetitive hypoxemia/hypercapnia, and daytime sleepiness. Obesity, particularly central adiposity, are potent risk factors for sleep apnea since they can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and also through the CNS via different interactions of adipokines and

TABLE 3.4 — Impact of BMI Category on Increasing Number of Concurrent Comorbidities

	Relative Odds of…		
BMI Category	**One or More**	**Two or More**	**Three or More**
Gender:			
Male	[Reference]	[Reference]	[Reference]
Female	1.28	1.33	1.36
Underweight	0.82	0.82	0.82
Normal weight	[Reference]	[Reference]	[Reference]
Overweight	1.25	1.29	1.36
Class I obesity	1.54	1.65	1.83
Class II obesity	1.81	2.04	2.34
Class III obesity	2.24	2.63	3.09

Booth HP, et al. *Fam Pract.* 2014;31(1):38-43.

adipocyte-binding proteins on binding receptors that may affect airway neuromuscular control.[14]

An OSA "event" can be either an apnea, characterized by complete cessation of airflow for at least 10 seconds, or a hypopnea in which airflow decreases by 50% for 10 seconds or decreases by 30% if there is an associated decrease in the oxygen saturation or an arousal from sleep. To assess the severity of OSA, the number of events per hour is reported as the apnea-hypopnea index (AHI). An AHI of <5 is considered normal. An AHI of 5-15 is mild; 15-30 is moderate, and >30 events per hour is severe sleep apnea.

In the general adult population, the prevalence of OSA is 2% to 3% among middle-aged women and 4% to 5% among middle-aged men. In contrast, the prevalence among obese individuals has been reported to be ≥30% and from 50% to 98% among the morbidly obese.[13,15] Among individuals referred for diagnostic sleep studies for OSA, 60% to 90% are overweight, and their RR for the development of OSA has been reported to be ≥10.[13,15,16]

The impact of changes in body weight on OSA has been demonstrated by the Wisconsin Sleep Cohort Study[17] and the Sleep Heart Health Study.[18] The overall incidence of moderate to severe OSA over a 5-year period was 11.1% in men and 4.9% in women, respectively. Men with >10-kg weight gain during the follow-up period had a 5-fold risk of increasing their severity of OSA. In contrast, for the same degree of weight gain in women, there was a 2.5-fold risk associated with a similar degree of weight gain. Complementing the available body of observational data are studies on the effects of weight loss which show that reducing OSA severity is possible with a decrease in body weight. Although often limited by few small study samples and the lack of appropriate control groups, the unvarying observation is that weight loss by any means (ie, surgery or caloric restriction) can improve severity of disease in many patients and may be completely curative in some.[15]

■ Osteoarthritis

An increasing body of evidence supports the role of obesity as an independent modifiable risk factor for the development of osteoarthritis (OA), particularly in weight-bearing joints such as the hips and knees.[19-21] In a recent study, 2764 Italian general practitioners provided data from 10 consecutive patients with OA pain.[22] In these 12,827 patients, the most painful joints were the knee (53.6%), the hip (23.6%), and the hand (22.8%). An association with a BMI of ≥25 was found in 74.8% of men and in 68.3% of women. The BMIs associated with knee and hip OA were consistently higher than those associated with hand OA.[22] A case control study also found that relative to a BMI of 24, the risk of knee OA increased progressively from 0.1 in individuals with a BMI <20 to 13.6 in those with a BMI of ≥36.[23]

Although the link between obesity and OA is well established, the etiological relationship has yet to be fully defined since OA has a multifactorial etiology. The biomechanical relationship is well known: increased loads on articular cartilage result in subsequent wear and cartilage breakdown.[21] Conversely, clinical studies have shown that weight loss can have a favorable effect on OA. For instance, one study reported that for every one pound of weight lost, there was a four-pound reduction in the load exerted on the knee for each step taken during daily activities.[24] However, since obesity-related OA can affect not only the weight-bearing joints (hips and knees) but also the hands, this suggests a role for circulating cytokines associated with adipose tissue, including leptin, adiponectin, and resistin, which may influence OA through direct joint degradation or control of local inflammatory processes.[21,25]

■ Cancer

Many prospective cohort studies and systematic reviews have confirmed a significant association between obesity and cancer. The strongest association is between an elevated BMI and cancer risk and

mortality. Historical data from the past 25 years indicate that obesity is a cause of approximately 14% of cancer deaths in men and up to 20% of cancer deaths in women.[26] The American Cancer Prevention Study II followed >900,000 subjects who were free from cancer in 1982 and had a mean follow-up of 16 years.[27] Among those with a BMI ≥40, mortality from all causes of cancer was 52% higher in men and 62% higher in women compared with those with a normal BMI. The Million Women Study from the United Kingdom recruited over 1.2 million women, aged 50 to 64 years during 1996 to 2001 and followed for a mean of 5.4 years for cancer incidence and 7 years for cancer mortality.[28] Increasing BMI was associated with a significant increase in risk for 10 out of 17 of the most common types of cancer. A prospective study among 287,700 men in the NIH-AARP Diet and Health Study found that during a mean follow-up of 5 to 6 years, the relative risk for mortality from prostate cancer was 1.46 and 2.12 for a BMI ≥30 and ≥35, respectively.[29]

A systematic review and meta-analysis of 221 datasets from 141 publications that included 282,137 incident cancer cases determined the RRs for 20 cancer types associated with each five-point increment in BMI.[30] For example, in a man with a BMI of 28, the RR for colon cancer would be 1.24 compared with a man with a BMI of 23. Similarly, in a man with a BMI of 32, the RR for colon cancer would be 2.48 compared with a man with a BMI of 23. In a woman with a BMI of 28, the RR for colon cancer would be 1.09 compared with a woman with a BMI of 23. If that women had a BMI of 32, her RR for colon cancer would be 2.18 compared with a woman with a BMI of 23.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study that followed more than 368,000 men and women who were cancer-free at for a mean of 6.1 years, a BMI ≥29.4 was significantly associated with the risk of colon cancer in men but not women.[31] Conversely, the RR for renal cell carcinoma associated with increased BMI in women was 2.25,

but no significant increase was observed for men (RR, 1.22).[32] Therefore, these results indicate a progressive increment in RR by BMI that can differ by cancer type and gender.

■ Depression

A reciprocal association between obesity and major depressive disorder (MDD) has long been recognized, specifically that obesity increases the risk of MDD (and other psychiatric disorders) and conversely, the presence of MDD increases the risk of weight gain. For example, the National Epidemiologic Survey on Alcohol and Related Conditions evaluated the relationship between BMI and psychiatric disorders in 41,654 individuals.[33] Compared with normal weight subjects, BMI was significantly associated with mood, anxiety, and personality disorders. The odds ratio for a psychiatric disorder was 1.21- to 2.08-fold greater among obese (BMI 30-39.9) and extremely obese (BMI ≥40) individuals, and the OR for a lifetime prevalence of MDD was 1.53 and 2.02 among obese and extremely obese compared with normal weight subjects.

Another major survey of 217,379 US community-dwelling adults found that individuals with current depression or a lifetime diagnosis of depression or anxiety were significantly more likely to have unhealthy behaviors including obesity, smoking, physical inactivity, binge drinking, and heavy drinking.[34] The adjusted OR for coincident depression and obesity (BMI ≥30) was 1.6 vs 1 for nonobese subjects, and the OR increased with increasing severity of MDD. In a study among 4641 middle-aged women, the prevalence of moderate or severe MDD increased from 6.5% with a BMI <25 to 25.9% with a BMI >35.[35] The OR for having MDD was 4.4 for a BMI of 30 to 35 and 4.95 for a BMI of ≥35.

A recent systematic review and meta-analysis of 15 studies ($n = 58,745$) found that obesity at baseline increased the risk of onset of depression at follow-up (OR 1.55; $P < 0.001$).[36] This association was more pronounced for MDD than for depressive symptoms

($P = 0.05$). Overweight also increased the risk of onset of depression at follow-up (OR 1.27; $P < 0.01$). Conversely, depression at baseline increased the odds for developing obesity (OR 1.58; $P < 0.001$).

■ Gallbladder Disease

The prevalence of cholesterol gallstones is increased in obese persons, more commonly in women than in men.[37-39] The risk is especially high in those with the highest BMI. The increased prevalence of stones is mostly due to supersaturation of bile with cholesterol because of an increased synthesis by the liver and secretion into bile.

The effects of overweight and obesity (BMI >30) on symptomatic gallstones were assessed in the 58,400 participants in a Swedish Twin Study. Overweight and obesity were both associated with a significant increase in the risk of symptomatic gallstones (OR = 1.86 and 3.38, respectively).[38] A separate analysis of the Health Professionals Follow-Up Study, a prospective cohort study in 29,847 US men, sought to determine whether abdominal obesity, as measured by abdominal circumference and/or waist-to-hip ratio, is a separate risk factor for symptomatic gallstones.[40] Men with waist circumference ≥102.6 cm (40.4 in) had a significantly greater risk (RR 2.29; $P < 0.001$ for trend) for symptomatic gall stones compared with men with waist circumference <86.4 cm (34 in). Men with a waist-to-hip ratio ≥0.99 also had a significantly greater risk for symptomatic gall stones (RR 1.78; $P < 0.001$ for trend) compared with men with a waist-to-hip ratio <0.89.

Gallbladder disease is a common cause of hospitalization, especially among women, and has a considerable impact on health care costs. A large epidemiologic study from England and Scotland found a significant association between obesity and symptomatic gall bladder disease among 1.3 million women (mean age, 56 years).[39] Women with a higher BMI at study entry were more likely to be admitted and to spend more days in the hospital for symptomatic gallbladder disease. For each 1000 person-years of follow-up, women with BMI

18.5 to 24.9 spent a mean of 16.5 days hospitalized vs 44 days for women with BMI 30 to 39.9.

Weight loss also increases the risk of gallstones. The prevalence of new gallstones reaches 10% to 12% after 8 to 16 weeks of a low-calorie diet and more than 30% within 12 to 18 months after gastric by-pass surgery.[37,39,41] About one third of the stones are symptomatic. Risk factors for gallstones during weight loss are; a relative weight loss >24% of initial body weight, weight loss rate of >1.5 kg per week, a very low calorie diet with no fat, a long overnight fast period, and a high serum triglyceride level.

■ Acute Pancreatitis

Many studies have shown a significant association between obesity and acute pancreatitis (AP), not only as a risk factor for its development but also as a prognostic factor for its associated outcomes.[42-46]

One meta-analysis of five studies, including a total of 739 patients, found that severe AP was significantly associated with obesity (OR 2.9). Among these obese patients, significantly more systemic (OR 2.3) and local complications occurred (OR 3.8), and mortality was higher (OR 2.1).[42] Another recent meta-analysis of 12 clinical studies with a total of 1483 patients found that compared with nonobese patients, obese patients had a significantly increased risk of severe AP (RR 2.20; $P < 0.05$), local complications (RR 2.68; $P < 0.05$), systemic complications (RR 2.14; $P < 0.05$), and in-hospital mortality (RR 2.59; $P < 0.05$).[46]

Although the association between AP occurrence and complications and BMI is well-established, such correlations in overweight individuals are less well known. A meta-analysis of eight studies that included 939 patients sought to determine if there is a correlation between overweight and the incidence and prognosis of severe AP.[47] The risks for severe AP, local complications, and mortality (OR 2.48, OR 2.58, and OR 3.81, respectively), were increased in overweight patients compared with normal-weight patients. However, there was no significant difference in the incidence

of systemic complications between overweight and normal-weight patients.

While most studies to date have used BMI as the measure of obesity, two recent prospective cohort studies assessed other measures of adiposity. One study found that the risk of AP among individuals with a waist circumference of >105 cm had a 2-fold increased risk (RR 2.37) for AP compared with individuals with a waist circumference between 75 and 85 cm.[48] The other study found significant associations between visceral fat volume as measured by computed tomography (CT) scanning and the subsequent development of severe AP ($P = 0.003$) as well as between mortality and visceral fat volume ($P = 0.019$).[49]

■ **Non-alcoholic Fatty Liver Disease (NAFLD)**

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disorders that range from simple steatosis to nonalcoholic steatohepatitis (NASH) and, ultimately, cirrhosis and hepatocellular carcinoma.[50] Studies of NAFLD prevalence and incidence indicate that the diagnosis is heterogeneous and relies on a variety of assessment tools, including liver biopsy, radiological tests such as ultrasonography, and blood testing such as liver enzymes.[51] NAFLD affects ~15% to 30% of the general population, and has a prevalence of ~70% in people with T2D.[52]

Many studies have identified obesity as a risk factor for NAFLD. In an analysis of data from 832 Hispanic adults in which the diagnosis of NAFLD was based on ultrasound and no history of alcohol abuse or hepatitis C infection, a BMI >26.9 was significantly and independently associated with NAFLD with an odds ratio of 6.2.[53] In a cross-sectional study of 326 Israelis who participated in a National Health Survey, the prevalence of NAFLD was 30%; NAFLD was more common in men (38%) than in women (21%), and obesity (BMI ≥30) was independently associated with NAFLD (odds ratio 2.9).[54] A recent meta-analysis found that NAFLD has an increased overall mortality (OR 1.57) deriving from liver-related and CV disease, and a 2-fold risk of diabetes.[55]

■ **Polycystic Ovarian Syndrome (PCOS)**

The polycystic ovary syndrome (PCOS) is a characterized by hyperandrogenism and chronic oligo-anovulation. However, many features of the metabolic syndrome are inconsistently present in the majority of women with PCOS.[56] Approximately 50% of PCOS women are overweight or obese and most of them have the abdominal obesity phenotype.[56] However, obesity is not a part of the PCOS phenotype in many parts of the world. Given the high prevalence of PCOS among relatively thin populations, obesity per se is likely not a direct cause of PCOS. However, obesity does exacerbate many aspects of the phenotype, especially CV risk factors such as glucose intolerance, insulin resistance, and dyslipidemia.[57] It is also associated with a poor response to infertility treatment and an increased risk for pregnancy complications in those women who do conceive.[58]

While many women with PCOS are overweight, obese, or centrally obese, the effect of excess weight on the outcomes of PCOS is inconsistent. A recent systematic review and meta-analysis of studies that enrolled a total of 15,129 women described the prevalence of overweight, obesity, and central obesity in women with and without PCOS.[59] Overweight or obese women with PCOS had decreased sex hormone-binding globulin (SHBG), increased total testosterone, free androgen index, hirsutism, fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance index, and worsened lipid profile. Obesity significantly worsened all metabolic and reproductive outcomes measured except for hirsutism compared with normal weight women with PCOS. In overweight women there were no differences in total testosterone, hirsutism, total cholesterol, and low-density lipoprotein cholesterol compared with normal weight women and no differences in SHBG and total testosterone compared with obese women. Central obesity was associated with higher fasting insulin levels. The Australian Longitudinal Study on Women's Health was

a community-based observational study that enrolled 9145 women aged 28-33 years.[60] Self-reported PCOS prevalence was 5.8%. Women reporting PCOS had higher weight, mean BMI (32.5), and greater 10-year weight gain (2.6 kg). BMI was the strongest correlate of PCOS status with every BMI increment increasing the risk of reporting PCOS by 9.2%.

The relationship between PCOS and obesity is a complicated one. Not all women who have PCOS are obese, and not all obese women have PCOS. Thus, it is not clear whether PCOS makes it easier for a woman to put on weight, or if the extra weight causes a woman to develop PCOS.[59] Certainly, obese is a common finding in PCOS and aggravates its metabolic features such as insulin resistance.

■ **Chronic Renal Failure (CRF)**

Although obesity has been implicated as a possible risk factor for microalbuminuria in individuals with hypertension and diabetes, general population studies suggest that obesity also may be harmful to the kidneys in individuals without hypertension, diabetes, or preexisting renal disease.[61] A nationwide, population-based, case-control study in Sweden assessed the effect of body weight and the risk of moderately severe CRF. Eligible cases were men (n =597) and women (*n* = 329) whose serum creatinine levels, for the first time and permanently were ≥3.4 mg/dL (300 μmol/L) and 2.8 mg/dL (250 μmol/L), respectively.[61] Using the World Health Organization (WHO) cut points for BMI levels, there were significant 3-fold increases in both men and women with a BMI ≥35. Men and women who reported a BMI ≥25 at age 20 had a significant 3-fold elevated risk for CRF compared with patients with BMI <25. BMI at age 40 and at age 60 showed similar relationships with CRF risk as did highest lifetime BMI.

Metabolically Healthy Obesity?

Although obesity is typically accompanied by unfavorable metabolic profiles, it has been reported that this may not always be the case. The term "metabolically healthy obesity (MHO)" has been used to describe an obese phenotype that does not have the burden of any metabolic abnormalities. Although the definitions of and criteria for MHO vary considerably,[62] one study examined the MHO phenotype using NHANES, a nationally representative sample of adults living in the United States and found a prevalence of 32% among obese adults over the age of 20.[63]

Several epidemiologic studies have shown that metabolically healthy obese participants are not at increased risk of developing CV disease over 3 to 13 years of follow-up compared with healthy nonobese[64-70] and are at lower risk compared with MHO participants.[71] However, there are inconsistencies in the data, and other studies with an extended follow up period (>15 years) showed that obese participants without metabolic syndrome at baseline were still at increased risk of major CV disease events compared with healthy nonobese.[72-74]

A recent systematic review and meta-analysis of eight studies (*n* = 61,386; 3988 events) that evaluated participants for all-cause mortality and/or CV events found that MHO individuals had an increased risk (RR; 1.24) for events only when compared with metabolically healthy normal-weight individuals in studies with 10 or more years of follow-up were considered.[75] All metabolically unhealthy groups had a similarly elevated risk: normal weight (RR: 3.14), overweight (RR: 2.70), and obese (RR: 2.65). The authors conclude that obese individuals have an increased risk for death and CV events over the long-term regardless of metabolic status, and that metabolically unhealthy overweight is also associated with these adverse outcomes.

REFERENCES

1. Nguyen XM, Lane J, Smith BR, Nguyen NT. Changes in inflammatory biomarkers across weight classes in a representative US and inflammation. *J Gastrointest Surg*. 2009;13:1205-1212.
2. Landsberg L, Aronne, LJ, Beilin LJ, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment. A Position Paper of the Obesity Society and the American Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2013;15:14-33.
3. Nguyen NT, Nguyen XM, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006. *Obes Surg*. 2011;21:351-355.
4. Haffner SM. Relationship of metabolic risk factors and development of cardiovascular disease and diabetes. *Obesity*. 2006;14(suppl):121S-127S.
5. Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health.* 2005;59:134-139.
6. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Strokes Statistics Subcommittee. Executive summary: heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):143-152.
7. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18-e209.
8. Nguyen NT, Magno CP, Lane KT, et al. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. *J Am Coll Surg.* 2008;207:928-934.
9. Nguyen NT, Nguyen XM, Wooldridge JB, et al. Association of obesity with risk of coronary heart disease: Findings from the National Health and Nutrition Examination Survey, 1999-2006. *Surg Obes Relat Dis.* 2010;6:465-469.
10. The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hafifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet.* 2014;383(9921):970-983.
11. Booth HP, Prevost AT, Gulliford MC. Impact of body mass index on prevalence of multimorbidity in primary care: cohort study. *Fam Pract*. 2014;31(1):38-43.
12. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care*. 2008;31(suppl 2):S303-S309.
13. Lam JC, Mak JC, Ip MS. Obesity, obstructive sleep apnea and metabolic syndrome. *Respirology*. 2012;17:223-236.
14. Schwartz AR, Patil SP, Laffan AM, et al. Obesity and obstructive sleep apnea—pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc*. 2008;5:185-192.
15. Punjabi N. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5:136-143.
16. Pi-Sunyer X. The medical risks of obesity. *Postgrad Med*. 2009;121:21-33.
17. Peppard PE, Young T, PaltaM, et al. Longitudinal study of moderate weight change of sleep-disordered breathing. *JAMA*. 2000;284:3015-3021.
18. Newman AB, Foster G, Givelber R, et al. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med*. 2005; 165:2408-2413.
19. Magliano M. Obesity and arthritis. *Menopause Int*. 2008; 14:149-154.
20. Grotle M, Hagen KB, Natvig B, et al. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord*. 2008;9:132.
21. Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint Bone Spine*. 2013;80(6):568-573.
22. Cimmino MA, Scarpa R, Caporali R, et al. Body mass and osteoarthritic pain: results from a study in general practice. *Clin Exp Rheumatol*. 2013;31(6):843-849.
23. Coggon D, Reading I, Croft P, et al. Knee osteoarthritis and obesity. *Intern J Obesity*. 2001;25:622-627.
24. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduced knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis Rheum*. 2005;52(7):2026-2032.

25. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol*. 2010;22:533-537.

26. Wolin KY, Carson K, Colditz GA. Obesity and cancer. *The Oncologist*. 2010;15:556-565.

27. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348:1625-1638.

28. Reeves GK, Pirie K, Beral V, et al; Million Women Study collaboration. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335:1134.

29. Wright ME, Chang SC, Schatzkin A, et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer*. 2007;109:675-684.

30. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.

31. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst.* 2006;98(13):920-931.

32. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer.* 2006;118:728-738.

33. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med*. 2008;70(3):288-297.

34. Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry.* 2008;30(2):127-137.

35. Simon GE, Ludman EJ, Linde JA, et al. Association between obesity and depression in middle-aged women. *Gen Hosp Psychiatry*. 2008;30(1):32-39.

36. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67:220-229.

37. Erlinger TP, Pollack H, Appel LJ. Nutrition-related cardiovascular risk factors in older people: results from the Third National Health and Nutrition Examination Survey. *J Am Geriatr Soc*. 2000;48(11):1486-1489.

38. Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall HU. Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. *J Intern Med*. 2007; 262(5):581-587.

39. Liu B, Balkwill A, Spencer E, Beral V; Million Women Study Collaborators. Relationship between body mass index and length of hospital stay for gallbladder disease. *J Public Health (Oxf)*. 2008;30(2):161-166.

40. Tsai CJ, Leitzmann MF, Willett WC, Biovannucci EL. Prospective study of abdominal adiposity and gallstone disease in US men. *Am J Clin Nutr*. 2004;80:38-44.

41. Everhart JE. Contributions of obesity and weight loss to gallstone disease. *Ann Intern Med*. 1993;119(10):1029-1035.

42. Martínez J, Sánchez-Payá J, Palazón JM, et al. Is obesity a risk factor in acute pancreatitis? A meta-analysis. *Pancreatology*. 2004;4:42-48.

43. De Waele B, Vanmierlo B, Van Nieuwenhove Y, Delvaux G. Impact of body overweight and class I, II and III obesity on the outcome of acute biliary pancreatitis. *Pancreas*. 2006; 32(4):343-345.

44. Al Mofleh IA. Severe acute pancreatitis: pathogenetic aspects and prognostic factors. *World J Gastroenterol.* 2008;14(5):675-684.

45. Hong S, Qiwen B, Ying J, et al. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2011;23:1136-1143.

46. Chen SM, Xiong GS, Wu SM. Is obesity an indicator of complications and mortality in acute pancreatitis? An updated meta-analysis. *J Dig Dis*. 2012;13:244-2451.

47. Wang SQ, Li SJ, Feng QX, et al. Overweight is an additional prognostic factor in acute pancreatitis: a meta-analysis. *Pancreatology*. 2011;11:92-98.

48. Sadr-Azodi O, Orsini N, Andrén-Sandberg Å, Wolk A. Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol*. 2013;108:133-139.

49. O'Leary DP, O'Neill D, McLaughlin P, et al. Effects of abdominal fat distribution parameters on severity of acute pancreatitis. *World J Surg*. 2012;36:1679-1685.

50. Preiss D, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, athogenesis and treatment considerations. *Clin Sci (Lond).* 2008;115(5):141-150.

51. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274-285.

52. Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. *Atherosclerosis*. 2007; 191(2):235-240.

53. Riquelme A, Arrese M, Soza A, et al. Non-alcoholic fatty liver disease and its association with obesity, insulin resistance and increased serum levels of C-reactive protein in Hispanics. *Liver Int*. 2009;29(1):82-88.

54. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. *Liver Int*. 2006;26(7):856-863.

55. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43:617-649.

56. Gambineri A, Pelusi C, Vicennati V, et al. Obesity and the polycystic ovary syndrome. *Int J Obes Relat Metab Disord*. 2002;26:883-896.

57. Pasquali R, Gambineri A. Glucose intolerance states in women with the polycystic ovary syndrome. *J Endocrinol Invest.* 2013; 36:648-653.

58. Legro RS. Obesity and PCOS: implications for diagnosis and treatment. *Semin Reprod Med.* 2012;30:496-506.

59. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev.* 2013;14:95-109.

60. Teede HJ, Joham AE, Paul E, et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring).* 2013;21:1526-1532.

61. Ejerblad E, Fored CM, Lindblad P, et al. Obesity and risk for chronic renal failure. *JASN*. 2006;17:1695-1702.

62. Roberson LL, Aneni EC, Maziak W, et al. Beyond BMI: The "Metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality – a systematic review. *BMC Public Health*. 2014;14:14.

63. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: Prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). *Arch Intern Med.* 2008;168:1617-1624.

64. Katzmarzyk PT, Janssen I, Ross R, et al. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. *Diabetes Care*. 2006;29:404-409.

65. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*. 2004;109:706-713.

66. Song Y, Manson JE, Meigs JB, et al. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. *Am J Cardiol*. 2007;100:1654-1658.

67. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91:2906-2912.

68. St-Pierre AC, Cantin B, Mauriège P, et al. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ*. 2005;172:1301-1305.

69. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care*. 2011;34:210-215.

70. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab*. 2012;97:2482-2488.

71. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in metabolically benign obese individuals. *Obesity (Silver Spring)*. 2012;20:651-659.

71. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121:230-236.

73. Flint AJ, Hu FB, Glynn RJ, et al. Excess weight and the risk of incident coronary heart disease among men and women. *Obesity*. 2010;18:377-383.

74. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care*. 2013;36(8):2294-2300.

75. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. *Ann Intern Med*. 2013; 159(11):758-769.

4

A Complications-Centric Approach to the Treatment of Obesity

A New Perspective

The revised Comprehensive Diabetes Management Algorithm published by the American Association of Clinical Endocrinologists (AACE) in April 2013 focuses on the whole patient and includes specific treatment algorithms for the management of overweight and obese patients and those with prediabetes and CV risk. Regarding overweight/obese patients, it proposes a "complications-centric model" for treatment of obesity (**Figure 4.1**). This evidence-based approach to the treatment of obesity incorporates lifestyle, medical, and surgical options, balances risks and benefits, and emphasizes medical outcomes that address the complications of obesity rather than cosmetic treatment goals.[1]

Is Obesity a "Disease"?

Of particular interest regarding this new algorithm is its stated fundamental premise namely: "Obesity is a disease with genetic, environmental, and behavioral determinants that confers increased morbidity and mortality."[1,2] This premise is not new. The 1998 National Heart, Lung, and Blood Institute (NHLBI) Clinical Guidelines for Clinical Treatment of Overweight and Obesity also stated that "obesity is a complex multifactorial chronic disease that develops from an interaction of genotype and the environment."[3] There is considerable evidence that obesity is associated with cardiometabolic and other comorbidities (see *Chapter 3*) and consequently, with increased risk for morbid-

FIGURE 4.1 — Complications-Centric Model for Care of the Overweight/Obese Patient

Garber AJ, et al. *Endocr Pract.* 2013;19(2):327-336.

ity, mortality, decreased quality of life, and increased health care cost.

A resolution stating that obesity should be reclassified as a multi-metabolic and hormonal disease state was presented to the American Medical Association (AMA) House of Delegates at its June 2013 meeting by the AACE, and supported by the American College of Cardiology, the Endocrine Society, and the American Society for Reproductive Medicine, as well as the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Society of Bariatric Physicians. Although this resolution was ultimately accepted by the AMA House of Delegates, arguments, pro and con, continue regarding the impact and implications of this decision. Regardless of how obesity is classified, there is a need for more clinically relevant and patient-focused treatment guidelines.

A New Focus: From Weight Loss to Risk Reduction

Obesity is typically defined in terms of anthropometric measures, primarily BMI, which originally was designed as an epidemiologic research tool, ie, a rough population-level indicator of body weight. Many observational studies have consistently reported strong associations between elevated BMI values and morbidity and mortality risk. In one large study, for example, each five-point increase in BMI above 25 kg/m^2 was associated with increases of 29% for overall mortality, 41% for vascular mortality, and 210% for diabetes-related mortality.[4] However, BMI is not an optimal method for measuring actual "body fatness" in an individual.[5,6] For example, as the 1998 NHLBI Guidelines pointed out, some people with a BMI in the "normal" range can have excessive body fat, as well as metabolic dysfunctions. Others with BMIs in the same obese range have no excess fat or cardiometabolic dysfunction. Conversely, some individuals with high

BMIs are normal metabolically and may have normal blood pressure and cholesterol levels.[3]

The difference between the long-established (1998) NHLBI Clinical Guidelines for Overweight and Obesity and the recent AACE guidelines does not reside in their specific clinical assessment and treatment recommendations. Rather, the AACE Obesity Treatment Algorithm adopts a complications-centric model that focuses on risk assessment, staging, and stage-specific interventions, one of which is weight loss treatment itself. Thus, one difference between a BMI-centric model and a complications-centric model is that the primary treatment goal of the former is weight loss itself, while with the complications-centric model, the primary treatment goal is reduction of the risk for (or at least slowing the progression of) the many comorbidities associated with obesity. In other words, in the AACE algorithm, *weight loss itself is a key therapeutic intervention* for risk reduction in an individual patient.

The Premise: Weight Loss Reduces Comorbidity and Mortality Risk

A fundamental premise of the complications-centric approach is that weight loss resulting from diet and lifestyle changes alone or in combination with pharmacologic or surgical treatment can reduce the risk of many of the obesity-associated comorbidities in a progressively "dose-related" manner. The large body of evidence demonstrating the clinical benefits of weight loss itself is reviewed in *Chapter 5*.

For example, 1-year results from the ongoing Look AHEAD (Action for Health in Diabetes) trial provide empirical support for the assertion that modest weight losses of 5% to 10% of initial weight are sufficient to produce significant, clinically relevant improvements in CVD risk factors in overweight and obese patients with T2D.[7] Look AHEAD is a multicenter, randomized clinical trial assessing the long-term effects of lifestyle interventions on CV morbidity and mortality in 5145

overweight or obese patients with type 2 diabetes who were randomized to intensive lifestyle intervention (ILI) or to usual care. After 1 year, patients were divided into the following categories based on their weight changes from baseline to 1 year: gained >2%; remained weight stable (±2%); lost ≥2% to 5%; lost ≥5% to 10%; lost ≥10% to 15%; or lost ≥15%. There was a strong graded association for changes in glucose, A1C, SBP, DBP, triglycerides, and HDL cholesterol (all *P* values <0.0001). Each higher increment of weight loss was associated with greater improvements in the risk factor. Furthermore, the odds of having a clinically meaningful improvement in risk were strongly related to the magnitude of weight loss achieved such that the odds of a clinically meaningful improvement also increased with each weight loss increment.

Evaluation, Risk Assessment, and Disease Staging

According to the 2013 AACE Obesity Treatment Algorithm, patients who will benefit the most from medical and surgical intervention have obesity-related comorbidities.[1] Therefore, the new guidelines recommend that "the presence and severity of complications, regardless of patient BMI, should guide treatment planning and evaluation. Once these factors are assessed, therapeutic goals can be set and appropriate types and intensities of treatment can be selected." Much, if not most, of the relevant information for clinical risk assessment and disease staging of overweight/obese patients is readily available to the clinician in routine clinical practice. Additional information can be obtained from several recently validated assessment and disease staging tools.

- **Edmonton Obesity Staging System (EOSS)**

In 2009, Sharma and colleagues proposed a new clinical staging system for obesity—the Edmonton Obesity Staging System (EOSS)—intended to complement (but not replace) current anthropometric clas-

sifications of obesity.[5] This measure ranks overweight/obese individuals according to a 5-point ordinal scale, which incorporates obesity-related comorbidities and functional status (**Table 4.1**). The EOSS is based on simple clinical assessments that include medical history and clinical and functional assessments, as well as simple routine diagnostic investigations.

Subsequently, Padwal and colleagues assessed the ability of the EOSS to predict all-cause mortality using a nationally representative US population sample (NHANES III [1988–1994] and NHANES [1999–2004] with mortality follow-up through to the end of 2006).[6] Final unweighted sample sizes were 4367 overweight/obese individuals from the NHANES III 1988–1994 population and 3600 from the NHANES 1999–2004 population. EOSS scores were a strong predictor of increasing all-cause mortality in the overall population (**Figure 4.2**). This ability was independent of BMI and the presence of other risk factors such as metabolic syndrome. The results also were similar among individuals who never smoked.[6]

There are several limitations of this staging system. For example, the comorbidities within EOSS, such as diabetes and OA, were initially and arbitrarily assigned to be equivalent in terms of their burden of illness. Therefore, it is not yet clear whether certain comorbidities should receive a higher weighting. Another limitation is that the EOSS was based on analysis of total mortality data only. A final limitation is that even though the EOSS system is based on a simple clinical rationale, its sensitivity, specificity, reliability, and utility in clinical practice has not yet been assessed. Such studies are currently underway.[6]

■ Metabolic Syndrome

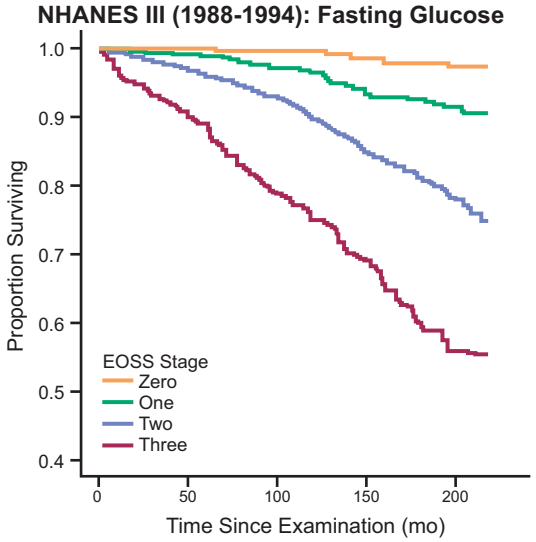
The metabolic syndrome is "a complex cluster of interrelated risk factors for CV disease and diabetes which occur together more often than by chance alone."[8] These risk factors include dyslipidemia, central obesity, hypertension, and/or insulin resistance.

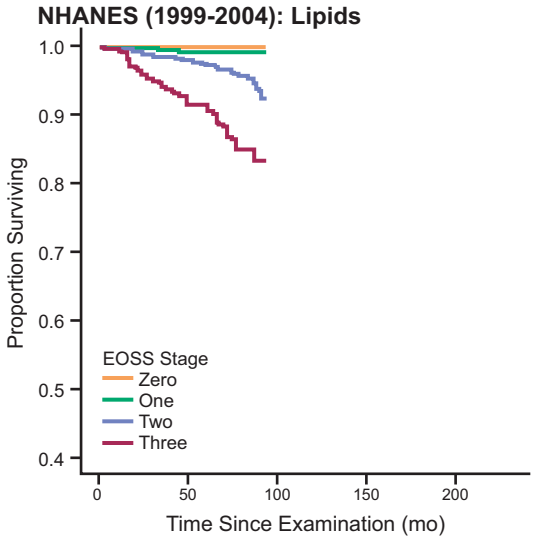
TABLE 4.1 — Edmonton Obesity Staging System (EOSS)

Stage	Cardiometabolic	Mechanical/Functional
0	No risk factors	No functional impairments or impairments in well-being
1	Subclinical risk factors: • Prediabetes • Metabolic syndrome • NAFLD	Mild limitations and impairment of well-being
2	End-stage metabolic disease: • Type 2 diabetes • Hypertension • Sleep apnea	Moderate limitations and impairment of well-being
3	End-stage CVD disease: • MI • Heart failure • Stroke	Significant limitations and impairment of well-being
4	Significant limitations and impairment of well-being	Severe limitations and impairment of well-being

Sharma AM, Kushner RF. *Int J Obes (Lond)*. 2009;33(3):289-295.

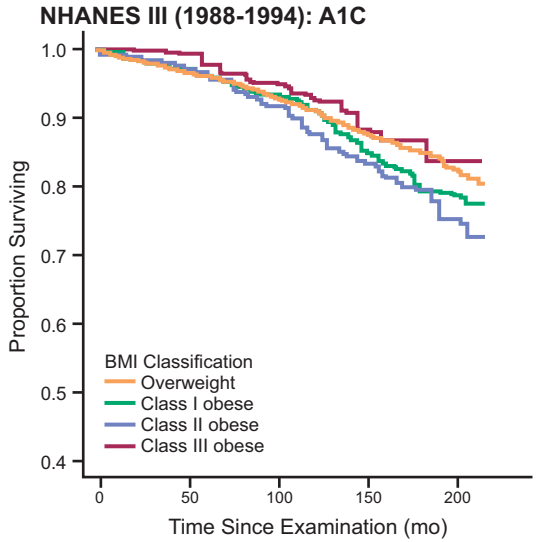
FIGURE 4.2 — Prediction of All-Cause Mortality Using EOSS or BMI Criteria

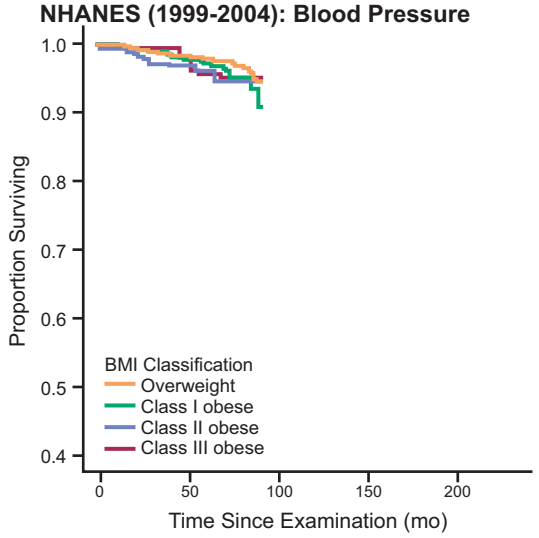




Continued

FIGURE 4.2 — *Continued*





Padwal RS, et al. *CMAJ*. 2011;183(14):E1059-E1066.

Different diagnostic criteria for the metabolic syndrome have been proposed by various organizations, including the:

- National Cholesterol Education Program's Adult Treatment Panel III report (ATP III)
- WHO
- International Diabetes Foundation (IDF)
- AACE
- AHA/NHLBI.

However, in 2009, a joint meeting of IDF Task Force on Epidemiology and Prevention, NHLBI, AMA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity resulted in a unified set of diagnostic criteria.[8] Three abnormal findings out of the five listed in **Table 4.2** would support a diagnosis of metabolic syndrome. The main difference among previous criteria was whether a measure of central adiposity, such as waist circumference, should be an obligatory component, and if so, what measurement cut points should be used. It was agreed that measurement of waist circumference should not be an obligatory component, but that waist measurement should continue to be a useful preliminary screening tool.[8]

The presence of the metabolic syndrome is a clinically useful indicator of high morbidity and mortality risk. However, it is not an absolute risk since it does not consider many of the patient-specific factors that determine absolute risk such as age, sex, ethnicity, cigarette smoking, and LDL-cholesterol levels. Nonetheless, patients with the metabolic syndrome are at twice the risk of developing CVD over the subsequent 5 to 10 years as those without the syndrome. In addition, the metabolic syndrome confers a 5-fold increase in the risk developing T2D.[8]

■ Cardiometabolic Disease Staging System (CMDS)

Given the strong relationship between a diagnosis of cardiometabolic syndrome and increased risk of

TABLE 4.2 — Risk Factors of Metabolic Syndrome

Trait	Categorical Cut Point
Elevated waist circumference	≥35 inch (female) ≥40 inch (male) *Note:* Population/country specific definitions
Elevated triglycerides (or drug treatment to reduce triglycerides)	≥150 mg/dL
Reduced HDL-C (or drug treatment for dyslipidemia)	<40 mg dL (male) <50 mg/dL (female)
Elevated blood pressure (or hypertension history or drug therapy)	≥Systolic 130 mm Hg and/or diastolic 85 mm Hg
Elevated fasting glucose (or drug therapy for diabetes or hyperglycemia)	≥100 mg/dL

NOTE: Three abnormal findings out of the five listed above would support a diagnosis of metabolic syndrome.

Alberti KG, et al. *Circulation*. 2009;120(16):1640-1645.

morbidity and mortality, Guo and associates proposed the 5-stage Cardiometabolic Disease Staging (CMDS) system (**Table 4.3**) for predicting the progressively increased risk for future T2D and all-cause and CVD mortality.[9] In order to demonstrate the progressive risk of the cardiometabolic disease spectrum, they validated the CMDS by using two large national cohorts, the CARDIA study for incident diabetes and the NHANES III linked mortality file for all-cause or CVD mortality.

Based on the 10-year follow-up period data from the CARDIA study, there were 203 cases of newly-diagnosed diabetes resulting in an overall crude cumulative diabetes incidence of 6.1%. The cumulative diabetes incidence across risk levels ranged across from 1.8%, 5.9%, 18.2%, and 41.8% at Stage level 0 to Stage 3, respectively (**Figure 4.3**). Among overweight or obese individuals, the cumulative diabetes incidence was 8.9% overall, and ranged from 2.2% 7.3%, 19.0%, and 41.0% at Stage levels 0 to Stage 3, respectively.[9] In addition to risk-stage–associated increases in cumulative incidence of diabetes, the HRs for diabetes also increased exponentially from 2.83 at stage 1 to 23.5 at stage 3. The impact of risk stage on diabetes incidence was similar in both genders and in Whites and Blacks.

Over a median follow-up of 173 months in the NHANES III cohort, there were 1012 ascertained all-cause mortality cases, resulting in a cumulative overall mortality rate of 14.7 per 1000 person-years. As with the progressive increases in cumulative diabetes incidence, the cumulative mortality rates also increased progressively with advancing CMDS risk stage (P <0.001 for trend). They ranged from 6.5 per 1000 person-years at stage 0 to 29.2 per 1000 person-years at stage 4 (**Figure 4.4**). In this cohort, there also were 404 cases of CVD-related deaths. The overall CVD cumulative mortality rate was 5.4 per 1000 person-years overall, and the rates also increased according to risk stage (P <0.001 for trend), ranging from 0.7 per 1000 person-years at stage 0 to 14.3 per 1000 person-years at stage 4.[9]

This study demonstrates that CMDS staging can discriminate a wide range of risk for diabetes, CVD mortality, and all-cause mortality independent of BMI, and can be used as a risk assessment tool to guide intervention. In particular, such a tool can be useful in a complications-centric approach to the treatment of obesity wherein the goal of weight loss is to ameliorate the complications of obesity. However, prospective interventional trials are needed to further validate the use of the CMDS will enhance patient outcomes and the cost-effectiveness of care.

A Medical Model for Management of Overweight/Obese Patients

Until recently, the management of overweight/obese individuals focused primarily on weight loss and employed dietary/lifestyle interventions with the occasional addition of a very limited number of weight-reducing, modestly effective, pharmacologic agents. Bariatric surgery, although generally more effective than the other options, was generally reserved for more severe or refractory cases. However, there has been a gradual change in the understanding and appreciation of obesity, its complex pathophysiology, interrelationships with a broad spectrum of comorbidities, as well as increased mortality. As noted previously, there is growing agreement that obesity should be considered (and treated as) a disease in its own right, a disease that cannot be defined for clinical management solely by specific increments in total body weight.

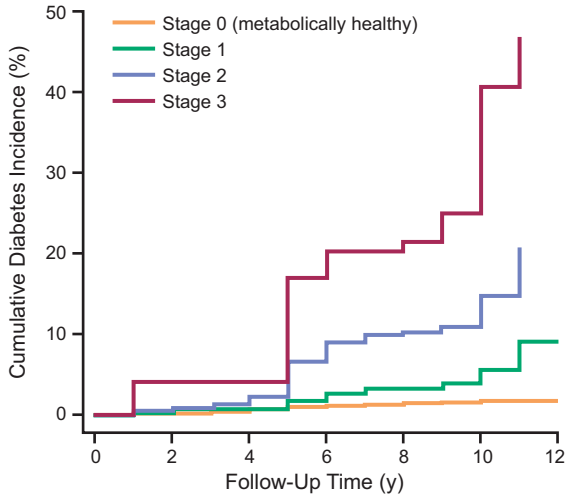
In contrast to the earlier BMI-centric guidelines (**Table 4.4**),[3] the new AACE guidelines are based on a complications-centric model for treatment of overweight or obese patients (**Figure 4.5**).[1] The goal is to identify those patients who will benefit most from obesity treatment, namely, those who have obesity-related complications. Given that medications and surgical procedures have inherent risks for patients and increase the cost of health care delivery, it is important

TABLE 4.3 — Cardiometabolic Disease Staging System (CMDS)

Stage	Descriptor	Criteria
0	Metabolically healthy	No risk factors
1	One or two risk factors	Have one or two of the following risk factors: • Elevated waist circumference (≥112 cm in men, ≥88 cm in women) • Elevated BP (SBP ≥130 mmHg and/or DBP ≥85 mmHg) or on antihypertensive medication • Reduced serum HDL cholesterol (<1.0 mmol/L or 40 mg/dL in men; <1.3 mmol/L or 50 mg/dL in women) or on medication • Elevated fasting serum triglycerides (≥1.7 mmol/L or 150 mg/dL) or on medication
2	Metabolic syndrome or prediabetes	Have only one of the following three conditions in isolation: • Metabolic syndrome based on three or more of four risk factors: – High waist circumference – Elevated BP – Reduced HDL-c – Elevated triglycerides • IFG (fasting glucose ≥5.6 mmol/L or 100 mg/dL) • IGT (2-h glucose ≥7.8 mmol/L or140 mg/dL)
3	Metabolic syndrome + prediabetes	Have any two of the following three conditions: • Metabolic syndrome • IFG • IGT
4	T2D and/or CVD	Have T2D and/or CVD: • T2D (fasting glucose ≥126 mg/dL or 2-hour glucose ≥200 mg/dL or on antidiabetic therapy) • Active CVD (angina pectoris or status post a CVD event, such as acute coronary artery syndrome, stent placement, coronary artery bypass, thrombotic stroke, nontraumatic amputation due to peripheral vascular disease)

Guo F, et al. *Obesity (Silver Spring)*. 2014;22(1):110-118.

FIGURE 4.3 — Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort

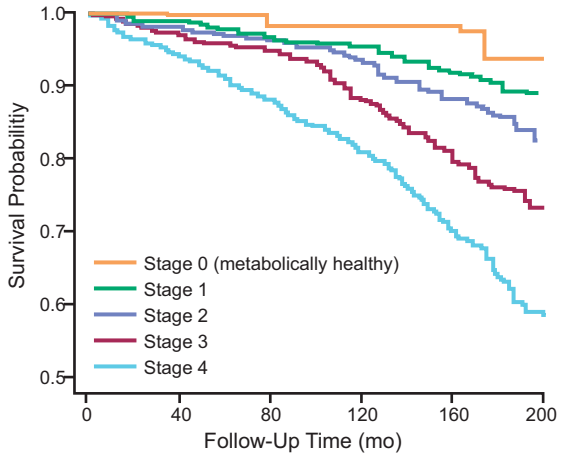


Guo F, et al. *Obesity (Silver Spring)*. 2014;22(1):110-118.

to develop and employ risk assessment steps in order to optimize the benefit/risk ratio for each patient.

Two weight-loss medications—phentermine plus topiramate extended-release (Qsymia), and the 5-HT_{2C} receptor agonist lorcaserin (Belviq)—were approved in the summer of 2012 and one fixed-dose combination of naltrexone SR and bupropion SR was approved in June 2014. Many others are in the late stages of the approval process (see *Chapter 9*). The new generation of anti-obesity drugs allows the provider to individualize therapy and use combination treatments in order to target the multiple pathways that contribute to the disease. Most importantly, the newer agents have been shown to not only result in significant weight loss but also to have significant beneficial effects on various cardiometabolic and anthropometric parameters.

FIGURE 4.4 — Survival Probability as a Function of Increasing CMDS Risk Stage: NHANES



Guo F, et al. *Obesity (Silver Spring)*. 2014;22(1):110-118.

In addition to the evolution of drug treatment, there have been new and refined options for dietary and lifestyle interventions (see *Chapter 8*) and further advances in bariatric surgery (see *Chapter 10*). Therefore, many recent changes, including the complications-centric algorithm, expanding availability of unique new medications, and surgical interventions, have enabled a medical model for the identification, assessment, and management of the overweight/obese patient.

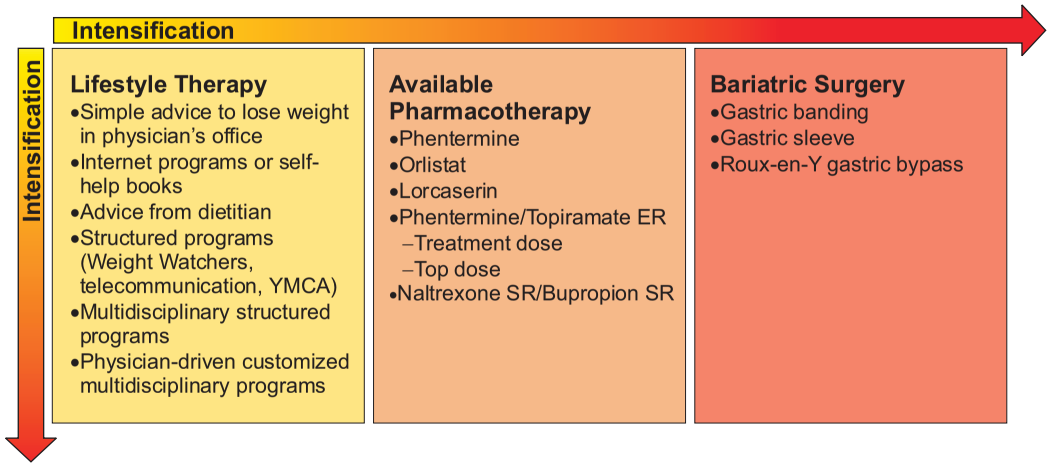
TABLE 4.4 — BMI-Centric Guide to Choosing Treatments for Obesity

	BMI Category				
Treatment	**25-26.9**	**27-29.9**	**30-34.9**	**35-39.9**	**≥40**
Diet, physical activity, behavior	Appropriate NHLBI Guidelines	+	+	+	+
Pharmacotherapy	Not appropriate	With comorbidities	+	+	+
Surgery[a]	Not appropriate	Not appropriate	LAGB approved for patients with ≥1 comorbidity[b]	With comorbidities	+

[a] Bariatric surgeries require lifestyle medical follow-up.
[b] FDA-approved lap band surgery for patients with BMI ≥30 are one weight-related medical condition (February 2011).

National Institutes of Health. *Obes Res.* 1998;6(suppl 2):51S-209S.

FIGURE 4.5 — Intensification of Therapies to Achieve Weight Loss Goals



REFERENCES

1. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. *Endocr Pract*. 2013;19(3):536-557.
2. Mechanick JI, Garber AJ, Handelsman Y, Garvey WT. American Association of Clinical Endocrinologists' position statement on obesity and obesity medicine. *Endocr Pract*. 2012; 18:642-648.
3. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. *Obes Res*. 1998;6(suppl 2):51S-209S.
4. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083-1096.
5. Sharma AM, Kushner RF. A proposed clinical staging system for obesity. *Int J Obes (Lond)*. 2009;33:289-295.
6. Padwal RS, Pajewski NM, Allison DB, Sharma AM. Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity. *CMAJ*. 2011;183:E1059-E1066.
7. Wing RR, Lang W, Wadded TA, et al; the LOOK AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481-1486.
8. Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640-1645.
9. Guo F, Moellering DR, Garvey WT. The progression of cardiometabolic disease: Validation of a new cardiometabolic disease staging system applicable to obesity. *Obesity (Silver Spring)*. 2014;22(1):110-118.

5 Benefits of Weight Loss

Introduction

There is a large and expanding body of evidence for the many benefits of intentional weight loss in overweight/obese individuals. While it is well known that there are significant improvements in patients both at risk for and who suffer from T2D, the benefits of weight loss extend beyond to include improvements in hypertension, dyslipidemia, metabolic syndrome, and OSA, as well as improvements in both mood and functional status.

To date, the largest body of data on the benefits of intentional weight loss has come from two long-term prospective, multicenter, randomized studies that compared the effects of intensive lifestyle intervention (ILI) to usual clinical care in two different populations. The Diabetes Prevention Program (DPP) was performed in overweight/obese individuals who were at high risk for T2D, while the participants in the Look AHEAD (Action for Health in Diabetes) study had previously been diagnosed with T2D.

DPP AND DPPOS

Objectives and Design

The DPP study was a multicenter, prospective, randomized clinical trial in 3234 adults in the United States who were at high risk for the development of T2D.[1] The primary objective was to assess whether an ILI or treatment with metformin could prevent or delay the onset of diabetes compared with standard lifestyle recommendations (eg, diabetes support and education [DSE]) in nondiabetic US adults at high risk for diabetes.

The primary outcome was development of T2D diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual fasting plasma glucose test. Metformin treatment was initiated at a dose of 850 mg once daily in one of the treatment groups, with placebo tablets also given once a day in the control group. At 1 month in the metformin group, the dose of metformin was increased to 850 mg twice daily.

The goals for the participants randomized to the ILI were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week. A 16-lesson curriculum covering diet, exercise, and behavior modification was taught by case managers on a one-to-one basis during the first 24 weeks and continued on a flexible schedule thereafter. Masked treatment was discontinued when the DPP study demonstrated that ILI reduced the incidence of diabetes by 58% and metformin by 31% compared with the DSE control group during an average duration for all participants of 2.8 years in the DPP.

The long-term persistence of the results of the DPP study was assessed in the subsequent Diabetes Prevention Program Outcomes Study (DPPOS).[2] All active DPP participants were eligible for continued follow-up, of whom 2766 (88%) enrolled for a median additional follow-up of 5.7 years. After this, there was a 13-month "bridge period" before implementation of the DPPOS protocol. During this bridge period, those in the metformin and DSE groups entered into a 1- to 2-week drug washout. After treatments were unmasked, the DSE intervention was stopped. All participants, including those in the original ILI group and those who had developed diabetes, were offered a group-administered version of the 16-session lifestyle curriculum followed by lifestyle sessions every 3 months, with provision of educational materials to reinforce the original weight loss and physical activity goals. All

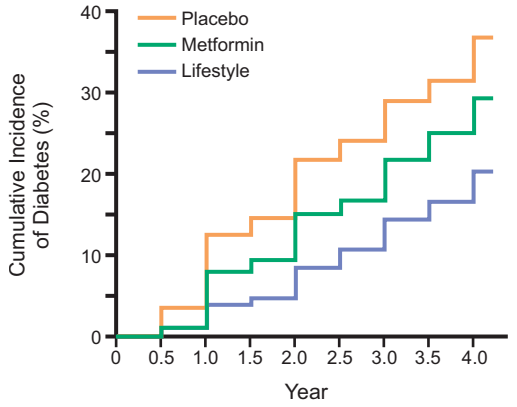
participants were followed in their original groups with their clinical care provided by practitioners outside of the study.

■ Prevention/Delay of Diabetes

The primary objective of the DPP and DPPOS trials was to assess whether an ILI or treatment with metformin could prevent or delay the onset of diabetes compared with standard lifestyle recommendations. After mean follow-up of 2.8 years, the cumulative incidence of diabetes was lower in the metformin and ILI groups than in the DSE group. The crude incidences of diabetes were 11.0, 7.8, and 4.8 cases per 100 person-years in the DSE, metformin, and ILI groups, respectively (**Figure 5.1**), and the estimated cumulative incidences of diabetes in the DSE, metformin, and ILI were 28.9%, 21.7 %, and 14.4%, respectively.[3]

These results translate into a risk reduction of 58% with ILI and by 31% with metformin compared with DSE. Given these results, the estimated numbers of

FIGURE 5.1 — DPP Study: Cumulative Incidence of Diabetes at 3 Years in Overweight/Obese Individuals at High Risk for Diabetes



Modified from Knowler WC, et al; Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346(6):393-403.

persons who would need to be treated for 3 years to prevent one case of diabetes during this period were 6.9 with ILI and 13.9 with metformin. Of particular interest is that these reductions in the cumulative incidences of diabetes were accomplished with only moderate degrees of weight loss namely 0.1 kg, 2.1 kg, and 5.6 kg in the DSE, metformin, and ILI groups, respectively.

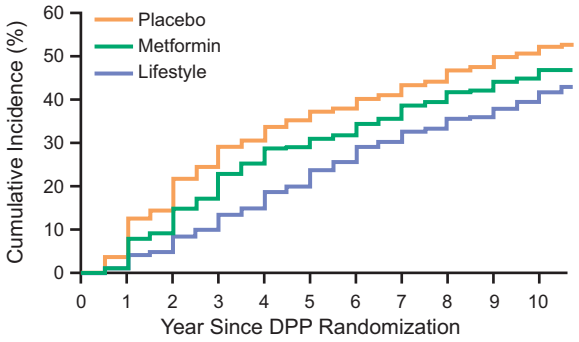
During the DPPOS study, the ILI group initially lost the most weight (mean of 7 kg by 1 year) but gradually regained it, although they still weighed about 2 kg less than they did at DPP randomization.[2] The metformin group lost a mean of 2.5 kg during DPP and maintained most of that weight loss. The mean weight loss in the DSE group was <1 kg from DPP randomization. The ILI group subsequently regained about 1 kg, whereas the metformin and DSE groups initially lost and then regained weight back to their respective levels at DPPOS baseline.

Diabetes incidence during DPPOS did not differ significantly between the three initial randomized groups (**Figure 5.2**). However, this finding was not attributable to a rebound effect in the ILI group but rather to a decrease in diabetes incidence in the placebo and metformin groups that resulted in similar rates as achieved by lifestyle intervention, which changed little throughout follow-up (**Table 5.1**). Therefore, 10 years after DPP randomization, the cumulative incidence of diabetes remained lower in the ILI and metformin groups than in the DSE group, despite changes in treatments after a mean of 3.2 years.

■ Reduction in Cardiovascular Risk Factors

In the original DPP cohort, 30% had hypertension, 29% had hypertriglyceridemia, and 44% had hypercholesterolemia at baseline. Annual assessments showed progressive increases in the prevalence of hypertension and dyslipidemia in the DSE and metformin groups compared with a decrease in the ILI group by year 3.[4] Triglyceride levels fell in all treatment groups but fell significantly more with ILI. Total cholesterol and LDL cholesterol levels were similar among treatment

FIGURE 5.2 — DPPOS Study: Cumulative Incidence of Diabetes at Over 10 Years Since Randomization in the DPP Study of Overweight/Obese Individuals at High Risk for Diabetes



Diabetes Prevention Program Research Group, et al. *Lancet.* 2009; 374(9702):1677-1686.

TABLE 5.1 — Incidence (Cases per 100 Person-Years) of Diabetes During DPP, Bridge Period, and DPPOS

Period	ILI Group	Metformin Group	DSE Group
DPP	4.8	7.8	11.0
End of masked treatment	5.0	7.7	10.8
Bridge period	5.5	10.6	7.8
DPPOS	5.9	4.9	5.6
Combined incidence	5.3	6.4	7.8

Diabetes Prevention Program Research Group, et al. *Lancet.* 2009; 374(9702):1677-1686.

groups. ILI significantly increased the HDL cholesterol level compared with the other interventions. After 3 years of follow-up, the use of medications to achieve pre-established treatment goals in the ILI group was reduced (by 27% to 28% for antihypertensive agents and 25% for lipid-lowering medications) compared with DSE and metformin groups.

The DPPOS study provided an additional ~5 years of follow-up of the randomized DDP study population, thereby allowing an assessment of the durability of the beneficial effect of ILI and DSE interventions and metformin treatment on CV risk factors over a ~10-year period. After unmasking of treatment and a brief bridge period, all groups received a lifestyle intervention. Also, metformin was continued (unless terminated by the care provider) in participants who were in the original metformin arm.[5] After 10 years of follow-up from the DPP baseline, there were reductions in SBP (-2 to -3 mm Hg) and DBP (-6 to -6.5 mm Hg), as well as in LDL cholesterol (-0.51 to -0.6 mmol/L) and triglycerides (-0.23 to -0.25 mmol/L) in all groups, with no between-group differences (**Figure 5.3**). In addition, HDL cholesterol levels rose significantly (0.14 to 0.15 mmol/L) in all groups. Analysis of medication use found reductions in the overall use of lipid-lowering ($P = 0.01$) and antihypertensive ($P = 0.09$) medications throughout the follow-up period, however, their use was lower in the original ILI group during DPPOS.

■ Weight Loss in Severely Obese Patients

There has been a long-held belief that dietary and lifestyle interventions are less effective in severely obese individuals than in those with less excessive body weight. A substudy from the Look AHEAD trial compared the effect of ILI on weight loss and CVD risk in patients with T2D who were severely obese (Class III; BMI ≥40 kg/m^2) to those who were overweight (BMI 25 to <30 kg/m^2), obese Class I (BMI 30 to <35 kg/m^2), and obesity class II (BMI 35 to <40 kg/m^2).[6] At 1 year, the weight loss in severely obese patients in the ILI group was -9.04% of initial body weight, which was significantly greater ($P < 0.05$) than patients who were overweight (-7.43%) and comparable to those with class I (-8.72%) or class II obesity (-8.64%).

There also were comparable improvements in fitness, physical activity, LDL cholesterol, triglycerides, BP, fasting glucose, and HbA1c at 1 year across all BMI groups. Finally, treatment adherence (eg, treatment session attendance) among severely obese individuals was excellent and did not differ among weight categories (severely obese 80% vs others 83%; $P = 0.43$). These results demonstrate that dietary and lifestyle interventions can be considered in severely obese individuals.

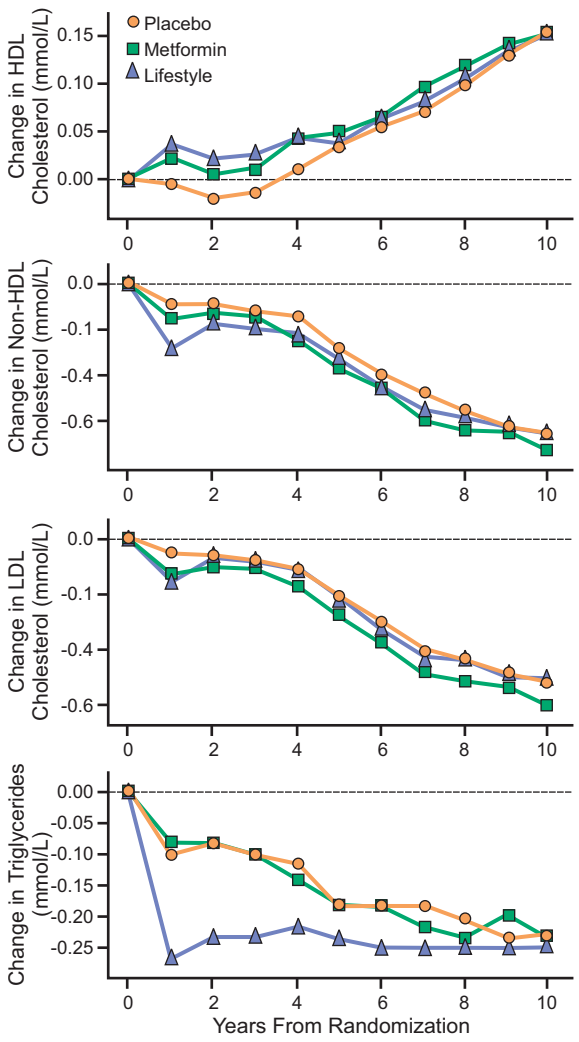
■ Incidence and Resolution of Metabolic Syndrome

The metabolic syndrome is "a complex cluster of interrelated risk factors for CV disease and diabetes which occur together more often than by chance alone."[7] Three abnormal findings out of the five listed in **Table 5.2** would support a diagnosis of metabolic syndrome. The presence of the metabolic syndrome is a clinically useful indicator of high morbidity and mortality risk. Patients with the metabolic syndrome are at twice the risk of developing CVD over the subsequent 5 to 10 years as those without the syndrome. In addition, the metabolic syndrome confers a 5-fold increase in the risk of developing T2D.[7]

At baseline in the DPP study, 53% of randomized patents had the metabolic syndrome defined as having three or more characteristics (increased waist circumference; elevated BP; low HDL, elevated triglycerides, and elevated fasting plasma glucose) that met criteria from the National Cholesterol Education Program Adult Treatment Panel III.[8]

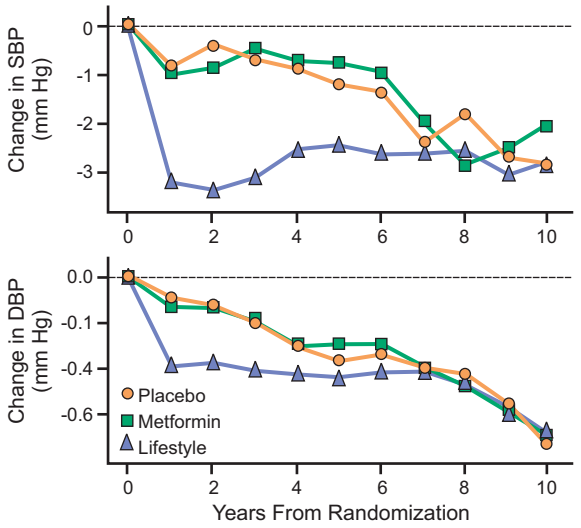
By year 3, the prevalence of metabolic syndrome among all study participants increased from 55% at baseline to 61% after 3 years in the DES group ($P = 0.003$) and from 54% to 55% in the metformin

FIGURE 5.3 — DPPOS Study: Changes From DPP Baseline in CVD Risk Factors During 10 Years of Follow-Up



Continued

FIGURE 5.3 — *Continued*



Diabetes Prevention Program Outcomes Study Research Group, et al. *Diabet Med*. 2013;30(1):46-55.

group (P >0.2). In the ILI group, overall prevalence decreased from 51% to 43% (P <0.001). Among individuals without metabolic syndrome at baseline, 53% of those in the DSE group had acquired the metabolic syndrome by year 3 compared with 47% in the metformin group and 38% in the ILI group. Thus, the ILI results in reduction of 41% in incidence of the metabolic syndrome compared with DSE and a significant 29% reduction compared with metformin (P <0.001), which itself yielded a 17% lower incidence than DSE (P = 0.03).

Among the individuals with the metabolic syndrome at baseline, the differences by treatment group were less striking; however, the prevalence at 3 years did vary significantly by treatment group (P <0.001): 18% of the DSE group, 23% of the metformin group, and 38% of the ILI group no longer had the syndrome.

TABLE 5.2 — Risk Factors of Metabolic Syndrome

Trait	Categorical Cut Point
Elevated waist circumference	≥35 inch (female); ≥45 inch (male) (Note: population-/country-specific definitions)
Elevated triglycerides (or drug treatment ↑ triglycerides)	≥150 mg/dL
Reduced HDL-C (or drug treatment ↓ HDL-C)	<40 mg/dL (male); <50 mg/dL (female)
Elevated BP (or hypertension history or drug therapy)	SBP ≥130 mm Hg and/or DBP ≥85 mm Hg
Elevated fasting glucose (or drug therapy for hyperglycemia)	≥100 mg/dL
Three abnormal findings out of the five listed above would support a diagnosis of metabolic syndrome.	

Modified from Alberti KG, et al. *Circulation*. 2009;120(16):1640-1645.

Look AHEAD

Objectives and Design

The Look AHEAD study was a prospective, multicenter, randomized, controlled trial designed to determine whether intentional weight loss reduces CV morbidity and mortality in overweight individuals with T2D.[9] The primary objective was to assess the long-term effects (up to 11.5 years) of an intensive weight loss program delivered over 4 years in overweight and obese individuals with T2D. The primary study outcome was time to incidence of a major CV event. Other outcomes included components of CVD risk, cost and cost-effectiveness, diabetes control and complications, hospitalizations, intervention processes, and quality of life.

Participants were randomly assigned to one of two intervention groups: an ILI designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity, or to enhanced usual care (ie, DSE).[10] The two principal goals of the ILIs were to induce a mean loss ≥7% of initial weight and to increase participants' moderately-intense physical activity to ≥175 minutes a week. A total of 5145 overweight/obese US individuals with T2D were randomized to ILIs ($n = 2570$) or DSE ($n = 2575$). Overall, 59% of the participants were women; 37% were from racial or ethnic minorities; 14% reported a history of CVD at baseline, their average age was 58.7, and their average BMI was 36 kg/m^2.

Reduction in Cardiovascular Events and Risk Factors

Although Look AHEAD did not achieve its primary efficacy outcome, ie, improvement in the time to incidence of a major CV event, it did demonstrate benefits in components of CVD risk.

After 1 year, patients in the ILI group lost an average 8.6% of their initial weight compared with 0.7% in the DSE group ($P < 0.001$).[11] Fitness, assessed by submaximal exercise test to determine ≥80% of age-

predicted maximal heart rate, increased by 20.9% in the ILI group compared with 5.8% in the DSE group (P <0.001). A greater proportion of ILI patients experienced reductions in the incidence of diabetes, hypertension, and the use of lipid-lowering drugs. Mean A1C decreased from 7.3% to 6.6% with ILI (P <0.001) vs from 7.3% to 7.2% with DES. In addition, there were significantly greater improvements in SBP and DBP, triglycerides, and HDL cholesterol among ILI-treated patients than among DSE-treated patients (all P <0.01).

Averaged over 4 years, patients in the ILI group had significantly greater improvements in weight, fitness, glycemic control, SBP, and levels of HDL cholesterol and triglycerides than those in the DSE group (**Table 5.3**). There was no significant difference in DBP. Although the DSE group experienced greater overall reductions in LDL cholesterol levels, changes in LDL cholesterol levels did not differ between the groups after adjusting for use of lipid-lowering medications.[12]

Changes in weight and risk factors at each of the 4 years are shown in **Figure 5.4**. The ILI group experienced significantly greater weight losses than the DSE group at each year. The maximal weight loss (8.6%) in the ILI group occurred at year 1 and the mean weight loss by year 4 was 4.7% compared with 1.1% in the DSE group (P <0.001). For several risk factors, the between group differences were most apparent at year 1. At each of the 4 years, the ILI group continued to have greater improvements in SBP and in A1C and HDL cholesterol levels. Among patients who were using antihypertensive to antihyperglycemic medications at baseline, a greater proportion of patients in the ILI group than the DSE group discontinued use of these medications.

Conversely, among those not using these medications at baseline, fewer patients in the ILI group initiated the use of these agents. However, the percentage of patients using lipid-lowering medications almost doubled during the 4 years, with greater initiation in

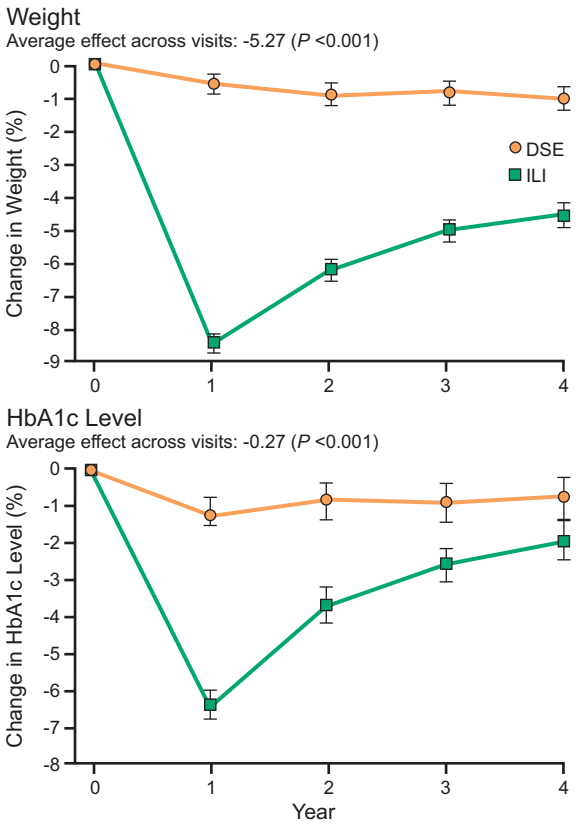
TABLE 5.3 — Look AHEAD Study: Mean Changes in Weight, Fitness, and CVD Risk Factors in ILI and DSE Groups and the Difference Between Groups Averaged Across 4 Years

	Mean Changes Over 4 Years		Difference (ILI-DSE)	
Measure	**DSE Group**	**ILI Group**		***P* Value**
Weight (% initial)	-0.88	-6.15	-5.27	<0.0001
Fitness (% METS)	+1.96	+12.74	+10.78	<0.0001
A1C	-0.09	-0.36	-0.27	<0.0001
SBP (mm Hg)	-2.97	-5.33	-2.36	<0.0001
DBP (mm Hg)	-2.48	-2.92	-0.43	0.012
HDL cholesterol (mg/dL)	+1.97	+3.67	+1.70	<0.0001
Triglycerides (mg/dL)	-19.75	-25.56	-5.81	0.0006
LDL cholesterol (mg/dL)	-12.84	-11.27	+1.57	0.009
LDL cholesterol (mg/dL)[a]	-9.22	-8.74	+0.47	0.42

[a] Adjusted for medication use.

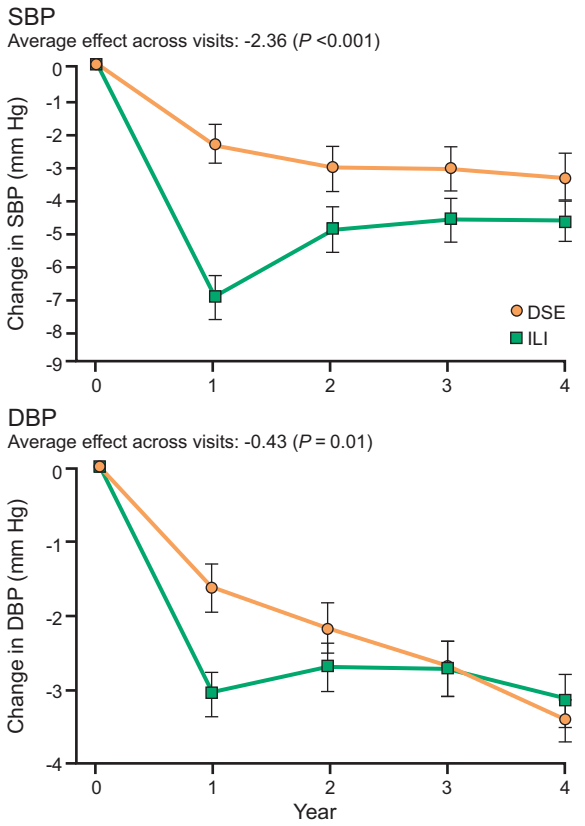
Look AHEAD Research Group, Wing RR. *Arch Intern Med.* 2010;170(17):1566-1575.

FIGURE 5.4 — Look AHEAD Study: Changes in Weight and CVD Risk Factors During 4 Years in Patients in the ILI and DSE Groups



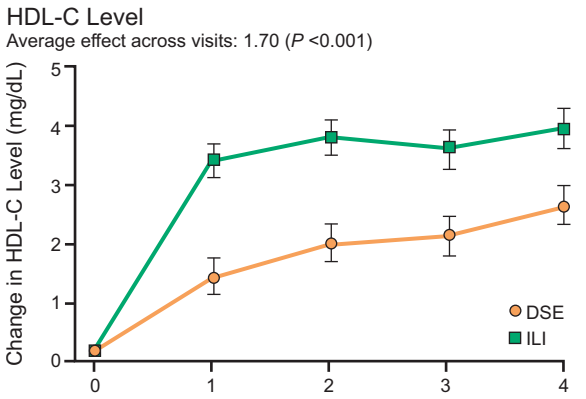
Continued

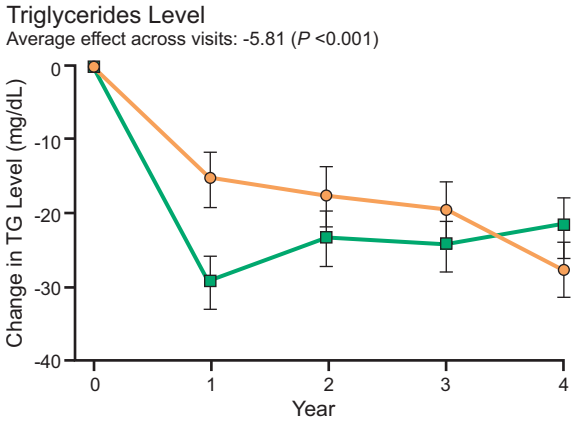
FIGURE 5.4 — *Continued*



Continued

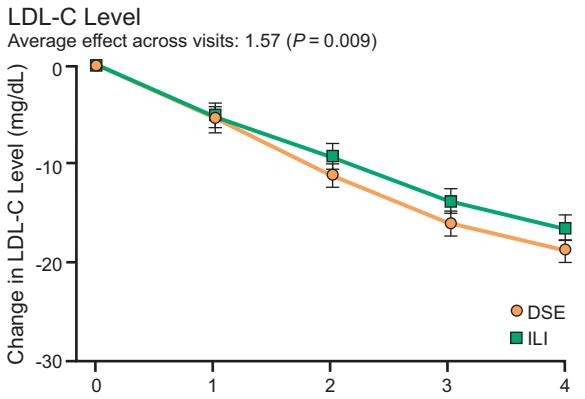
FIGURE 5.4 — *Continued*

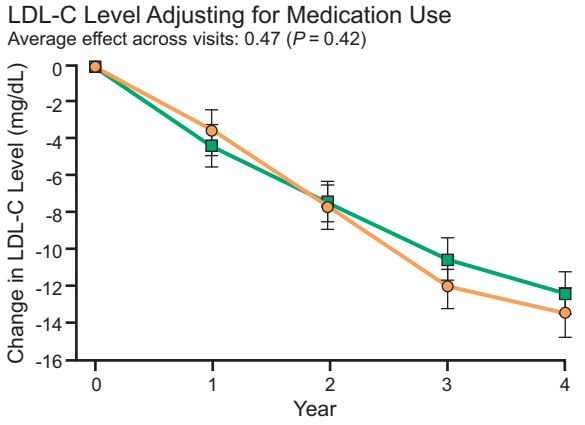




Continued

FIGURE 5.4 — *Continued*





Look AHEAD Research Group, Wing RR. *Arch Intern Med*. 2010; 170(17):1566-1575.

the DSE than in the ILI group. The ADA goals for A1C and BP were met by a significantly greater proportion of patients in the ILI group compared with the DSE group at years 1, 2, and 3. The percentage of patients achieving the ADA goals for LDL cholesterol level did not differ until year 4, when 64.5% of DSE patients compared with 61.0% of ILI patients ($P = 0.01$) met this goal.

Remission of Diabetes

An ancillary analysis of the 4-year Look AHEAD study results examined the association of long-term ILI with the frequency of remissions from T2D defined as transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycemia (fasting plasma glucose <126 mg/dL and A1C <6.5% with no antihyperglycemic medication).[13]

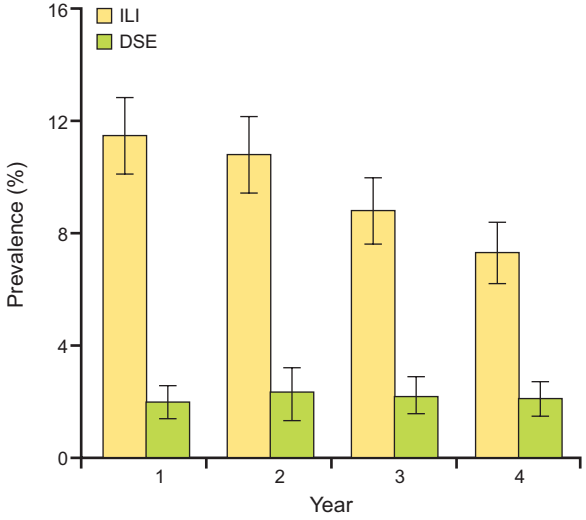
The results showed that the ILI group was significantly more likely to experience a partial or complete remission with prevalences of 11.5% during the first year and 7.3% at year 4 compared with 2.0% for the DSE group at both time points ($P < 0.001$ for each) (**Figure 5.5**). In the ILI group, 9.2%, 6.4%, and 3.5% of participants experienced continuous, sustained remission for at least 2, at least 3, and 4 years, respectively, compared with <2% of patients in the DSE group at the same time points.

Although the prevalence of complete remission was more common in the ILI group than in the DSE group across all years of the study (prevalence ratio, 6.6; $P < 0.001$), the absolute prevalence of complete remission was low, ranging from 1.3% with or ILI vs 0.1% with DSE ($P < 0.001$) in year 1 to 0.7% with ILI vs 0.2% with DSE at year 4.

Magnitude of Weight Loss and Clinical Benefits

Overweight and obese individuals are frequently encouraged to lose 5% to 10% of their weight and are told that weight losses of that magnitude will help improve their CVD risk factors. The Look AHEAD study provided the opportunity to assess the effects of

FIGURE 5.5 — Look AHEAD Study: Prevalence of Any Remission (Partial or Complete) by Intervention Condition and Year in Overweight/Obese Diabetic Patients



Gregg EW, et al. *JAMA*. 2012;308(23):2489-2496.

various magnitudes of weight loss on improvements in CVD risk factors.

An observational analysis of data from the Look AHEAD study examined the association between the magnitude of weight loss and changes in CVD risk factors at 1 year and the odds of meeting predefined criteria for clinically significant improvements in risk factors in individuals with T2D.[14]

After 1 year, patients were divided into the following categories based on their weight changes from baseline to 1 year: gained >2%; remained weight stable (±2%); lost ≥2% to 5%; lost ≥5% to 10%; lost ≥10% to 15%; or lost ≥15%. There was a strong graded association for changes in glucose, A1C, SBP, DBP, triglycerides, and HDL cholesterol (all P values <0.0001)

(**Figure 5.6**). Each higher increment of weight loss was associated with greater improvements in the risk factor. In contrast, the magnitude of improvement in LDL cholesterol did not differ across the weight categories. Furthermore, the odds of having a clinically meaningful improvement in risk were strongly related to the magnitude of weight loss achieved such that the odds of a clinically meaningful improvement also increased with each weight loss increment.

Individuals who lost 2% to 5% of their body weight had increased odds of having significant improvements in SBP (OR 1.24), glucose (OR 1.75), A1C (OR 1.80), and triglycerides (OR 1.46), while those who lost 5% to <10% of their body weight had increased odds of significant improvement in all risk factors. These results support for the assertion that modest weight losses of 5% to 10% (and even 2% to 5%) of initial weight are sufficient to produce significant, clinically relevant improvements in CVD risk factors in overweight and obese patients with T2D.[14]

■ Depression

Some evidence suggests there are bidirectional associations among depression, obesity, and diabetes.[15-17] Since the Look AHEAD study population consisted of overweight/obese individuals with T2D, a separate analysis of the Look AHEAD cohort was performed to determine whether moderate weight loss would be associated with incident symptoms of depression and suicidal ideation, and whether symptoms of depression at baseline would limit weight loss at 1 year.[18] Virtually all ($n = 5129$) trial participants completed the Beck Depression Inventory (BDI) and had their weight measured at baseline and 1 year. A BDI score of ≥10 indicated potentially significant symptoms of depression.

During this 1-year study, there was a significantly lower number of incident cases of symptoms of depression in the ILI group at 1 year than in the DSE group (6.3% vs 9.6%; $P < 0.001$), which remained significant after controlling for use of antidepressant medications.

The overall change from baseline weight at 1 year (regardless of a depression status) was -8.6% in the ILI group and -0.7% in the DSE group ($P < 0.001$) (**Figure 5.7**). ILI group participants who reported mild or symptoms of depression at baseline showed a decrease of 5.3 points on the BDI at 1 year compared with a decrease of 0.6 points in those individuals reporting no symptoms of depression. In the DSE group, there was a decrease of 3.7 points among individuals with symptoms of depression at baseline compared with an increase of 0.2 points in participants without depressive symptoms at baseline.[18]

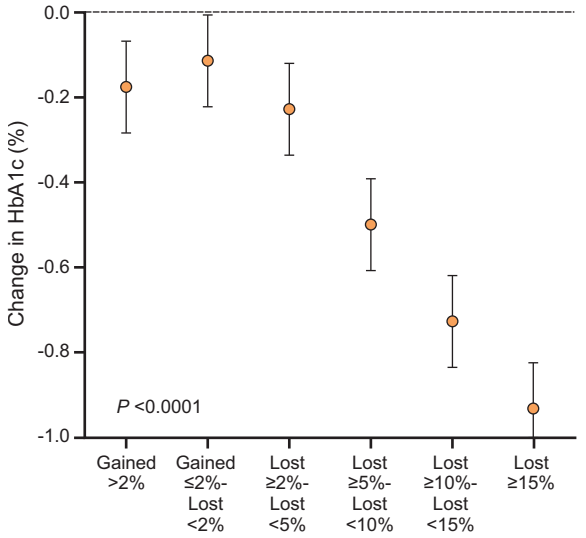
Although participants in both intervention groups with mild or greater symptoms of depression at baseline lost significantly less weight than individuals with no symptoms of depression (4.3% vs 4.8%), this difference cannot be considered as clinically meaningful. Similarly, the difference in weight loss between participants with and without symptoms of depression in the ILI group (7.8% vs 8.7%) is not clinically meaningful. According to the authors, these findings indicate that overweight/obese diabetic individuals with mild or greater symptoms of depression are able to lose similar degrees of weight loss as overweight/obese individuals without T2D.

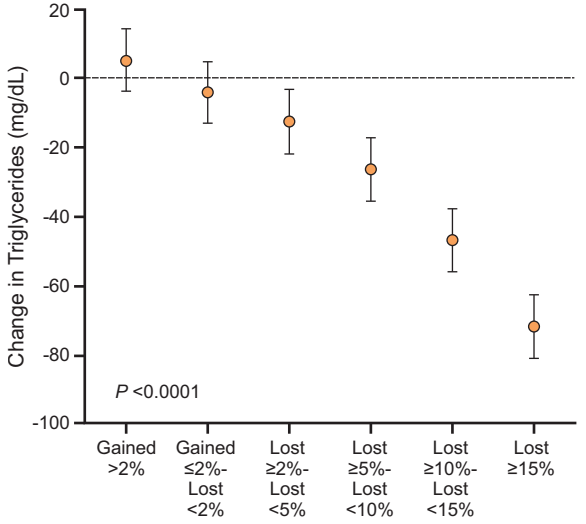
■ Obstructive Sleep Apnea

OSA is strongly associated with obesity and untreated OSA is associated with significant CVD morbidity and mortality, debilitating daytime symptoms, and increased risk of work and motor vehicle accidents.[19]

The Sleep AHEAD ancillary study of Look AHEAD assessed the prevalence of OSA among 305 overweight/obese diabetic individuals.[20] Almost all (86.6%) of these individuals had OSA of various levels of severity. The mean AHI was 20.5; 33.4% had mild OSA, 30.5% moderate OSA, and 22.6% severe OSA. Independent of other variables, a 1-cm increase in waist circumference was associated with a 10% increase in the predicted odds of the presence of OSA (AHI ≥5). In

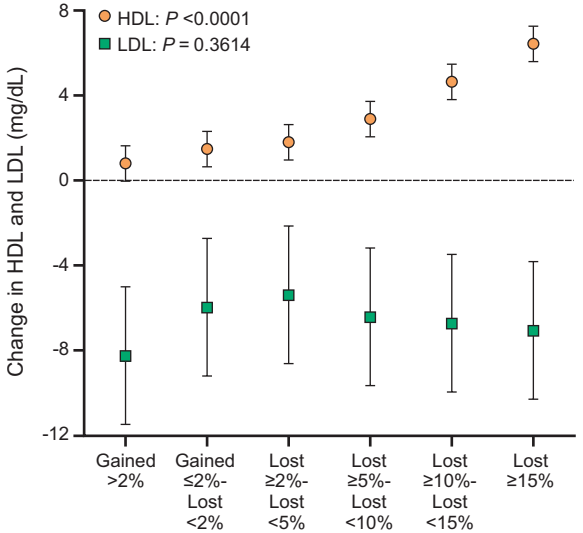
FIGURE 5.6 — Effect of Modest Weight Loss on Glycemic and CVD Risk Factors in Overweight/Obese Diabetic Patients

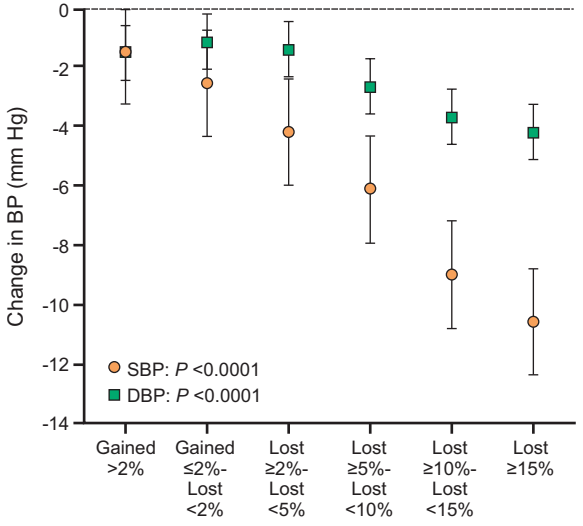




Continued

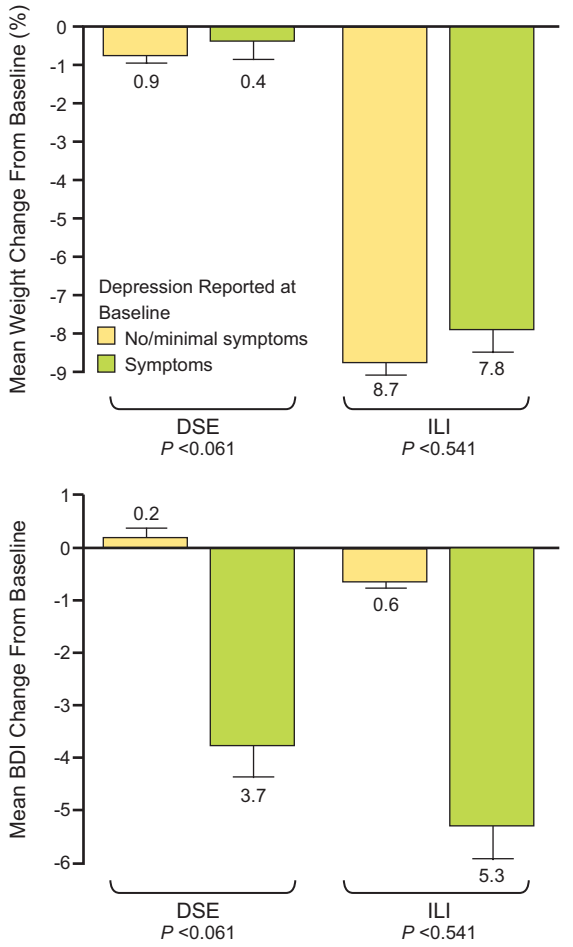
FIGURE 5.6 — *Continued*





Wing RR, et al; Look AHEAD Research Group. *Diabetes Care*. 2011;34(7):1481-1486.

FIGURE 5.7 — Look AHEAD Study: Changes in BDI Scores and Percent Weight Loss During 1 Year by Intervention and Baseline Depression Status



Faulconbridge LF, et al; Look AHEAD Research Group. *Obesity (Silver Spring)*. 2012;20(4):783-793.

participants with AHI ≥5, BMI was the only significant predictor of severe OSA.

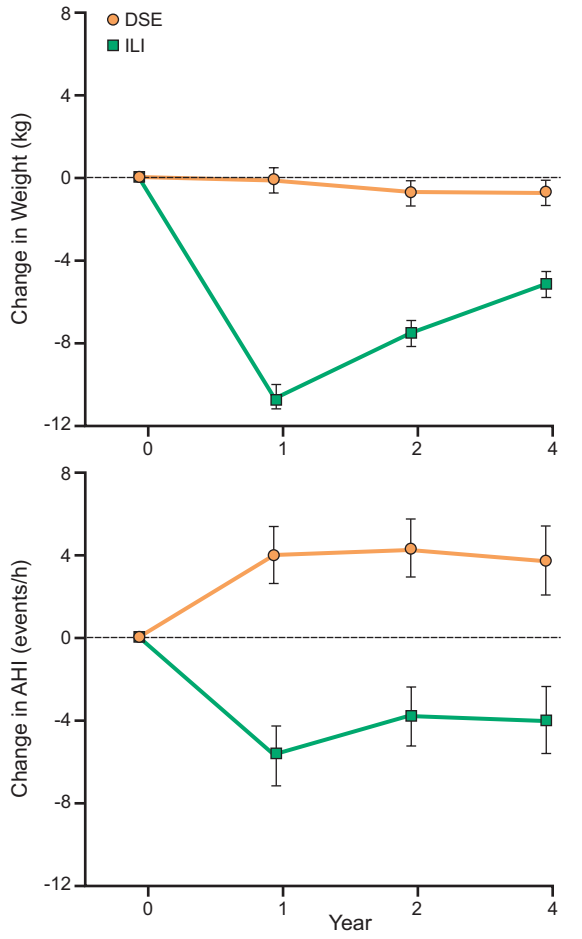
A total of 264 of the above individuals were assigned to either ILI or DSE intervention. Their mean baseline weight was 102.4 kg, their mean BMI was of 36.7, and their mean AHI was 23.2 (16.5 events/hour). At 1 year, more than three times as many patients in the ILI group than in the DSE group had total remission of their OSA, and the prevalence of severe OSA among ILI participants was half that of the DSE group.

Subsequently, these patients were followed to assess whether the initial benefit of weight loss on OSA severity at 1 year is maintained at 4 years.[21] Mean weight loss in the ILI group was 10.7, 7.4, and 5.2 kg at 1, 2, and 4 years, respectively, compared with a <1-kg weight loss in the DSE group at each time (P <0.001). The between-group differences in AHI were 9.7, 8.0, and 7.7 events/hour at 1, 2, and 4 years respectively (P <0.001) (**Figure 5.8**). Remission of OSA at 4 years was five times more common with the ILI (20.7%) than DSE (3.6%). Furthermore, these beneficial effects on the AHI group at 1 year persisted at 4 years, despite an almost 50% weight regain. However, it is important to note that while weight loss of 5% to 10% can result in significant benefits in many comorbidities, an ~10 kg average weight loss may be required to achieve a significant decrease in the AHI index.

There is considerable evidence that bariatric surgery has a beneficial effect on the risk of diabetes, blood pressure, dyslipidemia, and mortality in severely obese individuals (see *Chapter 10*). Bariatric surgery also has been shown to result in significant weight loss and risk factor reduction in severely obese individuals. A few studies have compared the effect of surgical and conservative weight loss strategies on OSA.

A recent 1-year study treated 133 morbidly obese subjects (BMI 45.1), 63% had OSA with mean AHI 17.1 (21.4 events/hour) with either a 1-year ILI-program (n = 59) or Roux-en-Y gastric bypass (RYGB) (n = 74) and repeated polysomnography.[22] The average

FIGURE 5.8 — Long-Term Effect of Weight Loss on Obstructive Sleep Apnea Severity in Obese Patients With T2D



Kuna ST, et al; Sleep AHEAD Research Group of the Look AHEAD Research Group. *Sleep*. 2013;36(5):641-649.

weight loss was 8% in the ILI-group and 30% in the RYGB-group (P <0.001). Mean AHI scores decreased in both treatment groups, although significantly more in the RYGB-group than in the ILI group (-13.1 vs -6.0, respectively). Twenty-nine RYGB-patients (66%) had remission of OSA compared with 16 ILI-patients (40%). However, after further adjustment for BMI change, the treatment group difference was no longer statistically significant (P = 0.709). As a result, the authors concluded that while the study demonstrated that RYGB was more effective than ILI at reducing the prevalence and severity of OSA, further analysis also suggests that weight loss, rather than the surgical procedure per se, explains the beneficial effects.[22]

■ Osteoarthritis

Obesity has been identified as an independent modifiable risk factor for the development of OA, particularly in knees.[23,24] Several studies have demonstrated the benefits of weight loss in overweight/obese individuals with OA of the knee.

The 18-month, randomized, single-blind Arthritis, Diet, and Activity Promotion Trial (ADAPT) in 316 community-dwelling overweight and obese (BMI >28 kg/m^2) adults ages 60 years and older, with knee pain, radiographic evidence of knee OA, and self-reported physical disability assessed, whether long-term exercise and dietary weight loss are more effective, either separately or in combination, than usual care in improving physical function, pain, and mobility in older overweight and obese adults with knee OA.[25] The primary outcome measure was self-reported physical function as measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Secondary outcomes included weight loss, 6-minute walk distance, stair-climb time, WOMAC pain and stiffness scores, and joint space width.

Both weight loss intervention groups (diet only, diet plus exercise) lost significantly (P <0.05) more weight compared with the healthy lifestyle group. Individuals in the diet-only group lost an average of

4.9% of their body weight and those in the diet plus exercise group lost 5.7% of their body weight. Mean weight losses in the exercise-only and healthy lifestyle groups were 3.7% and 1.2%, respectively. After 18 months, WOMAC physical function revealed that individuals in the diet plus exercise group significantly improved their physical function (P <0.05) relative to the healthy lifestyle control group. There were no significant differences between the exercise-only or diet-only groups and the healthy lifestyle group.

Summary

Data from both the DPP and LOOK AHEAD trials clearly demonstrate that modest weight loss can have significant improvements on obesity related comorbidities. Modest weight loss can reduce the incidence of diabetes by up to 58% and provide remission rates of up to 11% for those undergoing intensive lifestyle treatment. In addition, patients can achieve improvements in LDL, HDL, SBP as well as reduce the incidence of metabolic syndrome by 41%. Other obesity-related complications, including OSA, depression, and declining functional status may also be improved. Furthermore, this benefit is not limited to patients who have mild/moderate obesity but is actually achieved in those with severe obesity (BMI >40) and therefore all patients should be considered for treatment.

REFERENCES

1. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care*. 1999;22(4):623-634.
2. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.
3. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
4. Ratner R, Goldberg R, Haffner S, et al; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28(4):888-894.
5. Diabetes Prevention Program Outcomes Study Research Group, Orchard TJ, Temprosa M, Barrett-Connor E, et al. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. *Diabet Med*. 2013;30(1):46-55.
6. Unick JL, Beavers D, Jakicic JM, et al; Look AHEAD Research Group. Effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes: results from the Look AHEAD trial. *Diabetes Care*. 2011;34(10):2152-2157.
7. Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
8. Orchard TJ, Temprosa M, Goldberg R, et al; Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142(8):611-619.

9. Ryan DH, Espeland MA, Foster GD, et al; Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials*. 2003;24(5):610-628.
10. Look AHEAD Research Group, Wadden TA, West DS, Delahanty L, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)*. 2006;14(5):737-752.
11. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care*. 2007;30(6):1374-1383.
12. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med*. 2010;170(17):1566-1575.
13. Gregg EW, Chen H, Wagenknecht LE, et al; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA*. 2012;308(23):2489-2496.
14. Wing RR, Lang W, Wadden TA, et al; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;34(7):1481-1486.
15. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2006;23(11):1165-1173.
16. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069-1078.
17. Sutin AR, Zonderman AB. Depressive symptoms are associated with weight gain among women. *Psychol Med*. 2012; 42(11):2351-2360.
18. Faulconbridge LF, Wadden TA, Rubin RR, et al; Look AHEAD Research Group. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. *Obesity (Silver Spring)*. 2012;20(4):783-793.

19. Ge X, Han F, Huang Y, et al. Is obstructive sleep apnea associated with cardiovascular and all-cause mortality? *PLoS One*. 2013;8(7):e69432.
20. Foster GD, Borradaile KE, Sanders MH, et al; Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med*. 2009;169(17):1619-1626.
21. Kuna ST, Reboussin DM, Borradaile KE, et al; Sleep AHEAD Research Group of the Look AHEAD Research Group. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. *Sleep*. 2013;36(5):641-649A.
22. Fredheim JM, Rollheim J, Sandbu R, et al. Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention. *J Clin Sleep Med*. 2013;9(5):427-432.
23. Magliano M. Obesity and arthritis. *Menopause Int*. 2008;14(4): 149-154.
24. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord*. 2008;9:132.
25. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510.

6 Approach to the Obese Patient

Introduction

Obesity management can be perceived as a challenge in a routine practice. Clinicians often feel too busy and ill-equipped to address the issue and may even avoid it altogether. However, given that almost two thirds of the US population is either overweight or obese and the majority suffer at least one or more weight-related comorbidity, it is a disease that primary care physicians (PCPs) and other practitioners cannot afford to ignore.

Treatment of the obese individual is based on both the clinical and laboratory assessment of each patient. Combining this information can provide an assessment of the severity of the obesity, determine the associated risks, and guide an appropriate and individualized treatment approach.

Weight-Specific History

A medical evaluation must include specific questions about the person's weight and lifestyle in order to develop an individualized treatment plan.

- Review of the patients' current weight as well as his/her highest adult weight and lowest weight.
- Review of any specific periods of weight gain. Patients will often be able to pinpoint life events (marriage, child birth, new job, relocation, a death in the family) which may have been associated with significant lifestyle changes and or psychosocial stressors which triggered weight gain. In addition, determining whether the weight gain began in childhood can help

determine whether the patient needs an evaluation for secondary causes of obesity.

- What type of diets has the patient tried in the past? How many times has the patient attempted weight loss and did it work? It is important to understand what works well for the patient and to determine if the patient's weight cycles. By examining a weight-cycling history, the clinician can try to understand the previous challenges faced both in losing the weight but more importantly, with maintaining weight loss. Once this is discussed, the clinician can help determine what approach might work best for each patient.
- Review the patient's current dietary habits including general habits (do they skip breakfast or eat one large meal per day?), review frequency of eating out vs home meal preparation and determine who does the usual grocery shopping (to help determine whether patients have a perceived lack of control over their own intake).
- Review related psychiatric history, including anxiety or depression, which may translate into disordered eating habits. Determine whether the patient may suffer from binge eating or other maladaptive eating patterns (binge-purge, night-eating) as these may require further referral to a mental health specialist. Often patients may be ashamed of some of their behaviors but it is imperative to assess these in order to tailor the treatment plan and identify barriers to success.
- Evaluate the patient's physical lifestyle. It is important to determine whether the patient has a sedentary lifestyle, whether they exercise, and how you may be able to improve their physical activity and incorporate it into their daily lives (ie, you may be able to encourage them to walk where they would have otherwise driven, encourage them to use the stairs vs elevator, etc). It is important to uncover whether there are barriers in their ability to perform activities (eg, OA of the knees) and help address these issues as part of the treatment plan.
- Diet recall—it is important to fully understand the patient's daily food choices and portions. There are a number of tools including a 24-hour Diet Recall, food frequency questionnaire and/or food journal which can help make a basic assessment. It is also important to note frequency and quantity of both liquid/caloric drinks as well as alcohol intake.

Review of Weight-Promoting Medications

Certain medications can cause weight gain and increase body fat, thereby making weight loss more difficult. **Table 6.1** provides a partial list of drugs and drug classes that contain medications associated with weight gain. These drugs differ in their propensity to increase body weight. The mechanism responsible for medication-induced weight gain has not been carefully studied for most of these agents, but must be related to an increase in energy intake (eg, antipsychotics and steroid hormones), a decrease in energy expenditure (eg, β-adrenergic receptor blockers), a decrease in energy loss (eg, decreased glycosuria from diabetes therapy), or a combination of these factors.[1] Weight-loss therapy can be facilitated by decreasing the dose or substituting the medication with another drug that has less weight gain potential, if possible.

Patient Examination

Assessment of all patients should include the evaluation of BMI, waist circumference, and a complete physical examination.

BMI

Measuring the BMI is the first step to determine the degree of adiposity. BMI has been used by the WHO as the standard for recording obesity

TABLE 6.1 — Classes of Medications Promoting Weight Gain

Tricyclic Antidepressants
- Amitriptyline
- Nortriptyline
- Imipramine

Monoamine Oxidase Inhibitors
- Phenelzine

SSRIs
- Paroxetine
- Citalopram

Tetracyclic Antidepressant
- Mirtazapine

Atypical Antipsychotics
- Clozapine
- Olanzapine
- Risperidone
- Quetiapine

Antimanic Agent
- Lithium

Anticonvulsants
- Valproic acid
- Carbamazepine

Steroids
- Glucocorticoids
- Progestins

Antidiabetics
- Insulin
- Sulfonylureas-glyburide
- Thiazolidinediones
- Rosiglitazone
- Pioglitazone

α-Adrenergic Blockers
- Prazosin
- Doxazosin
- Terazosin

Continued

TABLE 6.1 — *Continued*

Nonselective β-Blockers
- Propranolol
- Atenolol
- Metoprolol

Antihistamines
- Diphenhydramine
- Meclizine
- Cyproheptadine

Antineoplastics
- Megestrol

statistics since the early 1980s. BMI can be calculated quickly and without expensive equipment. More importantly, it can identify patients with increased risk of morbidity and mortality.

However, BMI categories do not take into account many factors such as muscularity and frame size. BMI is particularly inaccurate for people who are fit or athletic, as the higher muscle mass tends to put them in the overweight category by BMI, even though their body fat percentages frequently fall in a normal range. BMI also does not account for body frame size; a person may have a small frame and be carrying more fat than optimal, but their BMI reflects that they are normal. Conversely, a large-framed individual may be quite healthy with a fairly low body fat percentage but be classified as overweight by BMI.

Despite this, BMI categories are regarded as a satisfactory tool for measuring whether individuals are underweight, overweight, or obese. To estimate BMI, multiply the individual's weight (in pounds) by 703, then divide by the height (in inches) squared. This approximates BMI in kilograms per meter squared (kg/m^2) (**Table 6.2**).

■ Waist Circumference and Waist-Hip Ratio

Although BMI has traditionally been the chosen indicator by which to measure body size, alternative measures that reflect abdominal adiposity, such as

TABLE 6.2 — BMI

Category	BMI Range (kg/m^2)
Low	≤18.5
Normal	18.5-25.0 (standard weight: 22)
Overweight	25.0-30.0
Obese:	
Class I	30.0-35.0
Class II	35.0-40.0
Class III	≥40.0

waist circumference, waist-hip ratio, and waist-height ratio, have been suggested as being superior to BMI in predicting CVD risk.

Visceral fat, also known as intra-abdominal fat, is located inside the peritoneal cavity, in between internal organs and the torso, as opposed to subcutaneous fat, which is found underneath the skin, and intramuscular fat, which is found interspersed in skeletal muscle. An excess of visceral fat is known as central obesity. Increased visceral adipose tissue is associated with a range of metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, which are risk factors for T2D and CVD.

The absolute waist circumference (>102 cm [40 in] in men and >88 cm [35 in] in women) and the waist-hip ratio (>0.9 for men and >0.85 for women) are both used as measures of central obesity. Waist circumference measurement is particularly useful in patients who are categorized as normal or overweight. Men who have waist circumferences >40 inches, and women who have waist circumferences >35 inches, are at higher risk. Individuals with waist circumferences greater than these values should be considered one risk category above that defined by their BMI.

According to the NIH guide to obesity (NHLBI Obesity Education Initiative, 2000), the waist circumference measurement should be made at the top of the iliac crest with the measuring tape held snuggling at

a level parallel to the floor. The patient should stand with their feet close together, arms at the side, and body weight evenly distributed. Waist circumference should be measured at the end of a normal expiration, when the lungs are at their functional residual capacity. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the two measurements exceeds 1 cm, the two measurements should be repeated.

■ Percent Body Fat

Since the pathology of obesity is increased when both the number and size of adipose cells are increased, estimation of body fat percentage is a useful step during risk assessment. Body fat percentage is the total mass of fat divided by total weight. Total body fat includes essential body fat and storage body fat. Essential body fat is necessary to maintain life and reproductive functions. The percentage of essential body fat for women is greater than that for men, due to the demands of childbearing and other hormonal functions. The percentage of essential fat is 2% to 5% in men, and 10% to 13% in women. Storage body fat consists of fat accumulation in adipose tissue, part of which protects internal organs in the chest and abdomen. The minimum recommended total body fat percentage exceeds the essential fat percentage value reported above. A number of methods are available for determining body fat percentage, such as measurement with calipers, bioelectrical impedance analysis, and dual energy x-ray absorptiometry (DXA, formerly DEXA).

Suggested body fat percentages have been proposed (**Table 6.3**) and the numbers vary based on sex, age, and ethnicity.[2]

The skin-fold estimation methods are based upon a test whereby a pinch of skin is precisely measured by calipers at several standardized points on the body to determine the subcutaneous fat layer thickness.[3] These

TABLE 6.3 — Variations in Percentage of Body Fat for Blacks, Asians, and Whites

	Females (Fat %)			Males (Fat %)		
BMI	**Black**	**Asian**	**White**	**Black**	**Asian**	**White**
Age 20-39						
18.5	20	25	21	8	13	8
25	32	35	33	20	23	21
30	38	40	39	26	28	26
Age 40-59						
18.5	21	25	23	9	13	11
25	34	36	35	22	24	23
30	39	41	41	27	29	29

Gallagher D, et al. *Am J Clin Nutr*. 2000;72(3):694-701.

measurements are converted to an estimated body fat percentage by an equation. Some formulas require as few as three measurements, others as many as seven. The accuracy of these estimates is more dependent on a person's unique body fat distribution than on the number of sites measured. Although it may not give an accurate reading of real body fat percentage, it is a reliable measure of body composition change over a period of time, provided the test is carried out by the same person with the same technique.

DXA is a method for estimating body fat percentage, and determining body composition and bone mineral density. X-rays of two different energies are used to scan the body, one of which is absorbed more strongly by fat than the other. A computer can subtract one image from the other, and the difference indicates the amount of fat relative to other tissues at each point. A sum over the entire image enables calculation of the overall body composition.

The bioelectrical impedance analysis (BIA) method is a low cost way to estimate body fat percentage. The general principle behind BIA: two or more conductors are attached to a person's body and a small electric current is sent through the body. The resistance between the conductors will provide a measure of body fat between a pair of electrodes, since the resistance to electricity varies between adipose, muscular, and skeletal tissue. Fat-free mass (muscle) is a good conductor as it contains a large amount of water (approximately 73%) and electrolytes, while fat is anhydrous and a poor conductor of electric current. Factors that affect the accuracy and precision of this method include instrumentation, subject factors, technician skill, and the prediction equation formulated to estimate the fat-free mass. There is little scope for technician error, but factors such as eating, drinking and exercising must be controlled since hydration level is an important source of error in determining the flow of the electric current to estimate body fat.[4]

■ **Physical Examination**

The physical exam should be focused on both characterizing obesity, as well as looking for causes and associated complications. As mentioned above, the patient's height and weight should be carefully measured and recorded in addition to their waist circumference. The patient's vital signs should be taken with special care to the fact that they may need specialized equipment to determine accurate readings. In assessing the BP, it is important to use an accurate size cuff because if it is too narrow, the BP may be falsely elevated. The cuff should be approximately 40% to 50% of the upper arm circumference. The clinician may need either a large adult cuff or thigh cuff, depending on the patient.

A routine physical exam should be performed in a supportive and nonthreatening manner. Attention should be paid towards looking for associated medical conditions including thin, atrophic skin (a feature of Cushing's disease), hyperpigmented skin around the neck or axilla (acanthosis nigricans, associated with insulin resistance), large neck circumference (increased risk of OSA), and hirsutism (may indicate polycystic ovarian syndrome).

Laboratory Evaluation

Basic laboratory evaluation should include examination for obesity-related conditions. This should include a fasting plasma glucose, fasting lipid panel, TSH (thyroid function modulates weight), liver transaminases to look for NASH, as well as basic metabolic panel (to assess kidney function). Laboratory testing for specific disease and medication should be done depending on the patient history. For example, HbA1C is important to monitor diabetic patients and their response to treatment.

■ **Baseline Laboratory Evaluation**

- Fasting plasma glucose
- Fasting lipid panel (total cholesterol, LDL, HDL, triglycerides)
- TSH
- ALT, AST
- Electrolytes
- Renal function (creatinine, BUN)
- Disease-related tests (eg, A1C for patients with diabetes)

Further evaluation for endocrine or genetic causes and related comorbidities may be warranted depending on the patient's medical history and physical exam. For example, depending on the physical exam, a work-up for Cushing's disease may be warranted (central obesity, abdominal striae, moon facies, buffalo hump) and this can be done with either a 24-hour urinary free cortisol or overnight dexamethasone suppression test.

Evaluation for Weight-Related Comorbidities

Upon completion of the basic medical assessment, additional medical problems may be unmasked. In the obese patient, many of these medical problems should be evaluated as they may complicate or alter the treatment plan:

- Respiratory—hypoventilation syndromes are common in obese patients and include both OSA and obesity hypoventilation syndrome. These conditions can lead to pulmonary hypertension, arrhythmias, and depression. The risk for OSA can quickly assessed by using the so-called STOP-BANG questionnaire (**Figure 6.1**). It is important to promptly evaluate for these conditions with the appropriate referrals for either a sleep study or pulmonary evaluation.

FIGURE 6.1 — STOP BANG Questionnaire for Sleep Apnea

STOP		
Snoring		
Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	□ Yes	□ No
Tired		
Do you often feel tired, fatigued, or sleepy during daytime?	□ Yes	□ No
Observed		
Has anyone observed you stop breathing during your sleep?	□ Yes	□ No
Blood ***P***ressure		
Do you have or are you being treated for high blood pressure?	□ Yes	□ No
BANG		
BMI >35 kg/m^2?	□ Yes	□ No
Age >50 years old?	□ Yes	□ No
Neck circumference >15.75 inches (40 cm)?	□ Yes	□ No
Gender male?	□ Yes	□ No
Calculate OSA Risk		
≥3 yes answers: high-risk for OSA		
<3 yes answers: low-risk for OSA		

- Cardiovascular—the American Heart Association classifies obesity as a major modifiable risk factor for coronary heart disease, independent of its comorbidities. Specific comorbid conditions may include coronary artery disease, hypertension, left ventricular hypertrophy, cor pulmonale, and obesity-associated cardiomyopathy.
- Gastrointestinal—common complications include NASH, fatty liver infiltration, and reflux esophagitis.
- Orthopedic—many patients suffer from OA which may limit their physical functioning and ability to perform an exercise program.

- Metabolic—numerous metabolic disturbances may be found including T2D, prediabetes, metabolic syndrome, and dyslipidemia. These conditions should be aggressively managed during the course of any weight loss intervention.
- Reproductive—women often have weight related reproductive challenges including anovulation, early puberty, infertility, hyperandrogenism, polycystic ovaries and pelvic stress incontinence. Screening and appropriate referrals should be made as needed.
- Cutaneous—intertrigo (bacterial and/or fungal) is a common challenge faced by obese patients. It is important to assess and subsequently counsel patients on good hygiene to prevent further complications.
- Psychiatric—major psychiatric illness may present an obstacle or even contraindication to treatment. A common finding is mild-moderate depression, and patients should be screened and may require behavioral therapy and/or medication with referral to psychiatry depending on the severity.

Disease Staging and Risk Assessment

The patient's risk status should be assessed by determining the degree of overweight or obesity based on BMI, the presence of abdominal obesity based on waist circumference, and the presence of concomitant CVD risk factors or comorbidities. Some obesity-associated diseases and risk factors place patients in a very high risk category for subsequent mortality. These diseases will require aggressive modification of risk factors in addition to their own clinical management.

Much, if not most, of the relevant information for clinical risk assessment and disease staging of overweight/obese patients is readily available to the clinician in routine clinical practice. Additional information

can be obtained from several validated assessment and disease staging tools such as the EOSS (discussed in *Chapter 4*).

Assessment of Motivation

Before initiating a treatment plan, it is important to determine whether a patient is ready to make the necessary changes, as not all patients are ready to lose weight. When counseling the patient, the plan should be individualized to their specific needs and allow for flexibility in order to prevent the patient from feeling like a failure.

Realistic Goal Setting

Patients often have unrealistic expectations about how much weight they would like to lose. These expectations are often driven by the desire for cosmetic outcomes rather than health outcomes. It is not necessary to achieve an "ideal" body weight or normal BMI because the health benefits are often achieved when a patient loses as little as 5% to 10% of their weight. The rate of weight loss is not necessarily important, however, usual goals target approximately 1-2 lb/week over the course of 6 months. Goal setting should occur in conjunction with the patient and may be modified over time. Weight loss alone should not be the only aim of treatment, rather improvement in obesity-related comorbidities should be a primary goal and monitored throughout treatment (see *Chapter 4*). Long-term treatment plans should be in place to assist with weight maintenance and avoidance of weight regain.

Office Equipment

The care of obese patients requires appropriate body size office equipment and supplies since patient comfort and perceived acceptance may dictate his or her willingness to participate in a weight-loss treatment plan. Office equipment should include oversized chairs in both the exam and waiting rooms, scales that can be used for patients up to at least 500 lb, long tape measures, oversized BP cuffs, and gowns of appropriate sizing.

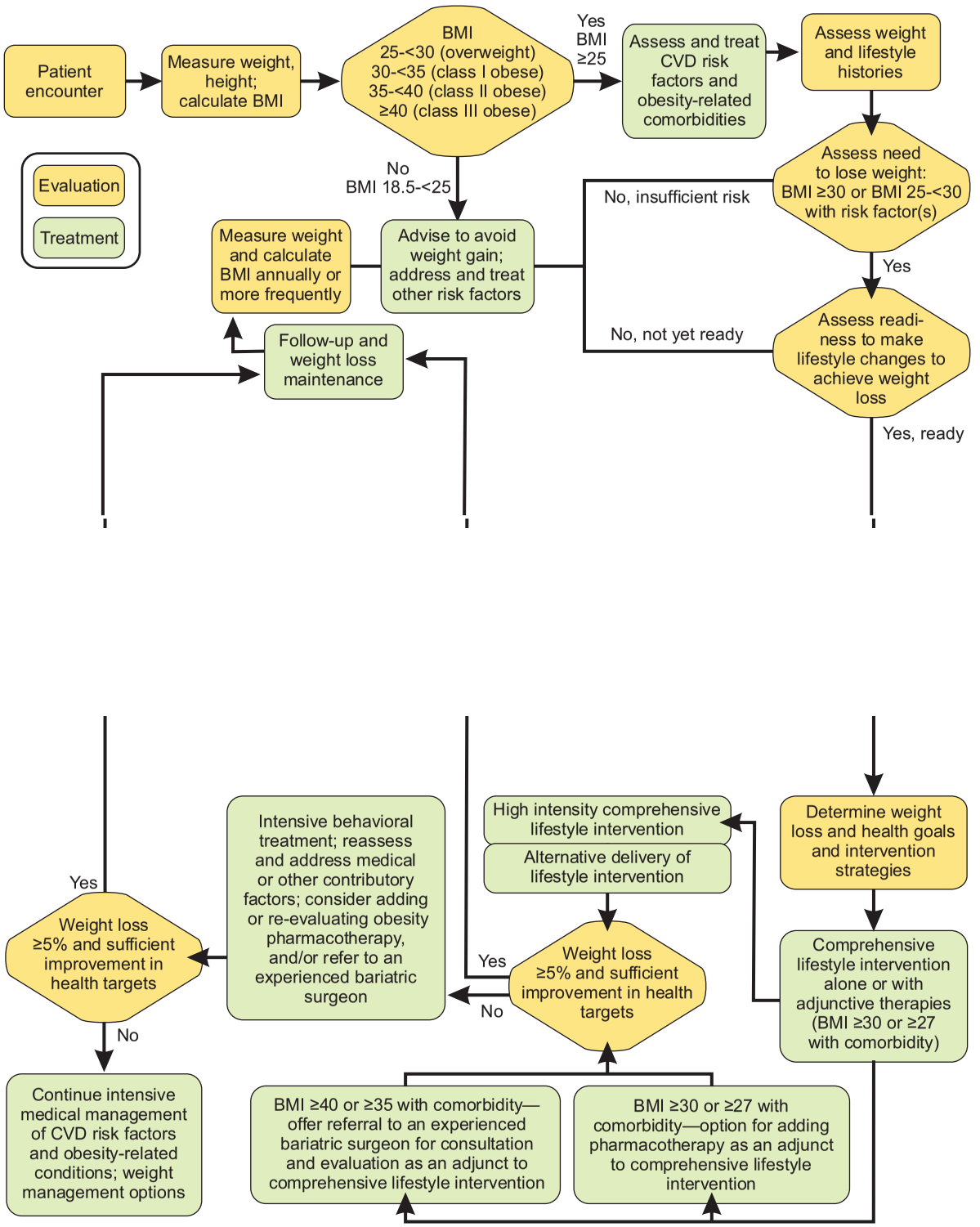
Creating a Treatment Plan

The treatment of obesity should be based upon the degree of adiposity and the prevalence and risks of weight-related comorbidities. A higher risk patient may require a more aggressive intervention such as pharmacotherapy and surgery. All plans should be flexible to accommodate an individual's needs and preferences. The Comprehensive Diabetes Management Algorithm published by the AACE in April 2013 provides an obesity-specific treatment algorithm for the management of overweight and obese patients (see *Chapter 4*).

In addition, **Figure 6.2** is the treatment algorithm from the 2013 AHA/ACC/TOS Guideline For The Management Of Overweight And Obesity In Adults.[5] It is based on the Chronic Disease Management Model for Primary Care of Patients with Overweight and Obesity to guide PCPs in the evaluation, prevention, and management of patients regarding excess body weight. The algorithm is not intended to supplant initial assessment for CV risk factors or diseases but rather focuses on the identification of patients with excess body weight and those at risk for obesity-related health problems. Its purpose is to guide weight management decision making. This intervention should be a foundation for additional weight management efforts, such as addition of medications or bariatric surgery.

All treatment programs should include a comprehensive team approach and may include a physician, registered dietician, social worker, psychiatrist, nurse, and surgeon. Effective management requires sufficient time and frequent monitoring in order to keep the patient motivated and provide accountability. Once a patient achieves a reasonable goal weight, it may take

FIGURE 6.2 — 2013 AHA/ACC/TOS Treatment Algorithm for Patients With Overweight and Obesity



Jensen MD, et al. [published online ahead of print November 12, 2013]. *Circulation.* doi: 10.1161/01.cir.0000437739.71477.ee.

as much, if not more, time to maintain the weight loss. Given that obesity is a chronic disease, it is paramount that patients have long-term monitoring in order to prevent or at least minimize weight regain.

REFERENCES

1. Pijl H, Meinders AE. Bodyweight changes as an adverse effect of drug treatment. *Drug Safety*. 1996;14:329-342.
2. Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: guidelines based on body fat index. *Am J Clin Nutr*. 2000;72:694-701.
3. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr.* 1974;32(1):77-97.
4. Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henzchel A. *Techniques for Measuring Body Composition.* Washington: National Academy of Sciences. 1961:224-244.
5. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American college of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published online ahead of print November 12, 2013]. *Circulation*. doi: 10.1161/01.cir.0000437739.71477.ee.

7 Drug-Induced Weight Gain

A variety of prescription medications have been associated with weight gain. These drugs differ in their propensity to increase body weight.[1] The mechanism responsible for medication-induced weight gain has not been carefully studied for most of these agents but may be related to an increase in energy intake (eg, antipsychotics and steroid hormones), a decrease in energy expenditure (eg, β-adrenergic receptor blockers), a decrease in energy loss (eg, decreased glycosuria from diabetes therapy), or a combination of these factors.[2] This chapter will review weight gain associated with several classes of prescription medications, including antidiabetics, antihypertensives, anticonvulsants, steroid hormones and contraceptives, antidepressives and antipsychotics, and antihistamines.

Treatment Selection to Prevent Drug-Induced Weight Gain

Drug-induced weight gain is a preventable cause of obesity, and can be avoided by selecting alternative treatments that promote weight neutrality or even weight loss. The desired level of clinical efficacy for a chosen therapy should be balanced against side effects, including the likelihood of weight gain. In cases where there are no acceptable therapeutic alternatives, the minimal dose required to produce clinical efficacy may prevent drug-induced weight gain. The patient's initial weight status, the presence of risk factors for CV disease, diabetes, and other obesity-related health complications, as well as the benefits of pharmacologic therapies warrant careful consideration when prescribing a first-line therapy or change in medication.[3] The expected length of treatment is also a factor, as some

medications may be associated with weight loss in the short-term (<1 year), but with weight gain in the long-term (>1 year) and vice versa.[4]

Patients should be informed of potential drug-induced weight gain and educated on weight management techniques, such as proper nutrition, physical exercise, and behavioral modification. Individual patient risk profiles can also be assessed. For appropriate medication selection, physicians should consider the weight gain potential of various drugs.[5]

Table 7.1 provides a partial list of drugs and drug classes that contain medications associated with weight gain, weight neutrality, and weight loss.

Antidiabetic Medications

Many patients with T2D are overweight or obese, both of which are associated with increased patient risk of CV events and mortality.[6] Unfortunately, weight gain is often associated with many diabetes therapies. Patients can gain as much as 10 kg after initiating treatment with insulin, sulfonylureas other insulin secretagogues, and the thiazolidinediones (TZDs). The causes of this weight gain are not fully understood but are thought to be due to drug-induced changes in the body's metabolic control, which result in a state of positive energy balance, eventually leading to weight gain.[7] Weight gain is of particular concern in patients with diabetes, because of the rise in insulin resistance associated with excess weight and obesity.[8]

The most common classes of drugs which can promote weight gain include insulin therapy, sulfonylureas, and thiazolidinediones (TZDs). The weight gain observed with insulin therapy appears to be greater than the weight gain associated with oral hypoglycemic agents, although it is difficult to compare, as patients who require insulin therapy generally have more severe diabetes and may experience more drastic changes in energy conservation. The amount of weight gain associated with insulin therapy is associated with the daily

insulin dose and mean plasma insulin level.[9] Weight gain–associated sulfonylurea medications, another class of antidiabetic drugs, is related to the resulting increased insulin secretion. TZDs are another class of commonly used oral antihyperglycemic agents, which are often associated with weight gain. These compounds, including rosiglitazone and pioglitazone, lower glucose concentrations by increasing peripheral insulin sensitivity. Pioglitazone is currently recommended as the preferred TZD for treatment of T2D.[3,10]

There are both weight neutral and weight loss–enhancing diabetes medications available. The most commonly used oral agent for the treatment of T2D is metformin. Metformin promotes mild weight loss by multiple mechanisms including reducing hepatic glucose production and intestinal absorption of glucose, while improving insulin sensitivity. Similarly, the dipeptidyl peptidase 4 (DPP-4) inhibitors are considered to a weight-neutral class.[11] DPP-4 inhibitors exert slightly less pronounced blood glucose reductions than metformin but have better GI tolerability.[12] DPP-4 inhibitors lower plasma glucose by enhancing insulin release and reducing glucagon secretion. DPP-4s in combination with metformin have been shown to be safe and effective for patients with T2D.[10] A study comparing a DPP-4 and metformin with pioglitazone in patients with T2D showed that the DPP-4/metformin treatment combination resulted in weight loss (-1.4 kg) while pioglitazone led to weight gain (3.0 kg).[10]

There are newer classes of drugs that target pathways which actually promote weight loss, including the injectable medications exenatide and liraglutide. They act by mimicking the GI incretin hormone glucagon-like peptide (GLP-1), which is normally released in response to food intake. GLP-1 agonists enhance glucose-dependent insulin secretion, suppress glucagon and slow gastric emptying. GLP-1 agonists lead to improved glycemic control, decrease food intake, and enhanced satiety. Data have shown that patients can lose up to 4.4 kg after 1 year of treatment with a GLP-1 agonist.[13]

TABLE 7.1 — List of Select Drugs That Are Weight Gaining, Weight Neutral, and Weight Reducing for Each Type of Treatment

Weight Gain	Weight Neutral	Weight Loss
Antidepressants		
Nortriptyline	Bupropion	Bupropion
Doxepin	Fluoxetine (<1 year)	
Amitryptyline, imipramine	Sertraline (<1 year)	
Phenelzine	Nefazodone	
Paroxetine		
Citalopram		
Fluoxetine (>1 year)		
Sertraline (>1 year)		
Mirtazapine		
Antihypertensives		
Prazosin	Carvedilol	
Doxazosin	Nebivolol	
Terazosin		
Metoprolol tartrate		
Propranolol		
Atenolol		
Metopropolol\		
Antidiabetics		
Insulin	Alpha-glucosidase inhibitors	Metformin
Sulfonylureas (glyburide)	Acarbose (Precose)	GLP-1 agonists
Thiazolidinediones (rosiglitazone and pioglitazone)	Miglitol (Glycet)	Exenatide
	DPP-4 inhibitors	Liraglutide
		Glimepiride
		Vidagliptin
		Sitagliptin
		Pramlintide
		Sodium glucose cotransporter 2 (SGLT2) inhibitors
Anti-epileptics		
Gabapentin	Lamotrigine	Felbamate
Pregabalin	Levetiracetam	Topiramate
Valproic acid	Phenytoin	Zonisamide
Vigabatrin		
Carbamazepine		

Continued

TABLE 7.1 — *Continued*

Weight Gain	Weight Neutral	Weight Loss
Contraceptives and Hormones		
Depo-medroxyprogesterone acetate		
Megestrol acetate (not a contraceptive but falls in the class of hormones)		
Antihistamines		
Diphenhydramine		
Meclizine		
Cyproheptadine		
Antipsychotics		
Clozapine	Ziprasidone	
Olanzapine	Aripiprazole	
Risperidone		
Quetiapine		
Perphenazine		
Lithium		
Steroids		
Glucocorticoids		
Progestins		
Corticosteroids (ie, prednisone)		

Another new class of drug for the treatment of patients with T2D, sodium glucose cotransporter 2 (SGLT2) inhibitors, reduces glucose reabsorption by the kidneys, resulting in increased urinary glucose excretion. Due to the subsequent caloric loss, treatment with SGLT2 agents may result in weight loss in addition to reduced hyperglycemia. Studies of SGLT2 inhibitors in patients with T2D have shown patient weight reductions from baseline of up to 4.7 kg.[6]

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society recommends weight-losing and weight-neutral medications as first- and second-line agents in the management of T2D.[3] Specific antidiabetic medications that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Antihypertensive Medications

β-blockers have long been used for the treatment of hypertension[14] and have been shown to be efficacious at decreasing CV morbidity and mortality. However, in certain populations, such as in patients with diabetes and hypertension, therapy with traditional β-blockers has been associated with adverse effects on lipid and insulin balance, leading to weight gain. Increased body weight is a particular clinical problem in the vast majority of hypertensive patients.[8,15] Treatment with β-blockers can decrease the metabolic rate by as much as 10%.[14] An analysis of eight randomized controlled hypertension trials showed that changes in body weight was higher in those that received β-blockers, with a median difference of 1.2 kg between the β-blocker group and the control group.[15]

However, not all β-blockers are associated with weight gain. Selective β-blockers with a vasodilating component such as carvedilol and nebivolol appear to have less weight gain potential and less of an impact on glucose and lipid metabolism.[15,16] Unlike metoprolol tartrate, carvedilol was not found in comparison studies

to be associated with significant weight gain in patients with hypertension.[8]

Treatments for hypertension that are not associated with weight gain or insulin resistance include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and calcium channel blockers (CCBs).[17] Angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, providing support for the use of ACE inhibitors. CCBs are also effective in the treatment of obesity-related hypertension and have not been associated with weight gain or adverse changes in lipids.

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society recommends the use of ACE inhibitors, ARBs, and CCBs rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2D and obesity.[8,14,18,19] Specific antihypertensive drugs that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Anticonvulsant Medications

Pharmacologic treatment for epilepsy may be associated with substantial weight changes that may increase morbidity and impair adherence to the treatment regimen.[20] Anti-epileptic drugs (AEDs) known to cause weight gain include valproic acid, carbamazepine, and gabapentin. Valproic acid has been shown to cause weight gain in both adults and children.[21] A study of long-term weight gain in adult epileptic patients on valproic acid therapy showed marked weight gain (>10% of baseline weight) in 47% of patients.[22] Carbamazepine has also been associated with weight gain, although not as significant as valproic acid or gabapentin,[23] and is sometimes classified as a weight-neutral AED.[20]

In clinical practice, it is critical to weigh patients regularly and AED selection should be based on each patient's profile without sacrificing therapeutic efficacy.

The first step in treatment is to weigh all patients at each visit, calculate BMI, and react to weight changes. In some patients, waist circumference may be an independent measure of health risk.[20] The CGS of The Endocrine Society recommends considering weight gain potential in choosing an AED for any given patient. Specific AEDs that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Contraceptives, Hormones, and Steroids

Weight gain is a complaint of some women using oral, injectable, and transdermal contraceptives and may cause discontinuation of treatment.[24,25] Specifically, the use of the progestins depo-medroxyprogesterone acetate and megestrol acetate has been associated with weight gain. Megestrol acetate has been prescribed to induce weight gain in wasting illnesses, such as acquired immunodeficiency syndrome (AIDS) and cancer. Studies have found that women who used depo-medroxyprogesterone continuously for 1 or 2 years experienced more average weight gain than those who did not.[26,27]

Specifically, weight gain after 1 year of use may range from 0.63-8.04 kg and increase further with ongoing use. Although not every patient will gain weight, predicting which patients will experience substantial weight gain is not simple. Le and colleagues found that women who experience >5% weight gain increase within 6 months of depot medroxyprogesterone acetate (DMPA) use puts them at high risk for continued weight gain.[28]

Still, the research on oral contraceptives and weight gain is conflicting. Some studies show significant increases in body weight, total cholesterol, and triglycerides in patients before and after contraceptive use,[29] while others emphasize the lack of concrete changes in weight gain over menstrual cycles.[25] In

2011, the Cochrane Review conducted a meta-analysis of 49 trials of contraceptives and determined that the current data are not sufficient to establish an effect of oral contraceptives on weight.[30] In women with a BMI >27 with comorbidities or >30, the CGS of The Endocrine Society recommends using barrier methods or non-hormonal IUDs before contraceptives that may be associated with weight gain.[3] Specific contraceptives that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

In menopausal women taking hormone replacement therapy (HRT), drug-induced weight gain may contribute to the poor patient compliance and greater CV disease risk. It is difficult to quantify the specific impact of HRT on body weight and fat distribution because menopause itself is associated with changes in body composition, energy metabolism, and physical activity. Weight gain has not been consistently observed as a side effect of HRT but rather varies considerably, not only with respect to weight change but also changes in fat distribution.[7,31]

Long-term anti-inflammatory treatment of asthma with systemic corticosteroids frequently leads to fluid retention and weight gain. Even inhaled corticosteroids, which act locally and are rapidly processed by the body, are associated with weight gain. A recent retrospective cohort study demonstrated that overweight and obese pregnant women were more at risk for asthma than lean women, and that women who gained ≥20 kg had a 2.7-fold increased odds of asthma compared with those who maintained their weight.[32] The CGS of The Endocrine Society recommends the use of nonsteroidal anti-inflammatory drugs (NSAIDs) where possible.[3]

Antipsychotic and Antidepressive Medications

Weight gain is a common adverse effect of psychotropic drugs such as antipsychotics, antidepressants, mood stabilizers, and anxiolytics.[5] Antidepressants

vary considerably with respect to their long-term weight gain potential, often depending on the length of therapy.[4] Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been associated with significant weight gain. Several reports suggest that weight gain with TCAs ranged from 0.57 kg (1.27 lb) to nearly 1.4 kg (3.1 lb) per month of treatment.[3] Newer drugs, such as selective serotonin reuptake inhibitors (SSRIs) are now the preferred treatment for patients with depression. However, it must be noted that some SSRIs have been associated with weight loss during short-term treatment, but weight gain during long-term treatment.[4] Therefore, when choosing an antipsychotic treatment, the duration of therapy is especially important.[5]

The CGS of The Endocrine Society recommends carefully weighing patient response and desired clinical efficacy with the potential of the antidepressant to cause weight gain. For example, while the SSRI paroxetine is associated with weight gain, bupropion is a weight neutral antidepressant. Although bupropion does not have the same efficacy or side-effect profile as SSRIs, it may be of benefit in those with depression. However, bupropion therapy is associated with an elevated risk of anxiety and may worsen some forms of depression.[3] Specific antidepressants that are associated with weight gain, weight neutrality, and weight loss are outlined in **Table 7.1**.

Many antipsychotic agents have weight gain as a side effect,[33] which may impede patient compliance, and exacerbate existing health issues in already overweight patients.[33,34] Different types of antipsychotic medications have different effects on histamine receptors, anticholinergic effects, and serotonin antagonistic response. A study investigating the effectiveness of five antipsychotic medications found that a weight gain of >7% from baseline occurred in 30% of those taking olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% of those taking ziprasidone.[35]

Since most antipsychotics are associated with weight gain, the CGS of The Endocrine Society recommends considering more weight neutral alternatives such as ziprasidone and aripiprazole when clinically indicated.[3] These drugs have been shown in clinical studies to cause less weight gain than other antipsychotics.[33,36,37]

Other Medications That May Induce Weight Gain

Potent antihistamines may contribute to weight gain. Histamine is a neurotransmitter released by the posterior hypothalamus. Intravascular administration of histamine reduced food intake in animal studies, whereas histamine antagonism stimulates food intake. H_1-receptor antihistamines, such as cetirizine, fexofenadine, and desloratadine, are among the most commonly prescribed medications for allergies and have been shown to stimulate appetite and weight gain as side effects of treatment.[38] Although it is not known whether the weight gain potential of sedating vs non-sedating antihistamines differ, it appears that it is proportional to the potency of the antihistamine.[7] A recent study demonstrated that the chances of being overweight were increased in patients who were prescribed antihistamines. Antihistamine users were also shown to have significantly higher weight, waist circumference, and insulin concentration than non-users.[39] The CGS of The Endocrine Society recommends the use of milder, less centrally acting antihistamines, when possible.[3]

Treatments for human immunodeficiency virus (HIV) include administration of antiretroviral therapy and protease inhibitors. Although effective for suppressing HIV viral activity, such treatments are associated with changes in the deposition of fat tissue in the body.[40,41] One study of 10 HIV patients treated with protease inhibitor-containing regimens found that patients gained an average of 19 lb after a period of 6 months.[40]

REFERENCES

1. Leslie WS, Hankey CR, Lean, ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. *QJM*. 2007;100(7):395-404.
2. Pijl H, Meinders AE. Bodyweight changes as an adverse effect of drug treatment. *Drug Safety*. 1996;14:329-342.
3. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of the obese patient: an Endocrine Society Clinical Practice Guideline. Paper presented at: 16th International Congress of Endocrinology & the Endocrine Society's 96th Annual Meeting & Expo; June 21-24, 2014; Chicago, IL.
4. Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J Clin Psychiatry*. 2001;62(4):256-260.
5. Masand PS. Weight gain associated with psychotropic drugs. *Expert Opin Pharmacother.* 2000;1(3):377-389.
6. Barnett AH. Impact of sodium glucose cotransporter 2 inhibitors on weight in patients with type 2 diabetes mellitus. *Postgrad Med*. 2013;125(5):92-100.
7. Aronne LJ. Drug-induced weight gain: non-CNS medications. In: *A Practical Guide to Drug-Induced Weight Gain*. Minneapolis, MN: McGraw-Hill: 2002:77-91.
8. Messerli FH, Bell DS, Fonseca V, et al; GEMINI Investigators. Body weight changes with beta-blocker use: results from GEMINI. *Am J Med*. 2007;120(7):610-615.
9. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130:389-396.
10. Wainstein J, Katz L, Engel SS, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2012;14(5):409-418.
11. Ross SA, Ekoé JM. Incretin agents in type 2 diabetes. *Can Fam Physician*. 2010;56(7):639-648.
12. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. *Diabetes Metab*. 2012;38(2):89-101.

13. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28(5):1083-1091.

14. Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. *Obes Rev*. 2001; 2(4):275-280.

15. Sharma, AM, Pischon T, Hardt S, Kunz I, Luft FC. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension*. 2001;37(2):250-254.

16. Manrique C, Whaley-Connell A, Sowers JR. Nebivolol in obese and non-obese hypertensive patients. *J Clin Hypertens*. 2009;11(6):309-315.

17. Wing LM, Reid CM, Ryan P, et al; Second Australian National Blood Pressure Study Group. A Comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348(7):583-592.

18. Lee P, Kengne AP, Greenfield JR, Day RO, Chalmers J, Ho KK. Metabolic sequelae of β-blocker therapy: weighing in on the obesity epidemic? *Int J Obes (Lond)*. 2011;35(11):1395-1403.

19. Kumpusalo EA, Takala JK. Do beta-blockers put on weight? *Hypertension*. 2001;38(1):E4-E5.

20. Ben-Menachem E. Weight issues for people with epilepsy–a review. *Epilepsia*. 2007;48(suppl 9):42-45.

21. Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. *Obes Rev*. 2011;12(5):e32-e43.

22. Corman CL, Leung NM, Guberman AH. Weight gain in epileptic patients during treatment with valproic acid: a retrospective study. *Can J Neurol Sci*. 1997;24(3):240-244.

23. Jallon P, Picard F. Bodyweight gain and anticonvulsants: a comparative review. *Drug Saf*. 2001;24(13):969-978.

24. Ness-Abramof R, Apovian CM. Drug-induced weight gain. *Timely Top Med Cardiovasc Dis*. 2005;9:E31.

25. Rosenberg, M. Weight change with oral contraceptive use and during the menstrual cycle. Results of daily measurements. *Contraception*. 1998;58(6):345-349.

26. Espey E, Steinhart J, Ogburn T, Qualls C. Depo-provera associated with weight gain in Navajo women. *Contraception*. 2000;62(2):55-58.

27. Bahamondes L, Del Castillo S, Tabares G, Arce XE, Perrotti M, Petta C. Comparison of weight increase in users of depot medroxyprogesterone acetate and copper IUD up to 5 years. *Contraception*. 2001;64(4):223-225.

28. Le YC, Rahman M, Berenson AB. Early weight gain predicting later weight gain among depot medroxyprogesterone acetate users. *Obstet Gynecol*. 2009;114(2 Pt 1):279-284.

29. Vrbikova J, Dvorakova K, Hill M, Starka L. Weight change and androgen levels during contraceptive treatment of women affected by polycystic ovary. *Endocr Regul*. 2006;40(4):119-123.

30. Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. *Cochrane Database Syst Rev*. 2011;9:CD003987.

31. van Seumeren I. Weight gain and hormone replacement therapy: are women's fears justified? *Maturitas*. 2000;34(1):S3-S8.

32. Fida NG, Enquobahrie DA, Gelaye B, Qiu C, Williams MA. Associations of asthma with body mass index and adult weight change among reproductive age women. *J Asthma*. 2011;48(7):701-706.

33. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry.* 2001;62(suppl 7):22-31.

34. Kurzthaler I, Fleischhacker WW. The clinical implications of weight gain in schizophrenia. J *Clin Psychiatry.* 2001;62(suppl 7):32-37.

35. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.

36. Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161(10):1837-1847.

37. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacol*. 2011;21(6): 517-535.

38. Kalucy RS. Drug-induced weight gain. *Drugs*. 1980;19(4):268-278.

39. Ratliff JC, Barber JA, Palmese LB, Reutenauer EL, Tek C. Association of prescription H1 antihistamine use with obesity: results from the National Health and Nutrition Examination Survey. *Obesity (Silver Spring)*. 2010;18(12):2398-2400.

40. Stricker RB, Goldberg B. Weight gain associated with protease inhibitor therapy in HIV-infected patients. *Res Virol*. 1998;149(2):123-126.

41. Reust CE. Common adverse effects of antiretroviral therapy for HIV disease. *Am Fam Physician*. 2011;83(12):1443-1451.

8

Dietary Interventions, Physical Activity, and Behavioral Approaches to the Treatment of Obesity

Dietary Interventions

In order to achieve weight loss, an energy deficit is required. There are multiple approaches in counseling a patient regarding achievement of this goal. The provider may create a specific caloric target, which typically ranges from 1200-1500 kcal/day for women and 1500-1800 kcal/day for men. The caloric goal may need to be adjusted for their baseline body weight and physical activity level. Another approach is to estimate the individual's specific requirements and reduce it by 500 kcal/day or approximately 30% energy deficit. Finally an ad libitum approach is where a formal energy deficit target is not defined, however, lower caloric intake is achieved by restricting or eliminating one or more particular food groups (for example, carbohydrates).[1]

Dietary intervention alone shows average weight loss is maximal at 6 months with small losses maintained for up to 2 years. Weight loss with dietary interventions ranges from 4 kg to 12 kg at 6 months, then slow weight regain is observed with total weight loss at 1 year of 4 kg to 10 kg and at 2 years, 3 kg to 4 kg.

■ Very Low Calorie Diets (VLCDs)

VLCDs are defined as diets providing <800 kcal/day. VLCDs are designed to provide rapid weight loss while maintaining lean body mass. They can be effective at improving some of the parameters of diseases that are associated with obesity, including uncontrolled diabetes, OSA, and hypertension. They often consistent

of four to five high protein shakes per day in addition to vitamin and mineral supplements. The protein content is typically high and fat content relatively low. Typically VLCDs are prescribed for no more than 16 weeks and are followed by a re-feeding diet before returning to regular food.

VLCDs are safe and effective when used in the appropriately selected obese individual (BMI >30) and requires close physician supervision. Patients need a thorough workup to ensure that a patient can endure such rapid weight change. Side effects may include fatigue, dizziness, hair loss, and increased risk of gallstones. VLCDs may induce weight loss of 20% to 25% of initial body weight during the first 12 to 16 weeks of treatment[2]; however, they are not well maintained. Patients typically regain 35% to 50% of the weight loss within the first year following treatment and regain all of the weight by years 3 to 5.[3] Thus, while VLCDs provide very good short-term weight loss and may be appealing for patients, one needs to consider the long-term success.

■ Protein-Sparing Modified Fast (PSMF)

Total fasting reduces or eliminates hunger and effectively induces rapid weight loss. However, its application is limited due to the significant protein catabolism coupled with undesirable physiologic effects. The Protein-Sparing Modified Fast (PSMF) was developed by Bistrian, Blackburn, and colleagues.[4] A total fast is modified with the addition of 1.5 g/kg of ideal body weight of animal protein from egg albumin, lean meat, or fish. By adding protein, the fasting-associated nitrogen loss declines and allows for preservation of normal liver, endocrine, and hematopoietic functions. Carbohydrates are prohibited on this diet and fat is restricted to the protein source. Patients also receive a daily multivitamin in addition to supplemented sodium chloride, potassium, and calcium. The PSMF is characterized by a fall in serum insulin and glucose concentrations, a rise in free fatty acid and

ketone levels, and the appearance of ketonuria, similar to what happens in a total fast. Ketone bodies are an important to protein sparing in total and semi-starvation, substituting for protein-derived glucose as a fuel for the brain. Weight loss ranges from 1 to 3 kg weekly, depending on the patient's age, height, weight, sex, and level of activity.[5] The PSMF should be restricted to patients who are at least 30% above their desirable weight with substantial increased risk of morbidity and mortality associated attributed to their obesity.[6]

■ Low Calorie Diets (LCDs)

Low calorie diets typically provide 1200 to 1500 kcal/day and intended to produce a more modest weight loss, typically producing an average of 0.5 kg/week of weight loss. Most of the diets marketed (**Table 8.1**) are considered low calorie diets. When comparing VLCDs vs LCDs, data have shown that VLCDs result in greater short-term weight loss (16.1% vs 9.7%) but similar weight losses after 1 year (6.3% vs 5%).[7]

TABLE 8.1 — Sample Dietary Compositions

- High protein (25% protein, 30% fat, 45% carbohydrate)
- High protein Zone™ type diet (5 meals/day: 40% carbohydrate, 30% protein, 30% fat)
- Low carbohydrate diet (<20 g/day)
- Low fat diet (10% to 25% of total calories from fat)
- Vegan diet
- Low glycemic diet
- Mediterranean style diet
- AHA style Step 1 diet (1500-1800 calories/day: <30% fat, <10% saturated fat)

■ Low Carbohydrate Diets

Low carbohydrate diets restrict carbohydrate intake to 50-100 g daily without limitations on fat and caloric intake. The consumption of high protein foods has been shown to promote satiety. Further, by limiting an entire food group, total daily caloric intake levels fall.

Low Energy Density Diets

Energy density is defined as the number of calories in a given weight of food. The principle behind low energy density diets is that for the same amount of calories: a great volume of food can be consumed when the food is low in energy density vs high density. Thus patients may be more satisfied for a lower number of calories. In a study by Ello-Martin and associates,[8] obese women were randomized to a diet focusing on reducing fat intake or one that emphasized both fat reduction and increased intake of water-rich foods (fruits and vegetables). Subjects assigned to increase their water-rich foods lost significantly more weight (8.9 kg vs 6.7 kg); however, at 12 months, weight-loss maintenance was not significantly different. However, those in the water-rich food group reported significantly less hunger.

Meal Replacements

The use of meal replacements (defined as functional foods in the form of a drink or a bar) as part of an overall treatment strategy has been shown to be beneficial and to an extent proportional to the number of meal replacements used over a period of several years.[9] A partial meal replacement (PMR) plan typically prescribes a low calorie (>800 or ≤1600 kcal/day) diet whereby one or two meals are replaced by commercially available, energy-reduced product(s) that are vitamin and mineral fortified, and includes at least one meal of regular foods. By reducing the variety of foods in the diet and increasing dietary structure, meal replacements facilitate adherence to the daily calorie goal. Meal replacements may also help patients who find themselves in challenging situations where they would otherwise make an unhealthy food choice (eg, when in car running late to work, may use meal replacement vs stopping at fast food restaurant). Furthermore, they are often very convenient and eliminate the need to make decisions about how and what type of food to eat.

A meta-analysis[10] revealed that subjects prescribed either both PMR or a standard calorie deficit treatment plans lost significant amounts of weight at both the 3-month and 1-year evaluation time points, however there was greater weight loss in subjects receiving the PMR plan. The PMR group lost approximately 7% to 8% body weight and the RCD group lost approximately 3% to 7% body weight.

Evaluation of factors associated with 1-year weight-loss success from the Look AHEAD study demonstrated that the number of meal replacements consumed in the first 6 months was significantly related to weight loss at week 26. Further, participants in the highest quartile of meal replacement use had four times greater odds of reaching the 7% weight-loss goal and 4.1 times greater odds of reaching the 10% weight-loss goal than participants in the lowest quartile.

Comparison of Macronutrient Content

There are multiple diet approaches available, each with specific regulations around nutrient content. In the past year, four meta-analyses of diet comparison studies have been published, each summarizing 13 to 24 trials. The only consistent finding among the trials is that adherence—the degree to which participants continued in the program or met program goals for diet and physical activity—was most strongly associated with weight loss and improvement in disease-related outcomes.[11] Macronutrient content may influence dietary adherence via the satiating properties of protein, carbohydrates, and fat. However, dietary content is only one of many factors influencing adherence. The assumption that one diet is optimal for all persons fails to acknowledge the variation in adherence influenced by food preferences, cultural or regional traditions, food availability, and food intolerances.

Sacks and colleagues compared weight-loss diets with different compositions of fat, protein, and carbohydrates.[12] The study randomly assigned 811 overweight adults to one of four diets; the targeted

percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%. The diets consisted of similar foods and patients were followed for 2 years. The primary outcome was the change in body weight between the low fat vs high fat and average protein vs high protein and in the comparison of highest and lowest carbohydrate content. At 6 months, participants assigned to each diet had lost an average of 6 kg, which represented 7% of their initial weight; they began to regain weight after 12 months.

By 2 years, weight loss remained similar in those who were assigned to a diet with 15% protein and those assigned to a diet with 25% protein (3.0 and 3.6 kg, respectively); in those assigned to a diet with 20% fat and those assigned to a diet with 40% fat (3.3 kg for both groups); and in those assigned to a diet with 65% carbohydrates and those assigned to a diet with 35% carbohydrates (2.9 and 3.4 kg, respectively) Among the 80% of participants who completed the trial, the average weight loss was 4 kg. Ultimately, all of the reduced-calorie diets resulted in clinically meaningful weight loss, regardless of which macronutrients they emphasized.

Ultimately, the specific diet itself does not determine the success with weight loss, but rather the ability of the patient to adhere to the defined diet is of utmost importance.[13] Furthermore, all approaches can lead to meaningful weight loss if a reduction in dietary energy is achieved.

Diet Composition Relative to Changes in Cardiometabolic Parameters

The effects of low-carbohydrate diets (≤45% of energy from carbohydrates) vs low-fat diets (≤30% of energy from fat) on metabolic risk factors were compared in a meta-analysis.[11] Compared with participants on low-fat diets, those on low-carbohydrate diets experienced a statistically significantly lower reduction

in total cholesterol (-2.7 mg/dL; 95% CI: 0.8, 4.6), and LDL cholesterol (-3.7 mg/dL; 95% CI: 1.0,6.4), but a greater increase in HDL cholesterol (3.3 mg/dL; 95% CI 1.9,4.7) and a greater decrease in triglycerides (-14.0 mg/dL; 95% CI: -19.4, -8.7). Reductions in body weight, waist circumference, and other metabolic risk factors were not significantly different between the two diets.

Foster and colleagues compared patients prescribed a low-carbohydrate diet (<20 g/d for 3 months with subsequent increase in their carbohydrate content once desired weight achieved) compared with a low-fat diet (limited energy intake 1200-1800 kcal/day, <30% fat).[14] Weight loss was approximately 11 kg (11%) at 1 year and 7 kg (7%) at 2 years. There were no differences in weight. During the first 6 months, the low-carbohydrate diet group had greater reductions in DBP, triglyceride levels, and very-LDL cholesterol levels, and lesser reductions in LDL cholesterol levels. The low-carbohydrate diet group had greater increases in HDL cholesterol levels at all time points.

Further, Sacks and associates compared four diets with varying nutrient composition; as mentioned above, the targeted percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%.[12] He concluded that all the diets reduced risk factors for CV disease and diabetes at 6 months and 2 years. At 2 years, the two low-fat diets and the highest-carbohydrate diet decreased LDL cholesterol levels more than did the high-fat diets or the lowest-carbohydrate diet (low-fat vs high-fat, 5% vs 1%; highest-carbohydrate vs lowest-carbohydrate, 6% vs 1%. The lowest-carbohydrate diet increased HDL cholesterol levels more than the highest-carbohydrate diet (9% vs 6%, $P = 0.02$). All the diets decreased triglyceride levels similarly, by 12% to 17%. All the diets except the one with the highest carbohydrate content decreased fasting serum insulin levels by 6% to 12%; the decrease was larger with the high-protein diet than

with the average-protein diet (10% vs 4%, *P*=0.07).

Some tips for counseling patients on diet are shown in **Figure 8.1**, along with visual aids to help patients to make portion sense (**Figure 8.2**).

FIGURE 8.1 — Simple Tips to Counsel Patients

1. The Plate Method: Patient should be encouraged to reduce the size of their plate to a 9-inch dinner plate. Half of the plate should be filled with nonstarchy vegetables (broccoli, cauliflower, lettuce, tomatoes, etc), a quarter of the plate with a lean source of protein (lean chicken, turkey, fish), and the remaining quarter with whole grains (brown rice, potato, whole grain breads).

2. Avoid liquid calories (regular soda, juice, coffee with cream) and focus on water, seltzer water, and other noncaloric alternatives.
3. Replace regular sugar with noncaloric sweeteners.
4. Avoid skipping meals: plan small regular meals throughout the day in order to keep your hunger controlled. Consider using a meal replacement if unable to plan a healthy meal (such as a protein shake or high protein bar).
5. Replace all white bread with whole wheat/whole grain alternatives.
6. Swap regular salad dressings, mayonnaise, and butter with low-fat or fat-free alternatives.
7. Avoid high fat, high calorie, high carbohydrate snacks (cookies, pastries, cakes).
8. Snack on fruits, low fat dairy (yogurt, cottage cheese)

FIGURE 8.2 — Visual Aids Make "Portion Sense"

Visual Cue	Approximate Portion Size
	~1 cup Food[a]: green salad, frozen yogurt, medium piece of fruit, baked potato
	~½ cup Food[a]: cut fruit, cooked vegetables, pasta, rice
	~¼ cup Food[a]: dried fruit (eg, raisins)
	~3 ounces Food[a]: meat, poultry
	~3 ounces Food[a]: grilled fish
	~1½ ounces Food[a]: natural cheese

Tools to help patients undersatnd proper portion size.

[a] Food = one FGP serving of food(s) listed.

Modified from USDA/ARS Children's Nutrition Research Center of Baylor College of Medicine (BCM) Web site. https://www.bcm.edu/research/centers/childrens-nutrition-research-center/consumer/archives/portioncues.htm. Accessed June 10, 2014.

Physical Activity

Physical activity is an essential component of a weight-loss treatment program. Physical activity influences the composition of weight loss so that a higher proportion of the weight loss is loss of fat as opposed to fat-free mass (or lean muscle) which is metabolically desirable.[15] Exercise may help offset the reduction in resting metabolic rate that results from weight loss itself. Further engaging in physical activity may help facilitate dietary adherence.

The AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults[1] recommend at least 150 minutes of aerobic activity per week (equal to at least 30 minutes per day, most days of the week). This level of activity produces an energy expenditure of approximately 1000 kcal per week. Physical activity becomes even more critical during the weight-loss maintenance phase. Members of the National Control Weight Registry report maintaining their weight loss by engaging in approximately 1 hour of physical activity per day, expending an average of 2825 calories per week.[16] In order to maintain weight loss, higher intensity activity (at least 200 to 300 minutes per week) is recommended.[17]

The aim of physical activity is not purely to increase CV activity (eg, walking, running) but it is also important to include resistance training exercises. The Centers for Disease Control and Prevention (CDC) recommend that adults engage in muscle-strengthening activities at least 2 days per week. Resistance training is an effective technique to improve muscle strength and endurance, prevent and modify chronic medical conditions, and modify coronary risk factors. Further, strength training can help preserve fat-free mass during weight loss to enhance metabolic rate.

It is often difficult for patients to achieve physical activity goals and time is often a limiting barrier. Research has demonstrated that continuous vs intermittent activity of the same total duration produce

equivalent improvements in CV health, weight, and fasting or postprandial lipemia.[18] Therefore, one may want to counsel patients to focus on achieving small bouts of exercise, multiple times per day (10 minutes of a brisk walk, three to four times daily) as a means to achieve their goal and improve compliance.

Behavioral Modification

Behavioral treatment is a critical component to a successful obesity intervention and can be used to support any type of dietary intervention. The goal of behavioral treatment is to target maladaptive eating behaviors that contribute to obesity. Various components of a behavioral treatment program may include the following.

- **Self-Monitoring of Dietary Intake**

Obese individuals have been shown to underestimate their food intake[19]; thus behavioral treatment programs focus on teaching participants to accurately record the type, amount, and total calories of the foods they consume throughout the day. They are also taught how to read food labels and use measuring tools to help improve the accuracy of their food records. Data have shown that individuals that regularly record their food intake lose significantly more weight than those who do so inconsistently.[20]

- **Trigger or Stimulus Control**

Techniques to help control a patient's environment is crucial in helping support their goal of eating healthy and exercising. As an example, patients may be taught to store food out of sight, limit the number of places they eat to the kitchen or dining table, and refrain from eating while engaging in other activities (eg, working on computer, watching television).

- **Problem-Solving Techniques**

In order to be successful, patients need to be taught problem-solving techniques for when they encounter barriers that limit their ability to be consistent with

a healthy diet and exercise plan. The goal is to plan solutions in advance such that the patient can overcome the challenge with ease. As an example, a patient may travel for work and not have access to their usual planned meals; however, with proper education and support, they can create solutions that allow them to overcome an uncertain situation.

- **Cognitive Restructuring**

Individuals attempting to lose weight often exhibit catastrophic thinking that leads them to abandon their weight control efforts. As an example, they may overeat one evening and decide to give up altogether. However, by teaching them to replace these thoughts with more rationale responses, they can recognize a setback as a temporary lapse and continue to move forward.

- **Relapse Prevention**

Techniques for long-term success must focus on relapse prevention, particularly focusing on high-risk situations that may create a set-back (eg, vacations, illness, or periods of high stress). Behavioral therapy focuses on teaching patients to plan for these events and incorporate them into the long-term weight management plan.

Behavioral treatment may be offered individually or in group sessions (usually 10 to 15 individuals who all begin the treatment program at the same time) and the sessions often last from 60 to 90 minutes. A group format provides social support, and individuals can help one another develop strategies to overcome barriers around achieving the diet and exercise goals. Group sessions are often held weekly during the active weight-loss phase and may taper to biweekly meetings that can help individuals focus on weight maintenance.

Intensive Lifestyle Intervention

The DPP was designed to determine whether a lifestyle intervention directed at reducing body mass

and increasing activity levels, or the medication metformin, would delay or prevent development of diabetes in a high-risk population.[21] The DPP lifestyle intervention was delivered by individual lifestyle coaches. Participants received a 16-week core curriculum over the first 6 months and then had at least one contact monthly for the remainder of the study (at least one in-person visit every 2 months with phone visits as needed to maintain once per month contact) (**Table 8.2**). Participants who received behavioral treatment achieved a weight loss on average of 7 kg at the end of 1 year (vs 0.1 kg for placebo).[22] Although on average, they regained one third of their weight in years 2 to 3, they were able to reduce their risk of developing T2D by 58% compared with participants treated in the placebo group. Further, even though all groups eventually received some amount of lifestyle intervention, at 10 years, the cumulative incidence of diabetes was lowest in the lifestyle intervention group; this intervention delayed onset of diabetes by 4 years relative to 2 years in the metformin group.[23]

The ongoing Look AHEAD Study is designed to evaluate the effect of an ILI in overweight people with T2D and its effect on CV outcomes. Subjects were randomly assigned to ILI or usual care (ie, diabetes support and education [DSE]).[24] The Look AHEAD intervention is delivered in a group plus individual format by intervention teams that include registered dietitians, behavioral psychologists, and exercise specialists. Participants are offered weekly sessions with three group sessions and one individual session per month in the first 6 months and two group sessions and one individual session per month during months 7 through 12, for a total of 42 sessions the first year. In years 2 to 4, participants are offered a minimum of monthly individual sessions and one additional contact by group, phone, mail, or e-mail (**Table 8.2**). Subjects in the ILI lost 8.6% of their weight at year 1 compared with 0.7% for DSE. At year 4, ILI participants lost an average of 4.7% of initial weight compared with 1.1% for DSE.

TABLE 8.2 — Comparison of Lifestyle Intervention Features of Diabetes Prevention Program and Look AHEAD Trial

	DPP	Look AHEAD
Intervention format	Individual sessions	Group plus individual sessions
Frequency of follow-up	16 sessions in the first 6 months with minimum of one in-person follow-up every 2 months thereafter	24 sessions in the first 6 months; 18 sessions in months 7-12; minimum of monthly individual sessions years 2-4
Refresher groups/campaigns	3 times/year after first 6 months	2-3 times/year in years 2 and beyond
Supervised activity sessions	2 times/week throughout the trial	Periodically in refreshers or campaigns

■ Commercially Available Lifestyle Interventions

Weight Watchers

Weight Watchers is a commercially available weight-loss program that emphasizes intensive behavioral counseling. Johnston and colleagues randomized patients to either a self-help program vs enrollment in the Weight Watchers program.[25] The Weight Watchers program allowed for three different avenues to access treatment: either weekly meetings, use of a mobile application, or online Weight Watchers tools. Weights were evaluated at baseline, 3 months, and 6 months. Patients enrolled in the Weight Watchers program lost an average of 10.1 lb at 6 months vs 1.3 lb for the self-help group. Importantly, those participants who assessed all of the Weight Watchers platforms more frequently (attended 50% of meetings and used the mobile app and online tools at least 2 times per week) lost on average 19 lb, those using two platforms lost 9.5 lb, and those only utilizing one platform lost 9.3 lb.

Jenny Craig

The Jenny Craig weight management program involves one-to-one behavioral counseling, as well as packaged prepared meal plans. Rock and associates evaluated the use of the Jenny Craig program (weekly in person or telephone-based counseling) for 2 years to see how it compared with usual care[26] (where participants received two individualized weight-loss counseling sessions and monthly contacts). The mean weight loss was 7.4 kg (or 7.9% of initial weight) at 24 months for the center-based group, 6.2 kg (or 6.8%) for the telephone-based group, and 2 kg (or 2.1%) for the usual care group.

NutriSystem

NutriSystem is a commercially available portion-controlled diet program which provides entrees and snacks to encourage weight loss. Foster and colleagues evaluated obese participants with T2D (mean BMI 39, mean HbA1c 7.5)[27] who were randomly assigned to the

portion-controlled diet (NutriSystem) or a DSE program. After the initial 3 months, the NutriSystem group continued on the portion-controlled diet for the remaining 3 months, and the DSE group crossed over to the portion-controlled diet for the remaining 3 months. At 3 months, the NutriSystem lost significantly more weight (7.1% ± 4%) than the DSE group (0.4% ± 2.3%). From 3 to 6 months, the change in weight for both groups was statistically significant. After 3 months, the NutriSystem group had greater reductions in HbA1c than the DSE group (-0.88 ± 1.1 vs 0.03 ± 1.09; P <0.001). From 3 to 6 months the NutriSystem group had no further change in HbA1c, while the DSE group showed a significant reduction. The data suggest that obese patients with T2D can have significant improvements in weight and glycemic control with the use of a commercially available portion-controlled diet.

■ Use of Remote and Mobile Technologies in Behavioral Weight-Loss Programs

Typical behavioral weight-loss programs involve weekly or twice-monthly, face-to-face counseling sessions and can be very effective as described above. However, it can be time and resource intensive and may not be convenient for the patient or provider. Mobile devices have been used successfully to provide dietary guidance and self-monitor weight and other health-related variables.[28] Electronic solutions can deliver a weight loss of up to 5 kg at 6 to 12 months, which is greater than that resulting from no or minimal intervention offered on the internet or in print.[1]

Appel and associates compared two behavioral weight-loss interventions in a primary care setting using remote vs in-person support.[29] Patients were randomized to remote weight-loss support via telephone, a study specific website and email, or offered in-person group and individual sessions along with the other three remote means of support. The groups were evaluated over 24 months. The data showed both groups clinically significant weight (-4.6 kg for remote support vs -5.1 kg for in-person) and it did not differ

significantly between the groups. The data support the notion that remote support can provide a meaningful alternative weight-loss solution.

Harvey-Benino evaluated an internet-based behavioral obesity treatment program.[30] Subjects were either randomized to an internet-based solution, in-person, or a combination of internet/in-person program (hybrid). Evaluation of the weight loss at 6 months was -5.5 kg, 8 kg, and 6 kg for the internet, in-person, and hybrid, respectively. Although weight was greater for the in-person program, meaningful weight was achieved via remote solutions at a fraction of the cost ($372 vs $706). Further, the addition of in-person to the internet solution did not appear to improve weight-loss outcomes.

Long-term weight maintenance is often one of the most challenging aspects of obesity treatment. Radcliff and colleagues evaluated the use of a telephone vs face-to-face extended-care lifestyle maintenance program after an initial weight-loss program. After 12 months of treatment, weight regain was evaluated in both groups compared with a control. Weight regain was 1.7 kg, 2.1 kg, and 3.1 kg for the in-person, telephone, and control group, respectively. Both interventions were helpful in keeping weight off, but the telephone format had a lower overall cost.

BMIQ Professionals Program

The BMIQ Professionals Program (www.bmiq.com) is an innovative approach which allows health care professionals and their staff to deliver a comprehensive weight-management program in the office setting. Developed by weight-management experts, the BMIQ Professionals Program offers health care providers all of the tools needed to learn the basics of weight management and deliver an evidence-based weight loss intervention. The program allows the professional to deliver up to 20 in-office or phone-based counseling sessions along with web-based support between visits to produce positive lifestyle change. The program

includes several dietary options, behavioral sessions, stepwise guidance to increase physical activity to 3 hours per week, and interactive tools to monitor food intake, physical activity, weight, and personal goals, everything needed to manage the overweight and obese patient in the office setting. Thus far, group and individual programs using BMIQ have produced a mean weight loss of approximately 5% over 26 weeks of treatment.

Using a BMIQ website customized for the health care professional, patients are able to log in to access program materials. Educational materials pertaining to each session, meal plans and low-glycemic menus based on target calorie levels, integrated tracking tools, as well as informational videos and resources are available. Tools for tracking food and activity, body weight, and health goals are included.

During each in-office or phone meeting with the health care professional, patients review their progress and are guided through a lesson focused on diet, activity, lifestyle change, or behavior modification. Additionally, the patient and professional are able to review pertinent patient-recorded data in real time, including daily calorie intake, food choices, and activity.

Between sessions, patients stay engaged by completing "homework" items pertaining to session materials and utilizing the tracking tools. Patients are able to access the BMIQ website for ongoing support using a computer, tablet, or smartphone. Built-in reminders and alerts increase compliance with program guidelines.

A separate portal is provided for the professional. Training videos, educational resources, clinical research, and other study materials are provided to educate professionals about weight management and allow them to deliver the intervention most effectively. Professionals can access patient data, including weights, food and activity logs, and recent log-in activity via the BMIQ website.

Summary

Ultimately, obesity treatment requires a long-term intervention. Patients increasingly rely on technology and mobile-based solutions for many of their day-to-day operations. The use of internet-based solutions as a tool in obesity treatment appears to provide a cost-effective alternative to traditional weight-loss interventions.

Comprehensive Lifestyle Interventions

The best diet and behavioral treatment programs typically result in a 10% weight loss during the first 6 months of treatment. Key components to success include three critical components:

- First, one must provide a diet that appeals to the patients' preferences so that they can easily adhere to it.
- Second, the patient must incorporate significant physical activity (ideally 300 minutes/week).
- Finally, provide a behavioral treatment plan to reinforce the necessary strategies to maintain the weight lost.

Long-term, ongoing contact between the patient and practitioner enhances weight-loss maintenance.

REFERENCES

1. Jensen MD, Ryan DH, Apovian C, et al. 2013 AHA/ACC/TOS obesity guideline for the management of overweight and obesity in adults: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published online ahead of print November 12, 2013]. *Circulation*. 2013. doi: 10.1161/01.cir.0000437739.71477.ee.
2. Tsai AG, Wadden TA. The evolution of very-low-calorie diets. An update and meta-analysis. *Obesity*. 2006;14(8)1283-1293.
3. Wadden TA. Berkowitz RI. Very low-calorie diets. In: Fairburn CG, Brownell KD. *Eating Disorders and Obesity: A Comprehensive Handbook*. 2nd ed. New York, NY: Guildford Press; 2002:534-538.
4. Bistrian BR, Blackburn GL, Flatt JP, Sizer J, Scrimshaw NS, Sherman M. Nitrogen metabolism and insulin requirements in obese diabetic adults on a protein-sparing modified fast. *Diabetes*. 1976;25(6):494-504.
5. Bistrian BR. Clinical use of a protein sparing modified fast. *JAMA*. 1978;240(21):2299-2302.
6. Blackburn GL, Bistrian BR, Flatt JP, Sizer J. Role of a protein sparing modified fast in a comprehensive weight reduction program. In: Hoard A, ed. *Recent Advances in Obesity Research: I*. London: Newman Publishing Ltd; 1975.
7. Nonas C. Clinical monioring. In: Foster GD, Nonas C. *Obesity: A Clinical Guide*. Chicago, IL: ADA; 2004.
8. Ello Martin JA, Ledikwe JH, Rolls BJ. The influence of food portion size and enegy density on energy intake: implications for weight management. *Am J Clinic Nutrition*. 2005;82(suppl 1):236S-241S.
9. Cheskin LJ, Mitchell AM, Jhaveri AD, et al. Efficacy of meal replacements versus a standard food-based diet for weight loss in type 2 diabetes. A controlled clinical trial. *Diabetes Educ*. 2008;34:118-127.
10. Heymsfield SB1, van Mierlo CA, van der Knaap HC, Heo M, Frier HI. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes Relat Metab Disord*. 2003;27(5):537-549.
11. Hu T, Mills KT, Yao L, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol*. 2012;176(suppl 7):S44-S54.

12. Sacks, FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein and carbohydrates. *N Engl J Med*. 2009;360:859-873.
13. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A to Z Weight Loss Study: a randomized trial. *JAMA*. 2007;297:969-977.
14. Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med*. 2010;153(3):147-157.
15. Hill JO, Wyatt HR. Role of physical activit in preventing and treating obesity. *J Appl Physiol*. 2005;99(2):765-770.
16. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr*. 1997; 66(2):239-246.
17. Wadden TA, Neiberg RH, Wing RR, et al. Four-year weight losses n the Look AHEAD study: factors associated with long term success. *Obesity*. 2011;19:1987-1998.
18. Murphy MH, Blair SN, Murtagh EM. Accumulated versus continuous exercise for health benefit. *Sports Med*. 2009;39(1) 29-43.
19. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self reported and actual caloric intake and exercise in obese subjects. *N Engl J Med*. 1992;327(27):1893-1898.
20. Boutelle KN, Kirschenbaum DS. Further support for consistent self-monitoring as a vital component of success weight control. *Obes Res*. 1998;6(3):219-224.
21. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
22. The Diabetes Prevention Program Research Group. The Diabetes Prevention Program. *Diabetes Care*. 2002;25(12): 2165-2171.
23. Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.
24. The Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity*. 2014;22(1):5-13.

25. Johnston CA1, Rost S, Miller-Kovach K, Moreno JP, Foreyt JP. A randomized controlled trial of a community-based behavioral counseling program. *Am J Med*. 2013;126(12):1143.

26. Rock CL1, Flatt SW, Sherwood NE, Karanja N, Pakiz B, Thomson CA. Effect of a free prepared meal and incentivized weight loss program on weight loss and weight loss maintenance in obese and overweight women: a randomized controlled trial. *JAMA*. 2010;304(16):1803-1810.

27. Foster GD, Borradaile KE, Vander Veur SS, et al. The effects of a commercially available weight loss program among obese patients with type 2 diabetes: a randomized study. *Postgrad Med*. 2009;121(5):113-118.

28. Morak J, Schindler K, Goerzer E, et al. A pilot study of mobile phone-based therapy for obese patients. *J Telemed Telecare*. 2008;14(3):147-149.

29. Appel LJ, Clark JM, Yeh HC, et al. Comparative effectiveness of weight-loss interventions in clinical practice. *N Engl J Med*. 2011;365(21):1959-1968.

30. Harvey-Berino J, West D, Krukowski R, et al. Internet delivered behavioral obesity treatment. *Preventive Med*. 2010; 51:123-128.

9

Pharmacologic Treatment

The development and approval of new antiobesity drugs is particularly challenging. In addition to safety concerns, the FDA criteria for a drug to be approved for treatment of obesity are quite stringent. A new agent must induce statistically significant placebo-adjusted weight loss of ≥5% at 1 year or that ≥35% of patients should achieve >5% weight loss (which must be at least twice that induced by placebo). In addition, the FDA also requires that the medication shows evidence of improvement in metabolic biomarkers, including BP, lipids, and glycemia.

The search for safe and effective pharmacologic weight-loss agents began in the late 19th century with the discovery that sheep thyroid extract increased metabolic rate and induced significant weight loss. However, the use of thyroid hormone treatment in euthyroid patients increased the risk of cardiac arrhythmias and cardiac arrest. Subsequently, many different classes of pharmacologic agents, such as centrally acting amphetamine derivatives and 5-HT–releasing agents appeared (and subsequently disappeared) over the next half century.[1-3] As a result, very few approved weight-loss drugs were available prior to 2012 (**Table 9.1**).

Centrally acting amphetamine derivatives (desoxyephedrine, phentermine, and diethylpropion) were among the earliest pharmacologic agents used for weight loss.[3] However, growing concerns about CV risk and abuse potential led to a decline in their use by the early 1970s. Although still available in many countries, phentermine and diethylpropion were largely superseded in the 1970s and 1980s by the 5-HT–releasing agents fenfluramine and dexfenfluramine. In the early 1990s, evidence of superior efficacy over either compound given alone led to the widespread use in the

TABLE 9.1 — Obesity Medications Available Prior to 2012

	FDA Date of…	
Medication	**Approval**	**Withdrawal**
Phentermine	5/1959	—
Diethylpropion	8/1959	—
Benzphetamine	10/1960	—
Fenfluramine	6/1973	9/1997
Phendimetrazine	9/1982	—
Dexfenfluramine	4/1996	9/1997
Orlistat	4/1999	—
Sibutramine	11/1997	10/2008
Rimonabant	6/2006[a]	10/2008

[a] Withdrawn by FDA; approved in Europe but subsequently withdrawn.

Powell AG, et al. *Clin Pharmacol Ther*. 2011;90(1):40-51.

United States of the combined treatment with phentermine and fenfluramine. Within only a few years, reports of cardiac valvulopathy, particularly when these agents were combined with phentermine, resulted in withdrawal of fenfluramine and dexfenfluramine from the market. Although these agents were withdrawn, phentermine was not, and it continued to be the most commonly prescribed drug.

Despite an inauspicious history, the pharmacologic management of obesity is at an exciting crossroad. Ongoing recent research has identified many new therapeutic targets. Four new treatments, a fixed-dose combination of phentermine and topiramate ER, lorcaserin, a fixed-dose combination of naltrexone SR and bupropion SR, and liraglutide, have recently been approved by the FDA. Of particular interest is that these agents may result in significant weight loss, which can have a beneficial effect on many cardiometabolic risk factors, thereby contributing to reductions in obesity-related comorbidities.

Currently, six antiobesity medications are approved by the FDA:

- Phentermine
- Orlistat
- A fixed-dose combination of phentermine and topiramate ER
- Lorcaserin
- A fixed-dose combination of naltrexone SR and bupropion SR
- Liraglutide.

Table 9.2 provides summaries of the prescribing information for these medications.

Phentermine

Phentermine, approved in 1959, has been the most commonly prescribed antiobesity agent in the United States. Phentermine is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class (eg, amphetamines). It is believed to suppress appetite. The approved duration of treatment is only 3 months because of a lack of understanding of the chronic nature of obesity.

Efficacy

The efficacy of continuous vs intermittent phentermine was evaluated in an early 36-week, double-blind, placebo-controlled study in 108 women who were clinically overweight or obese. Patients were randomized into three groups: one group received phentermine continuously for 36 weeks, another group received placebo continuously, and the third group alternated phentermine and placebo every 4 weeks (**Figure 9.1**).[4] The mean weight loss was -12.2 and -13.0 kg in patients who received phentermine continuously and intermittently compared with -4.8 kg in the group treated with placebo. Attrition was 41% and data were presented for completers only. Statistical differences were not reported. Individual responses to therapy

TABLE 9.2 — Summaries of Prescribing Information for Currently Available Obesity Medications

	Phentermine[1]	**Orlistat**[2] **(Xenical)**	**Phentermine/ Topiramate ER**[3] **(Qsymia)**	**Lorcaserin**[4] **(Belviq)**	**Naltrexone SR/ Bupropion SR**[5] **(Contrave)**	**Liraglutide**[6] **(Saxenda)**
Estimated % weight loss (drug minus placebo, ITT data)	5.1%: 28 weeks[7] 15 mg qd	3.1%: 1 year[8] 120 mg tid	6.6%: 1 year[9] 7.5 mg phen/46 mg top ER qd	3.6%: 1 year[10] 10 mg bid	4.8%: 56 weeks[11] 8 mg nal/90 mg bup 2 tabs bid	4.5%: 56 weeks[6]: 3 mg qd
Indication(s)	• Short-term adjunct (a few weeks) in a regimen of weight reduction based on exercise, behavioral modification, and caloric restriction in the management of exogenous obesity for patients with an initial BMI of ≥30, or ≥27 in the presence of other risk factors (eg, controlled hypertension, diabetes, hyperlipidemia)	• For obesity management, including weight loss and maintenance when used in conjunction with a reduced-calorie diet • Also indicated to reduce the risk for weight re-gain after prior weight loss	• Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with initial BMI of ≥30, or ≥27 in the presence of ≥1 weight-related comorbidity (eg, hypertension, type 2 diabetes, or dyslipidemia)	• Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with initial BMI of ≥30, or ≥27 in the presence of ≥1 weight-related comorbidity (eg, hypertension, type 2 diabetes, or dyslipidemia)	• Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with initial BMI of ≥30, or ≥27 in the presence of ≥1 weight-related comorbidity (eg, hypertension, type 2 diabetes, or dyslipidemia)	• Adjunct to reduced calorie diet and increased physical activity for chronic weight management in adult patients with initial BMI of ≥30 (obese) or ≥27 (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, type 2 diabetes, or dyslipidemia)
Limitations	The risk/benefit profile of short-term use should be addressed for each patient	GI side effects can limit patient tolerability and long-term use	• Effect on CV morbidity and mortality has not been established • The safety and effectiveness of phen/top ER in combination with other products intended for weight loss, including prescription and OTC drugs, and herbal preparations, have not been established	• Effect on CV morbidity and mortality has not been established • Safety and efficacy of coadministration with other products for weight loss have not been established	• Effect on CV morbidity and mortality has not been established • Safety and effectiveness in combination with other products intended for weight loss, including prescription drugs, OTC drugs, and herbal preparations, have not been established	• Not indicated for treatment of type 2 diabetes • Should not be used in combination with any other GLP-1 receptor agonist • Should not be used with insulin • Effects on CV morbidity and mortality have not been established • Safety and efficacy of coadministration with other products for weight loss have not been established • Has not been studied in patients with a history of pancreatitis

Continued

TABLE 9.2 — *Continued*

	Phentermine[1]	**Orlistat**[2] **(Xenical)**	**Phentermine/ Topiramate ER**[3] **(Qsymia)**	**Lorcaserin**[4] **(Belviq)**	**Naltrexone SR/ Bupropion SR**[5] **(Contrave)**	**Liraglutide**[6] **(Saxenda)**
Contraindications	•Pregnancy •Nursing •History of CVD (eg, CAD, stroke, arrhythmias, CHF, uncontrolled hypertension) •During or within 14 days following administration of MAOIs •Hyperthyroidism •Glaucoma •Agitated states •History of drug abuse •Known hypersensitivity, or idiosyncrasy to sympathomimetic amines	•Pregnancy •Chronic malabsorption syndrome •Cholestasis •Known hypersensitivity to orlistat or to any component of this product	•Pregnancy •Glaucoma •Hyperthyroidism •Use during or within 14 days of taking MAOIs	•Pregnancy	•Pregnancy •Uncontrolled hypertension •Seizure disorder or history of seizures •Use of other bupropion-containing products •Bulimia or anorexia nervosa •Chronic opioid or opioid agonist (eg, methadone) or partial agonists (eg, buprenorphrine) use or acute opiate withdrawal •Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs •Use during or within 14 days of taking MAOIs •Known allergy to bupropion, naltrexone, or any other component of this drug	•Pregnancy •Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 •Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the product components
Most frequently reported side effects	Dizziness, dry mouth, difficulty sleeping, constipation, irritability	Bloating, diarrhea	Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth	In nondiabetic patients, •Headache, dizziness, fatigue, nausea, dry mouth, and constipation In diabetic patients: •Hypoglycemia, headache, back pain, cough, and fatigue	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea	•Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase

Continued

TABLE 9.2 — *Continued*

	Phentermine[1]	**Orlistat**[2] (**Xenical**)	**Phentermine/ Topiramate ER**[3] (**Qsymia**)	**Lorcaserin**[4] (**Belviq**)	**Naltrexone SR/ Bupropion SR**[5] (**Contrave**)	**Liraglutide**[6] (**Saxenda**)
Warnings/ precautions	•Rare cases of primary pulmonary hypertension and/or serious regurgitant cardiac valvular disease •Risk of abuse and dependence •Concomitant alcohol use •Impairment in the ability to perform potentially hazardous activities •Reduction in the doses of antidiabetic agents in some patients	—	•Fetal toxicity •Increased heart rate •Suicide, mood, and sleep disorders •Acute myopia and glaucoma •Cognitive impairment •Metabolic acidosis •Creatinine elevations •Risk of hypoglycemia with diabetic agents •Risk of hypokalemia in patients on potassium-wasting diuretics	•Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions •Safety and coadministration with other serotonergic or antidopaminergic agents has not been established •Valvular heart disease •Cognitive impairment, disturbances of attention and memory •Monitor for depression or suicidal thoughts •Risk of hypoglycemia with antidiabetic agents	•Suicidal behavior and ideation •Risk of seizure may be minimized by adhering to dosing schedule and avoiding coadministration with high-fat meal •Increased blood pressure and heart rate •Hepatotoxicity •Angle-closure glaucoma •Use of antidiabetic medications: weight loss may cause hypoclycemia	•Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis •Acute gallbladder disease: substantial or rapid weight loss can increase risk of cholelithiasis •Serious hypoglycemia can occur when used with an insulin secretagogue (eg, sulfonylurea) •Increased heart rate •Renal impairment •Hypersensitivity reactions •Suicidal behavior and ideations
REMS program	No	No	Yes	No	No	No
Available formulations	Various	Capsules: 120 mg	Capsules (mg/mg): 3.75/23, 7.5/46, 11.25/69, 15/92	Tablets: 10 mg	Tablets: 8 mg naltrexone HCl/ 90 mg bupropion HCl	Prefilled pen for subcutaneous injection (mg): 0.6, 1.2, 1.8, 2.4, 3.0 (6 mg/mL, 3 mL)
Schedule IV controlled substance	Yes	No	Yes	Yes	No	No
Dosage/ administration	One tablet daily	One tablet 3 times per day before meals	•Once daily in morning. Avoid evening dose to prevent insomnia • Start with phen/top ER 3.75/23 mg daily for 14 days then increase to 7.5/46 mg daily •Discontinue/escalate dose if 3% weight loss not achieved after 12 weeks on 7.5/46-mg dose •Discontinue if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15/92 mg	•10 mg twice daily •Discontinue if 5% weight loss is not achieved by week 12	•Week 1: 1 morning tablet; Week 2: 1 morning tablet, 1 evening tablet; Week 3: 2 morning tablets, 1 evening tablet; Week 4 and onward: 2 morning tablets, 2 evening tablets •A total daily dosage of 2 tablets twice daily reached at start of Week 4 •Not to be taken with high-fat meal	•Subcutaneous injection once daily into the abdomen, thigh, or upper arm, irrespective of meals •Recommended dose is 3 mg daily, to be initiated at 0.6 mg/ day for 1 week, then increased at weekly intervals until 3 mg is reached

Continued

TABLE 9.2 — *Continued*

	Phentermine[1]	Orlistat[2] (Xenical)	Phentermine/ Topiramate ER[3] (Qsymia)	Lorcaserin[4] (Belviq)	Naltrexone SR/ Bupropion SR[5] (Contrave)	Liraglutide[6] (Saxenda)
Dosage/ administration *(cotinued)*			•Discontinue 15/92-mg dose gradually to prevent possible seizure •Do not exceed 7.5/46-mg dose for patients with moderate or severe renal impairment or moderate hepatic impairment		•Discontinue if 5% weight loss not achieved after 12 weeks at maintenance dose	

[1] Suprenza [package insert]. Cranford, NJ: Akrimax Pharmaceuticals, LLC; Revised 06/2013.
[2] Xenical [package insert]. San Francisco, CA: Genetech USA, Inc; 2012.
[3] Qsymia [package insert]. Mountain View, CA: Vivus, Inc; 2012-2013.
[4] Belviq [package insert]. Zofingen, Switzerland: Arena Pharmaceuticals GmbH; 2012.
[5] Contrave [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 09/2014.
[6] Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk; 2014.
[7] Aronne LJ, et al. *Obesity (Silver Spring).* 2013;21(11):2163-2171.
[8] Yanovski SZ, Yanovski JA. *JAMA.* 2014;311(1):74-86.
[9] Gadde KM, et al. *Lancet.* 2011;377(9774):1341-1352.
[10] Smith SR, et al. *N Engl J Med.* 2010;363(3):245-256.
[11] Greenway FL, et al. *Lancet.* 2010;376(9741):595-605.

FIGURE 9.1 — Weight Loss With Continuous or Intermittent Treatment With Phentermine

Munro JF, et al. *Br Med J.* 1968;1(5588):352-354.

were variable but irrespective of the method employed, weight loss diminished with duration of treatment. Furthermore, there seemed to be no advantage in taking phentermine continuously.

Studies investigating the use of phentermine alone for weight loss published in the 1960s and 1970s typically presented only completer analyses and had high dropout rates leading to an overstatement of efficacy.[5] A more recent study by Aronne and colleagues investigating the differences in weight loss using phentermine alone vs in combination reports weight loss of 5.1% at 28 weeks.[6]

■ Safety

The most common treatment-emergent adverse events (TEAEs) with phentermine include:

- Dizziness
- Dry mouth
- Difficulty sleeping

- Irritability
- Nausea
- Vomiting
- Diarrhea
- Constipation.

■ Prescribing and Administration

The recommended dosage of phentermine is 15 mg to 37.5 mg orally once daily before breakfast or 1 to 2 hours after breakfast (**Table 9.2**). Dosage should be individualized to obtain an adequate response with the lowest effective dose. The usual adult dose is one tablet (37.5 mg) daily. For most patients, a half tablet (18.75 mg) daily may be adequate, while in some cases, it may be desirable to give half tablets (18.75 mg) two times a day. Administration in the late evening should be avoided because of the possibility of insomnia.

Phentermine is not recommended for use in pediatric patients ≤16 years of age. Phentermine is a schedule IV controlled substance.

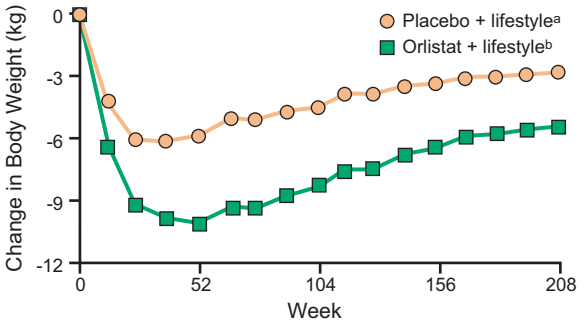
Orlistat (Xenical)

Orlistat is indicated for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet. It also is indicated to reduce the risk for weight regain after prior weight loss. Unlike the other weight-loss agents which reduce appetite and/or enhance energy expenditure, orlistat inhibits pancreatic lipases, thereby reducing fat absorption from the gut.[7]

■ Efficacy

The efficacy of orlistat was demonstrated in a 4-year, double-blind, prospective study in which 3305 patients were randomized to lifestyle changes plus either orlistat 120 mg or placebo three times daily.[8] Patients had a BMI ≥30 and normal (79%) or impaired (21%) glucose tolerance (IGT). Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs 3.0 kg with placebo; P <0.001) and similar between orlistat recipients with impaired or normal glucose tolerance at baseline (**Figure 9.2**). In addition to causing significant weight loss after 4 years relative to placebo, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (P <0.0032).

FIGURE 9.2 — Effects of Orlistat as an Adjunct to Lifestyle Modification Diet on Weight Loss and Incidence of Diabetes in Obese At-Risk Patients



Torgerson JS, et al. *Diabetes Care.* 2004;27(1):155-161.

■ Safety

Most common TEAEs with orlistat (5% and at least twice that of placebo) include:

- Oily spotting
- Flatus with discharge
- Fecal urgency
- Fatty/oily stool
- Oily evacuation
- Increased defecation
- Fecal incontinence.[7]

■ Prescribing and Administration

The recommended dosage of orlistat is one 120-mg capsule three times a day with each main meal containing fat during or up to 1 hour after the meal (**Table 9.2**).[7]

- Advise patients to take a nutritionally balanced, reduced-calorie diet that contains approximately 30% of calories from fat.
- Distribute the daily intake of fat, carbohydrate, and protein over three main meals.
- Advise patients to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition.

(*Note*: Orlistat is available as two formulations: Xenical containing 120 mg of orlistat and available only by prescription, and a lower dose formulation [Alli] available without a prescription.)

Phentermine/Topiramate ER (Qsymia)

This fixed-dose combination formulation of phentermine and topiramate ER (phen/top ER) was approved by the FDA in 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are obese (BMI≥30) or overweight (BMI≥27) who have at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, or T2D).

Although the exact mechanism of action is not known, the effect of phentermine on body weight is likely mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption, but other metabolic effects may also be involved. The precise mechanism of action of topiramate on body weight also is not known, although it may be due to its effects on both appetite suppression and satiety enhancement induced by a combination of pharmacologic effects with various neurotransmitters.[9,10] The combination of phentermine with topiramate has been shown to have an enhanced weight-loss benefit than either medication alone while mitigating the side-effect profile.

■ Efficacy

The efficacy of phen/top ER on weight loss was assessed in two 1-year randomized, double-blind, placebo-controlled studies (EQUIP and CONQUER),[9,11] and a 2-year extension trial (SEQUEL).[12] Both studies included a 4-week titration period followed by 52 weeks of treatment. The SEQUEL study was a placebo-controlled, double-blind, 52-week extension (for a total of 108 weeks of treatment) in patients who completed the CONQUER study.[12] During these studies, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended to all patients, and patients were offered nutritional and lifestyle modification counseling. The two co-primary efficacy outcomes in these studies after 1 or 2 years of treatment were:

- Percent weight loss from baseline
- Treatment response defined as achieving ≥5% weight loss from baseline.

The efficacy results from these trials of phen/top ER are summarized in **Table 9.3**.

The EQUIP trial included only patients with Class II and III obesity (BMI≥35), while the CONQUER trial included both overweight and obese patients (BMI 27-45) with ≥2 significant comorbidities, including elevated BP or requirement for ≥2 antihypertensive medications; triglycerides >200-400 mg/dL or treatment with ≥2 lipid-lowering agents; elevated FPG (>100 mg/dL) or diabetes; and/or waist circumference ≥102 cm for men or >88 cm for women.[9] Patients with T2D were excluded from participating in the EQUIP study while diabetic patients were neither specifically included nor excluded in the CONQUER study.

EQUIP

This trial randomized a total of 1267 patients to receive placebo, phen/top ER 3.75/23, or phen/top ER 15/92 once daily.[9] Overall, mean age was 42.7 years, BMI was 42.0, mean waist circumference was 120.8 cm, and 83% were female, with a substantial represen-

tation of black patients (16% to 18%). There were no significant between-group differences in any baseline variable. A total of 59.9% of randomized patients completed the study regardless of whether they continued taking their assigned treatment (52.9% placebo, 61.0% phen/top ER 3.75/23, 66.4% phen/top ER 15/92; (P <0.0001 for difference), while 53.7% reported taking the assigned study drug/placebo for the full intended treatment period (46.9% placebo, 57.3% phen/top ER 3.75/23, 58.8% phen/top ER 15/92 mg; P = 0.0003 for difference). The most common reasons for discontinuation were lost to follow-up or withdrawal of consent (more common in placebo than active treatment groups) or AEs (more common in active treatment than placebo groups). Overall, discontinuations were lower in patients receiving active treatments.

Treatment with each phen/top ER dosage resulted in statistically significant weight loss from baseline compared with placebo during 56 weeks of treatment (**Figure 9.3**). The percent weight loss from baseline was significantly greater with phen/top ER 15/92 than with phen/top ER 3.75/23. In addition, a significantly greater proportion of patients randomized to either dosage of phen/top ER achieved weight loss of either ≥5% or ≥10% (**Table 9.3**). In this study in which all patients were obese, a separate analysis showed that these results did not differ significantly according to baseline BMI.[9]

CONQUER

In this trial, a total of 2487 patients were randomized to treatment with placebo, (n = 979), phen/top ER 7.5/46 (n = 488), or phen/top ER 15/92 (n = 981) once daily. Baseline patient characteristics were similar across treatment groups[11]: 70% patients were women and 86% were white. Overall, 11% of patients were black. Mean age for the whole group was 51.1 years, mean body weight was 103.1 kg, and BMI was 36.6 kg/m². At baseline, 52% of patients had hypertension, 36% had hypertriglyceridemia, 68% had IGT or IFG (including T2D), and 16% had T2D. Overall, half of

patients had ≥3 protocol-specified comorbidities, and virtually all (98%) had abdominal obesity. A total of 38% of patients prematurely discontinued the study drugs (43% placebo, 31% phen/top ER 7.5/46, and 36% in the phen/top ER 15/92 groups). However, 69% of all randomized patients had an endpoint (week 56) assessment.

Compared with placebo, both dosages of phen/top ER resulted in and maintained significantly greater weight losses throughout the 56-week course of treatment (**Figure 9.4**). The reductions from baseline body weight with both dosages of phen/top ER were significantly greater than with placebo (**Table 9.3**). In addition, the reduction with phen/top ER 15/92 was significantly greater compared with phen/top ER 7.5/46. Significantly more patients who received either phen/top ER dosages achieved a ≥5% and/or ≥10% weight reduction from baseline compared with placebo. Significantly more patients achieved these goals with the phen/top ER 15/92 dosage compared with the lower dosage.

■ Long-Term Efficacy

SEQUEL

The study was a placebo-controlled, double-blind, 108-week extension study in which volunteers who had completed the CONQUER study continued with their original randomly assigned treatment: placebo (n = 227), phen/top ER 7.5/46 (n = 153), or phen/top ER 15/92 (n = 295) to complete a total of 108 weeks of treatment. All patients participated in a lifestyle-modification program. Baseline demographic, anthropometric, and clinical characteristics, including comorbidities, were similar among patients in all three treatment arms of the study.[12] Overall, 84.0% of patients completed the extension study, including 86.3% of those assigned to placebo, 82.5% of those assigned to phen/top ER 7.5/46, and 83.1% of those in the phen/top ER 15/92 group.

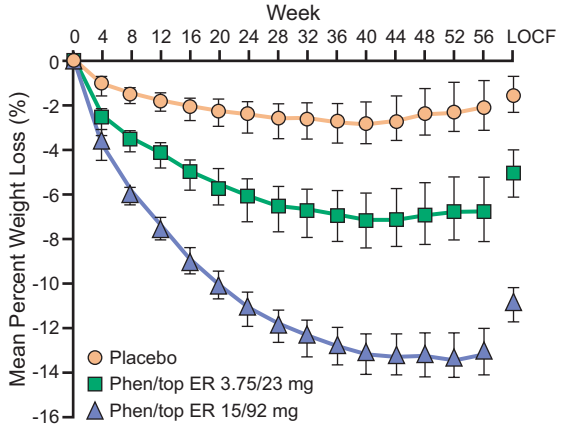
TABLE 9.3 — Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Combination Treatment With Phentermine/Topiramate ER in Overweight/Obese Patients

		Phentermine/Topiramate ER (mg/mg)		
	Placebo	**3.75/23**	**7.5/46**	**15/92**
EQUIP: Obese Patients (BMI ≥35)/1-Year				
mITT-LOCF population (*n*)	498	234	—	498
Weight loss from baseline (kg)	-1.6	-5.1[a]	—	-10.9[a]
Patients losing ≥5% baseline weight (%)	17	45[a]		67[a]
Patients losing ≥10% baseline weight (%)	7	19[a]	—	47[a]
CONQUER: Obese or Overweight (BMI 27-45) Patients With ≥2 Risk Factors/1-Year				
mITT-LOCF population (*n*)	979	—	488	981
Weight loss from baseline (kg)	-1.2	—	-7.8[a]	-9.8[a]
Patients losing ≥5% baseline weight (%)	21	—	62[a]	70[a]
Patients losing ≥10% baseline weight (%)	7	—	37[a]	48[a]
SEQUEL: Overweight and Obese (BMI 27-45) Patients With ≥2 Risk Factors/2-Year Double-Blind, Placebo-Controlled Extension Study of CONQUER Trial				
Patients who continued original blinded treatment (*n*)	227	—	153	295
Weight loss from baseline (kg) difference from placebo	-2.1	—	-9.6[a]	-10.9[a]
Patients losing ≥5% baseline weight (%)	30.0	—	75.2[a]	79.3[a]
Patients losing ≥10% baseline weight (%)	11.5	—	50.3[a]	53.9[a]

[a] P <0.0001 vs placebo.
[b] P <0.01 vs 7.5 mg/46 mg dose.

[1] Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342.
[2] Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.
[3] Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):297-308.

FIGURE 9.3 — EQUIP Study: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Obese (BMI ≥35 kg/m^2) Patients

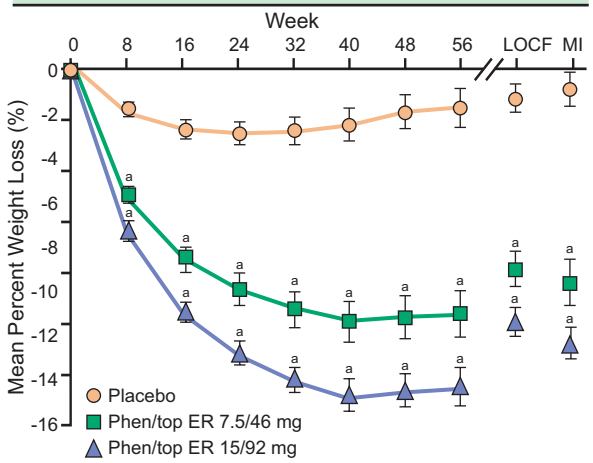


Data from ITT-LOCF population.

Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342.

Patients in both active treatment arms experienced significantly greater percentage weight losses compared with those in the placebo arm, and these weight losses were maintained at all time points during 108 weeks of treatment compared with placebo (**Figure 9.5**). At week 108, the mean percentage changes from baseline in body weight were significantly greater (P <0.0001) in the phen/top ER groups compared with placebo (-1.8%, -9.3%, and -10.5% with placebo, phen/top ER 7.5/46 mg, and phen/top ER 15/92, respectively). In addition, significantly greater proportions of patients treated with each dosage of phen/top ER achieved weight losses of ≥5% and ≥10% compared with placebo-treated patients (**Table 9.3**).

FIGURE 9.4 — CONQUER: Time Course of Weight Change During 52 Weeks of Treatment With Phentermine/Topiramate ER in Overweight and Obese (BMI 27-45 kg/m^2) Patients With ≥2 Risk Factors



Data from ITT-LOCF population.

[a] P <0.0001.

Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352.

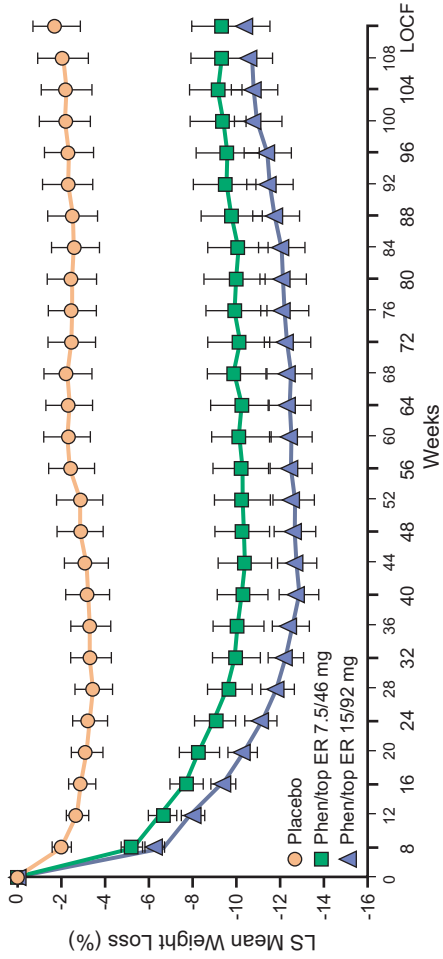
Secondary Efficacy Endpoints

All three of these trials also assessed changes from baseline in metabolic, CV, and anthropomorphic risk factors associated with obesity.

In the EQUIP trial, patients treated with phen/top ER 15/92 had significantly greater changes compared with those in the placebo group in:

- SBP and DBP
- Heart rate
- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- Fasting glucose
- Waist circumference (**Table 9.4**).

FIGURE 9.5 — SEQUEL: Time Course of Weight Change During 108 Weeks of Treatment With Phentermine/Topiramate ER in Overweight/Obese Patients



Data from overall study completer population.

Garvey WT, et al. *Am J Clin Nutr.* 2012;95(2):297-308.

Patients in the phen/top ER 3.75/23 group experienced numerically, but not always significantly different changes, except the changes in SBP and waist circumference were significant.[9]

In the CONQUER study, phen/top ER 15/92 compared with placebo showed significant changes in:

- BP
- Waist circumference
- Concentrations of lipids
- Fasting glucose and insulin (**Table 9.4**).[11]

Improvements in risk factors were most pronounced in patients with pre-existing comorbid diseases. In patients with hypertension at baseline, there were greater reductions in SBP with both dosages of phen/top ER than with placebo, and more patients had their antihypertensive drugs withdrawn in the phen/top ER 7.5/46 group. Patients with diabetes at baseline had greater reductions in A1C with both dosages. Patients with prediabetes had greater reductions in fasting blood glucose and fewer patients progressed to T2D.

In the SEQUEL study, treatment with phen/top ER 15/92 compared with placebo resulted in significantly greater changes from baseline in:

- Lipid parameters and triglycerides
- Fasting glucose and insulin
- Waist circumference (**Table 9.4**).[12]

In the phen/top ER 7.5/46 group, changes were significantly greater compared with placebo in LDL cholesterol, triglycerides, fasting insulin, A1C, and waist circumference. Among patients without diabetes at baseline, the annualized incidence rates for progression to T2D were 3.7%, 1.7%, and 0.9% in the placebo, phen/top ER 7.5/46, and phen/top ER 15/92 treatment groups, respectively. These findings indicate a 54% reduction in the progression to T2D.

■ Safety

In the 1-year clinical trials with phen/top ER, AEs that occurred at a rate of ≥5% and at a rate at least 1.5

TABLE 9.4 — Summary of Mean Changes From Baseline in Metabolic and CV Risk Factors and Waist Circumference in Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Phentermine/Topiramate ER in Overweight/Obese Patients

	EQUIP[1]: Obese Patients (BMI ≥35)			CONQUER[2]: Obese or Overweight (BMI 27-45) Patients With ≥2 Risk Factors			SEQUEL[3]: 2-Year Double-Blind, Placebo-Controlled Extension of CONQUER Trial		
		Phen/Top ER (mg/mg)			Phen/Top ER (mg/mg)			Phen/Top ER (mg/mg)	
Change From Baseline	**Placebo (*n* = 498)**	**3.75/23 (*n* = 234)**	**15/92 (*n* = 498)**	**Placebo (*n* = 994)**	**7.5/46 (*n* = 498)**	**15/92 (*n* = 995)**	**Placebo (*n* = 227)[a]**	**7.5/46 (*n* = 153)[a]**	**15/92 (*n* = 295)[a]**
Total cholesterol (%)	-3.5	-5.4	-6.0	-3.3	-4.9	-6.3	NA	NA	NA
LDL cholesterol (%)	-5.5	-7.7	-8.4	-4.1	-3.7	6.9	-10.7	-4.6	-5.6
HDL cholesterol (%)	0.0	+0.5	+3.5	+1.2	+5.2	+6.8	+4.7	+7.3	+11.9
Triglycerides (%)	+9.1	+5.2	-5.2	+4.7	-8.6	-10.6	+0.4	-12.5	-13.7
Systolic BP (mm Hg)	+0.9	-1.8	-2.9	-2.4	-4.7	-5.6	-3.2	-4.7	-4.3
Diastolic BP (mm Hg)	+0.4	-0.1	-1.5	-2.7	-3.4	-3.8	-3.9	-3.7	-3.5
Heart rate (bpm)	-0.2	-0.3	+1.2	-0.1	+0.1	+1.7	+0.4	+1.3	+1.7
Fasting glucose (mg/dL)	+1.9	+0.8	-0.6	+0.13	-0.01	-0.07	+3.7	+0.1	-1.2
Fasting insulin (mU/mL)	NA	NA	NA	+5.1	-24.0	-27.6	-2.6	-5.3	-5.2
A1C (%)	NA	NA	NA	+0.1	0	-0.1	+0.2	+0.01	0.0
Waist circumference (cm)	-3.1	-5.6	-10.9	-2.4	-7.6	-9.2	-3.6	-9.8	-10.6

Highlighted results indicate significantly better results with phentermine/topiramate ER compared with placebo.

[a] The results from this trial are from patients who continued their original, blinded-study treatments from baseline to week 108, including a 4-week titration period.

[1] Allison DB, et al. *Obesity (Silver Spring).* 2012;20:330-342.
[2] Gadde KM, et al. *Lancet.* 2011;377:1341-1352.
[3] Garvey WT, et al. *Am J Clin Nutr.* 2012;95(2):297-308.

times placebo included paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth (**Table 9.5**). Dose-related trends in the incidences of such AEs were noted. Other less frequent events occurring more commonly with the highest phen/top ER dosage included:

- Depression
- Irritability
- Alopecia
- Anxiety
- Disturbance in attention
- Hypoesthesia.

Serious AEs were similar across treatment groups. Most AEs reported were mild in severity and the rates of serious AEs were similar across treatment groups.[10]

In the 1-year placebo-controlled clinical studies, the rates of discontinuations due to AEs were:

- Phen/top ER 3.75/23: 11.6%
- Phen/top ER 7.5/46: 11.6%
- Phen/top ER 15/92; 17.4%
- Placebo: 8.4%.

The most common AEs that led to discontinuation of treatment are shown in **Table 9.5**.

In the SEQUEL study, the most common treatment emergent AEs were upper respiratory tract infection, constipation, paraesthesia, sinusitis, and dry mouth.[10] The types of TEAEs that occurred between weeks 56 and 108 were similar to those reported in the overall CONQUER population sample from weeks 0 to 56, However, the incidence of individual TEAEs was markedly lower in the second year (weeks 56 to 108) than in the first year (weeks 0 to 56). The incidences of serious AEs from weeks 0 to 108 were 6.2% with placebo, 5.9% with both phen/top ER 3.75/23 and phen/top ER 7.5/46 mg, and 8.1% with phen/top ER 15/92 mg. The percentage of patients who discontinued due to AEs by week 108 was also similar across treatment groups (3.1%, 4.5%, and 4.4% in the placebo, phen/top ER 7.5/46 mg, and phen/top ER 15/92 mg groups, respectively).

TABLE 9.5 — Summary of Adverse Events With Incidence ≥1% Leading to Treatment Discontinuation in the EQUIP and CONQUER Clinical Trials

		Phentermine/Topiramate ER (mg/mg) (%)		
AE Leading to Discontinuation	**Placebo (%) (*n* = 1561)**	**3.75/23 (*n* = 240)**	**7.5/46 (*n* = 498)**	**15/92 (*n* = 1580)**
Blurred vision	0.5	2.1	0.8	0.7
Headache	0.6	1.7	0.2	0.8
Irritability	0.1	0.8	0.8	1.1
Dizziness	0.2	0.4	1.2	0.8
Paresthesia	0.0	0.4	1.0	1.1
Insomnia	0.4	0.0	0.4	1.6
Depression	0.2	0.0	0.8	1.3
Anxiety	0.3	0.0	0.2	1.1

Qsymia [package insert]. Mountain View, CA: Vivus, Inc; 2012-2013.

■ Prescribing and Administration

Phen/top ER is available in four dosage levels of phentermine and topiramate ER (**Table 9.2**). The lowest-dose formulation contains phentermine 3.75 mg and topiramate ER 23 mg, the mid-level formulation contains phentermine 7.5 mg and topiramate ER 46 mg, and the highest dosage formulation contains phentermine 15 mg and topiramate ER 92 mg. Another dosage level containing phentermine 11.25 mg and topiramate ER 69 mg is recommended for use during dosage titration. The dosages of the individual component agents are considerably lower than the previously approved maximum recommended doses for other indications. This was by design in order to minimize AEs.

Phen/top ER should be taken once daily in the morning with or without food. Avoid dosing in the evening due to the possibility of insomnia. Gradual dose titration is required (**Table 9.2**).[10]

All dosage formulations of phen/top ER are controlled in Schedule IV of the Controlled Substances Act because they contain phentermine, a Schedule IV drug. Topiramate ER is not controlled as a Schedule IV drug.

Lorcaserin (Belviq)

Lorcaserin was approved by the FDA in 2012 and is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are obese (BMI≥30) or overweight (BMI≥27) who have at least one weight-related comorbid condition, (eg, hypertension, dyslipidemia, and T2D).[13]

Lorcaserin is a 5-HT_{2C} receptor agonist. Its precise mechanism of action is not known but it is believed to decrease food consumption and promote satiety by selectively activating 5-HT_{2C} receptors on anorexigenic POMC neurons located in the hypothalamus. Serotonin affects multiple central and peripheral biologic functions in addition to modulating appetite. At the recommended daily dose, lorcaserin selectivity interacts with 5-HT_{2C} receptors compared to 5-HT_{2A} and 5-HT_{2B} receptors, which have been were implicated in both the risk of hallucinations and cardiac valve insufficiency, respectively.[13] This selectivity was designed to mitigate the potential risks associated with former weight-loss agents of this class.

■ Efficacy

The effects of lorcaserin on body weight as well as anthropometric and metabolic parameters were evaluated in three randomized, double-blind, placebo-controlled trials of 52- or 104-week duration. The BLOOM trial[14] and the BLOSSOM trial[15] enrolled obese patients and overweight patients, while the third study (BLOOM-DM) was performed specifically in adults with T2D.[16] The primary efficacy parameters were weight loss at 1 year assessed as the proportion of patients achieving ≥5% weight loss, percent of patients achieving ≥10% weight loss, and mean weight change. All patients received one-on-one instruction for a reduced-calorie diet and exercise counseling that began with the first dose of study medication and continued every 4 weeks throughout the trials. The efficacy results of these trials with lorcaserin are summarized in **Table 9.6**.

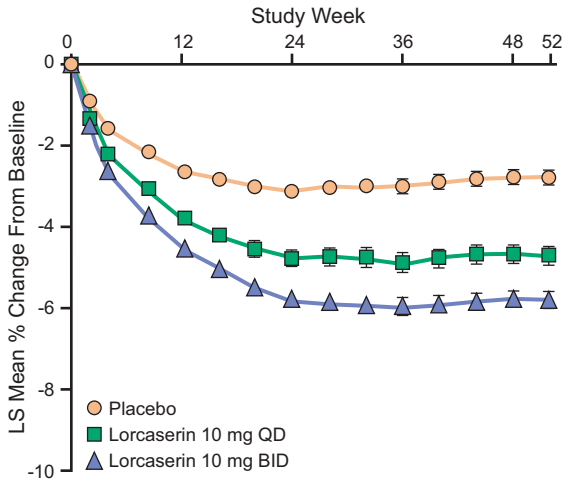
BLOSSOM

The BLOSSOM study evaluated two dosages of lorcaserin in a total of 4008 patients, aged 18 to 65 years, with a BMI between 30 and 45 or between 27 and 29.9 with an obesity-related comorbid condition.[15] Key exclusion criteria included recent CV events, major surgeries, diabetes, SBP≥150 mm Hg, or DBP≥95 mm Hg. Patients were randomly assigned in a 2:1:2 ratio to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo. All patients received diet and exercise counseling. The primary endpoints were proportion of patients achieving at least 5% or 10% reduction in body weight and mean change

from baseline body weight. Of the 4008 randomized patients, 55.5% patients completed the trial: 57.2%, 59.0%, and 52.0% in the lorcaserin twice daily, lorcaserin once daily, and placebo groups, respectively.

Compared with placebo, both dosages of lorcaserin resulted in and maintained significantly greater weight losses from baseline throughout the 56-week course of treatment (**Figure 9.6**). The reductions from baseline body weight with both dosages of lorcaserin were significantly greater than with placebo (**Table 9.6**). Significantly more patients receiving lorcaserin 10 mg twice daily or once daily lost ≥5% and ≥10% body weight at 1 year than those patients in the placebo group. Lorcaserin twice daily was associated with significantly greater weight losses than lorcaserin once daily.

FIGURE 9.6 — BLOSSOM: Changes From Baseline in Mean % Change From Baseline Body Weight



Data from mITT-LOCF population.

Fidler MC, et al. *J Clin Endocrinol Metab*. 2011;96(10):3067-3077.

BLOOM

The BLOOM trial randomized 3182 obese or overweight adults (mean BMI of 36.2) to receive lorcaserin 10 mg twice daily or placebo for 52 weeks.[14] All patients also underwent diet and exercise counseling. At week 52, patients in the placebo group continued to receive placebo, but those in the lorcaserin group were randomly reassigned to receive either placebo or lorcaserin for an additional 52 weeks. Primary outcomes were weight loss at 1 year and maintenance of weight loss at 2 years. The completion rates at year 1 were 55.4% in the lorcaserin group and 45.1% in the placebo group. Overall, the completion rate was 72.6% of patients who completed year 1, with a slightly higher rate of discontinuation among patients who received placebo in both years (27.3%) than among patients who received lorcaserin in both years (25.7%).

During year 1, mean weight loss in the lorcaserin group was significantly greater than that in the placebo group (-5.8 kg vs -2.2 kg, respectively; $P<0.001$) and was maintained through year 2 (-8.1 kg vs -3.3 kg, respectively; $P<0.001$) (**Figure 9.7**). The proportions of patients who achieved a ≥5% loss of their body weight at 1 year were 47.5% and 20.3% with lorcaserin or placebo, respectively (**Table 9.6**). Among patients in the lorcaserin group who had weight loss of ≥5% at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 than in those who were reassigned to receive placebo (67.9% vs 50.3%, $P<0.001$). Mean body weight among patients who received lorcaserin in both years was lower than that among patients who received placebo in both years and lower than that among patients who received lorcaserin in year 1 and placebo in year 2.

BLOOM-DM

Patients in the BLOOM-DM study had to have T2D with a baseline A1C of 7% to 10%, a BMI of 27 to 45, and treatment with metformin, a sulfonylurea, or both.[16] A total of 604 patients were assigned to treat-

TABLE 9.6 — Summary of Primary Efficacy Endpoints From Three Randomized, Placebo-Controlled Trials of Lorcaserin in Overweight/Obese Patients

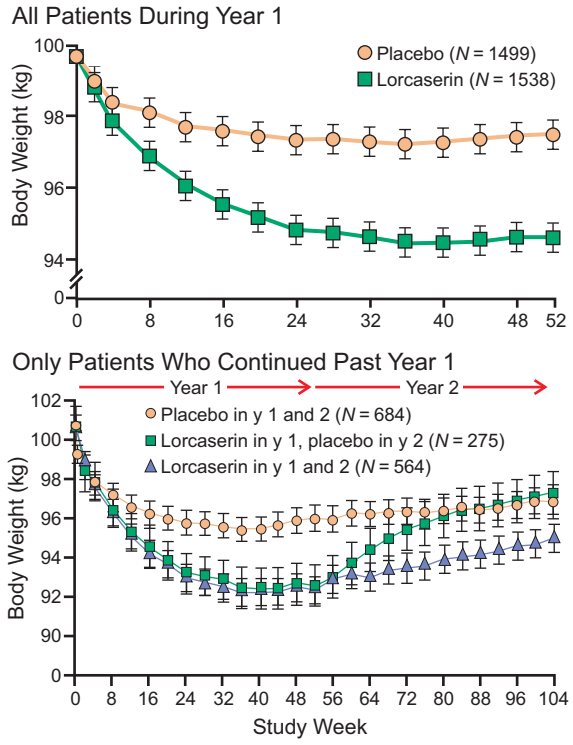
	BLOSSOM[1]: 1-Year Obese or Overweight Patients With ≥1 Obesity-Related Comorbid Condition			BLOOM[2]: 2-Year, 2-Period Obese or Overweight Patients With ≥1 Obesity-Related Comorbid Condition			BLOOM-DM[3]: 1-Year Obese and Overweight Patients With Type 2 Diabetes Treated With Metformin ± Sulfonylurea		
		Lorcaserin (10 mg)			Lorcaserin (10 mg)			Lorcaserin (10 mg)	
	Placebo	BID	QD	Placebo	BID	QD	Placebo	BID	QD
mITT/LOCF population (*n*)	1541	1561	771	1499	1538	—	248	261	95
Weight change from baseline (kg)	-2.9	-5.8[a]	-4.7[a,b]	-2.2	-5.8[a]	—	-1.6	-4.7[a]	-5.0[a]
Weight change from baseline (%)	-2.8	-5.8[a]	-4.7[a,b]	—	—	—	-1.5	-4.5[a]	-5.0[a]
Patients losing ≥5% baseline weight (%)	25.0	47.2[a]	40.2[a,b]	20.3	47.5[a]	—	16.1	37.5[a]	44.7[a]
Patients losing ≥10% baseline weight (%)	9.7	22.6[a]	17.4[a,b]	7.7	22.6[a]	—	4.4	16.3[a]	18.1[a]

Highlighted results indicate significantly better results with lorcaserin compared with placebo.

[a] P <0.001 vs placebo.
[b] P <0.01, lorcaserin QD vs lorcaserin BID.

[1] Fidler MC, et al. *J Clin Endocrinol Metab*. 2011;96:3067-3077
[2] Smith SR, et al. *N Engl J Med*. 2010;363:245-256
[3] O'Neil PM, et al. *Obesity (Silver Spring)*. 2012;20:1426-1436.

FIGURE 9.7 — BLOOM: Changes From Baseline Body Weight (kg) During Year 1 and During Year 1 and Year 2



Data from mITT-LOCF population.

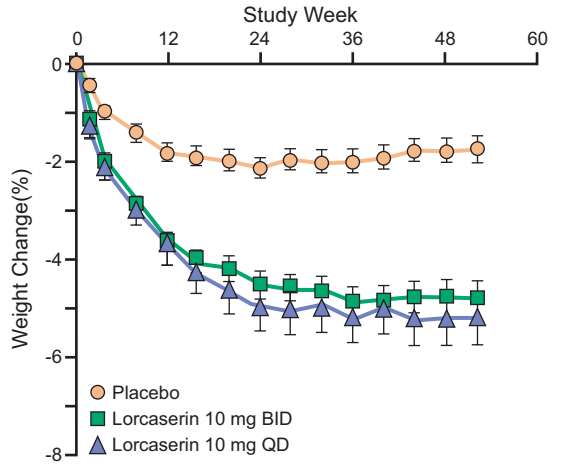
Smith SR, et al. *N Engl J Med*. 2010;363(3):245-256.

ment with placebo ($n = 253$), lorcaserin 10 mg twice daily ($n = 256$), or lorcaserin 10 mg once daily ($n = 95$). The study completion rates were lorcaserin twice daily (66.6%), lorcaserin once daily (78.9%), and placebo (62.1%). More discontinuations were attributed to AEs (lorcaserin twice daily 8.6%, lorcaserin once daily 6.3%, and placebo 4.3%).

One-year weight loss was significantly greater with lorcaserin 10 mg twice daily compared with placebo, and significantly greater proportions of people treated with lorcaserin experienced ≥5% and ≥10% reductions in body weight than in those who received placebo (**Figure 9.8**).

Reduction in waist circumference was also significantly greater with lorcaserin treatment. Changes in A1C, FPG, BP, and plasma lipids were secondary endpoints. Compared with placebo, lorcaserin treatment resulted in statistically significantly greater reductions from baseline in A1C (placebo-subtracted difference ≥0.5%; $P < 0.001$) and FPG (placebo-subtracted difference ≥5.1 mg/dL; $P < 0.001$). Changes in BP, heart rate, and plasma lipids with either lorcaserin or placebo were generally small and not clinically or significantly different.

FIGURE 9.8 — BLOOM-DM: Change From Baseline in Body Weight During 52 Weeks of Treatment



Data from mITT population.

O'Neil PM, et al. *Obesity (Silver Spring)*. 2012;20(7):1426-1436.

■ Secondary Efficacy Endpoints

In addition to the primary efficacy endpoints, the BLOSSOM, BLOOM, and BLOOM-DM studies also assessed several secondary efficacy endpoints, including change from baseline in CV, metabolic, and anthropometric risk factors associated with obesity.

In the BLOSSOM trial, patients who received lorcaserin 10 mg once daily had significantly greater changes compared with placebo in lipid parameters (total cholesterol, LDL cholesterol, HDL-cholesterol, and triglycerides), and waist circumference, while the changes with lorcaserin 10 mg twice daily vs placebo were significantly greater only for HDL cholesterol, triglycerides, and waist circumference (**Table 9.7**).

In the BLOOM study, the changes from baseline in all total cholesterol were significantly greater with lorcaserin 10 mg twice daily than with placebo (**Table 9.7**).

In the BLOOM-DM study, there were significant changes in heart rate with both dosages of lorcaserin compared with placebo, and in HDL and waist circumference with lorcaserin 10 mg twice daily (**Table 9.7**).

■ Safety

In placebo-controlled clinical trials of at least 1 year in duration, 8.6% of lorcaserin-treated patients prematurely discontinued treatment due to AEs compared with 6.7% of placebo-treated patients.[13] In patients without T2D, the most common AEs with lorcaserin included headache, dizziness, fatigue, nausea, dry mouth, and constipation (**Table 9.8**). The most common AEs among diabetic patients were hypoglycemia (defined as blood glucose ≤65 mg/dL and with symptoms), headache, back pain, nasopharyngitis, cough, and fatigue (**Table 9.8**). The incidence of hypoglycemia was similar among lorcaserin-treated patients (7.4%) and placebo-treated patients (6.3%).

In light of previous concerns about valvulopathy, patients in these trials were monitored by serial echocardiograms. In BLOSSOM, 2.0% of patients who received lorcaserin twice daily, 1.4% who received lorcaserin once daily, and 2.0% on placebo developed new echocardiographic findings consistent with the FDA-defined valvulopathy at week 52.[15] In patients with preexisting valvulopathy identified by the echocardiogram obtained at randomization (5.2% lorcaserin twice daily, 3.9% lorcaserin once daily, and 4.1% placebo), the proportions of patients who experienced any increase in mitral or aortic regurgitation at week 52 were 12.1% in the lorcaserin twice-daily group ($P = 0.014$) and 11.1% in the lorcaserin once-daily group ($P = 0.056$) compared with 30.6% in the placebo group.[15]

In the BLOOM study, FDA-defined valvulopathy developed in 2.3% of patients in the placebo group and 2.7% of patients in the lorcaserin group ($P = 0.70$ at year 1). At year 2, the valvulopathy rate was 2.7% in the placebo group and 2.6% among patients who received lorcaserin during year 1 and year 2.[14]

In the BLOOM-DM trial, 2.3% of patients in the placebo group and 2.7% in the lorcaserin group ($P = 0.70$) had developed FDA-defined valvulopathy. By year 2, the valvulopathy rate was 2.7% in the placebo group and 2.6% among patients who received lorcaserin during years 1 and 2.[16]

■ Prescribing and Administration

The recommended daily, as well as maximum dose is one 10 mg tablet twice daily with or without food. Lorcaserin should be discontinued if ≥5% weight loss is not achieved by week 12. Since lorcaserin is a serotonergic agent, coadministration with other serotonergic drugs may lead to the development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome–like reactions. Lorcaserin is listed in Schedule IV of the Controlled Substances Act.

TABLE 9.7 — Mean Changes From Baseline in Metabolic and Cardiovascular Risk Factors in Randomized, Placebo-Controlled Trials With Lorcaserin in Overweight/Obese Patients

	BLOSSOM[1]: 1-Year Obese or Overweight Patients With ≥1 Obesity-Related Comorbid Condition			BLOOM[2]: 1-Year, 2-Period Obese or Overweight Patients With ≥1 Obesity-Related Comorbid Condition			BLOOM-DM[3]: 1-Year Obese and Overweight Patients With Type 2 Diabetes Treated With Metformin ± Sulfonylurea		
		Lorcaserin (10 mg)			Lorcaserin (10 mg)			Lorcaserin (10 mg)	
Change From Baseline	**Placebo**	**BID**	**QD**	**Placebo**	**BID**	**QD**	**Placebo**	**BID**	**QD**
(*n*)	1541	1561	771	1499	1538	—	248	251	95
Total cholesterol (%)	0.0	-0.7	-1.3	+0.57	-0.90	—	-0.1	-0.7	+1.4
LDL cholesterol (%)	+1.7	+0.3	-0.1	+4.03	+2.87	—	+5.0	+4.2	+4.2
HDL cholesterol (%)	+1.3	+3.7	+3.5	-0.21	+0.05	—	+1.6	+5.2	+4.4
Triglycerides (%)	-0.9	-4.3	-5.5	-0.14	-6.15	—	-4.8	-10.7	-5.5
Systolic BP (mm Hg)	-1.2	-1.9	-1.3	-0.8	-1.4	—	-0.9	-0.8	+0.56
Diastolic BP (mm Hg)	-1.4	-1.9	-1.1	-0.6	-1.1	—	-0.7	-1.1	+0.29
Heart rate (bpm)	-1.6	-2.3	-1.1	-1.6	-2.0	—	-0.4	-2.0	-2.9
Fasting glucose (mg/dL)	—	—	—	+1.1	-0.8	—	-11.9	-27.4	-28.4
Fasting insulin (μU/mL)	—	—	—	-1.28	-3.33	—	-1.6	-3.0	-2.3
A1C (%)	-0.14	-0.19	-0.17	0.03	-0.04	—	-0.4	-0.9	-1.0
Waist circumference (cm)	-4.1	-6.3	-5.8	-3.9	-6.8	—	-3.3	-5.5	-5.0

Highlighted results indicate significantly better results with lorcaserin compared with placebo.

[1] Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077
[2] Smith SR, et al. *N Engl J Med.* 2010;363:245-256
[3] O'Neil PM, et al. *Obesity (Silver Spring).* 2012;20:1426-1436.

222

TABLE 9.8 — Summary of Adverse Events Reported by ≥2% of Lorcaserin Patients and More Commonly Than With Placebo in Patients Without Diabetes in the BLOSSOM, BLOOM, and BLOOM-DM Studies

	BLOSSOM and BLOOM (Without Diabetes)		BLOOM-DM (With Diabetes)	
Adverse Event (%)	**Placebo (*n* = 3195)**	**Lorcaserin 10 mg BID (*n* = 3185)**	**Placebo (*n* = 252)**	**Lorcaserin 10 mg BID (*n* = 256)**
Nausea	5.3	8.3	7.9	9.4
Diarrhea	5.6	6.5	—	
Constipation	3.9	5.8	—	—
Dry mouth	2.3	5.3	—	—
Vomiting	2.6	3.8	—	—
Peripheral edema	—	—	2.4	4.7
Fatigue	3.6	7.2	4.0	7.4
Seasonal allergy	—	—	0.8	3.1
Cough	3.4	4.3	4.4	8.2
Upper respiratory infection	12.3	13.7	—	—
Nasopharyngitis	12.0	13.0	9.9	11.3
Urinary tract infection	5.4	6.5	6.0	9.0
Gastroenteritis	—	—	2.0	3.1
Back pain	5.6	6.3	7.9	11.7
Musculoskeletal pain	1.4	2.0	—	—
Muscle spasms	—	—	3.6	4.7
Headache	10.1	16.8	7.1	14.5
Dizziness	3.8	8.5	6.3	7.0
Oropharyngeal pain	2.5	3.5	—	—
Sinus congestion	2.4	2.9	—	—
Rash	1.8	2.1	—	—
Hypoglycemia	—	—	21.0	29.3
Decreased appetite	—	—	0.4	2.3
Worsening diabetes	—	—	0.8	2.7
Hypertension	—	—	3.2	5.1
Anxiety			3.2	3.5
Depression			2.3	2.0
Insomnia			2.4	3.5
Stress			1.2	2.7

Belviq [package insert]. Zofingen, Switzerland: Arena Pharmaceuticals GmbH; 2012.

223

Naltrexone SR/Bupropion SR (Contrave)

The fixed-dose formulation of naltrexone SR/bupropion SR (nal/bup) was developed based on preclinical evidence that this combination has complementary actions in the CNS that result in reduced food intake. Bupropion stimulates hypothalamic POMC neurons, with downstream effects to reduce food intake and increase energy expenditure. Naltrexone blocks opioid receptor-mediated POMC autoinhibition, augmenting POMC firing in a synergistic manner. Given the known individual effects of naltrexone and bupropion on addiction (alcohol and nicotine, respectively), a fixed combination of NB was hypothesized to induce weight loss through sustained modulation of CNS reward pathways.

■ Efficacy

The efficacy of nal/bup was been assessed in several clinical trials that used various dosage combinations.[17-20] An early dose-ranging study in a total of 419 patients with uncomplicated obesity randomized patients to 24 weeks of treatment with bupropion SR (400 mg/day), immediate-release naltrexone (48 mg/day), or placebo, and three combination therapy groups consisting of immediate-release naltrexone, 16, 32, or 48 mg/day, plus bupropion SR (400 mg/day), with a 24-week extension. A minimal diet and exercise component was also included.[17] Weight loss with combination therapy was statistically significant vs monotherapy for all three nal/bup combinations with the exception of nal/bup 48/360 vs bupropion. Weight loss with nal/bup continued after week 24.

Subsequent, four 56-week phase 3 trials (Contrave Obesity Research I [COR-I], Contrave Obesity Research II [COR-II], Contrave Obesity Research Behavioral Modification [COR-BMOD], and Contrave Obesity Research-Diabetes [COR-Diabetes])[18-23] enrolled obese (BMI 30-45) or overweight (27-45) patients with dyslipidemia and/or hypertension to 56 weeks of treatment with fixed-dose combination formulations of nal/bup or placebo. All patients in the COR-I, COR-II, and COR-Diabetes trials were also prescribed a mild hypocaloric diet and exercise. All patients in the COR-BMOD trial were prescribed an energy-reduced diet and 28 group behavioral modification sessions. The co-primary endpoints in all of these trials were percentage change in weight and the proportion of participants who lost ≥5% weight at week 56. All trials included a ~3-week dose escalation period. The efficacy results from these trials of nal/bup are summarized in **Table 9.9**.

COR-I

In the COR-I study, 1742 patients were randomized in a 1:1:1 ratio to receive placebo, nal/bup 16/360 or nal/bup 32/360.[18] Throughout the study, decreases in body weight were greater with nal/bup (**Figure 9.9**). At week 56, the mean changes in body weight with both nal/bup 16/360 (-5.0%) and nal/bup 32/360 (-6.1%) were significantly greater (P <0.0001) than with placebo (-1.3%). The change with nal/bup 32/360 was significantly greater (P <0.0099) than with nal/bup 16/360 (**Table 9.9**). In addition, significantly greater (P <0.0001) proportions of patients in both nal/bup groups had a decrease in body weight of ≥5% and ≥10% compared with those who received placebo (**Figure 9.9**).

COR-II

The COR-II study randomized 1496 patients in a 2:1 ratio to nal/bup 32/360 or placebo for up to 56 weeks.[19] Patients in the nal/bup 32/360 arm with a <5% weight loss at visits between weeks 28 and 44 inclusive were re-randomized (double-blind, 1:1 ratio) to continue receiving nal/bup 32/360 or escalate to nal/bup 48/360 for the remainder of the study. In the mITT-LOCF population, weight loss was significantly greater for nal/bup 32/360 vs placebo at week 28 (6.5% vs 1.9%; P <0.001), and was maintained with continued

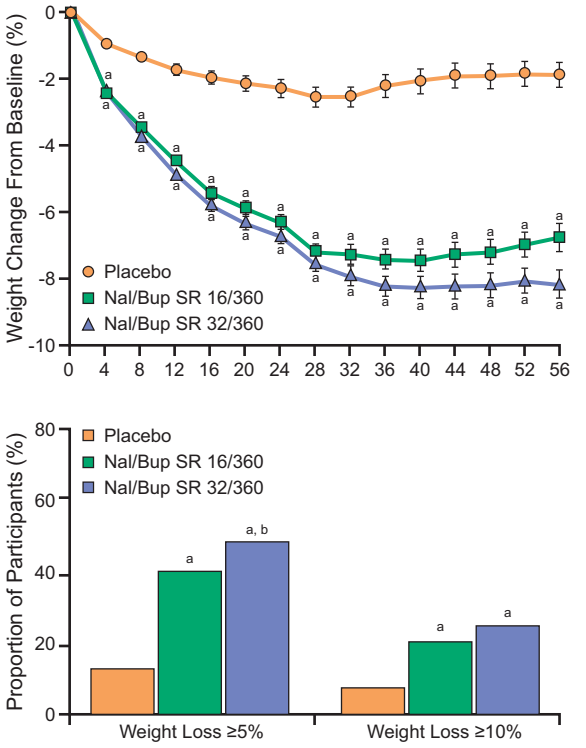
TABLE 9.9 — Summary of Primary Efficacy Endpoints From Four Randomized, Placebo-Controlled Trials of Combination Treatment With Naltrexone ER/Bupropion ER in Overweight/Obese Patients

	Obese (BMI 30-45) or Overweight/Obese (BMI 27-45) Patients With Dyslipidemia and/or Hypertension / 56 Weeks										
	COR-I[a,1]			COR-II[a,2]			COR-BMOD[a,3]			COR-Diabetes[a,4]	
		Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)
	Placebo	16/360	32/360	Placebo	16/360[b]	32/360	Placebo	16/360[b]	32/360	Placebo	32/360
mITT-LOCF population	*n* = 511	*n* = 471	*n* = 471	*n* = 456	—	*n* = 825	*n* = 202	—	*n* = 591	*n* = 159	*n* = 265
Weight loss from baseline (%)	-1.3	-5.0[c]	-6.1[c,d]	-1.2	—	-6.4[e]	-7.3	—	-11.5[e]	-1.8	-5.0[e]
Patients losing ≥5% baseline weight (%)	16	39[c]	48[c]	17.1	—	50.5[e]	42.5	—	66.4[e]	18.9	44.5[e]
Patients losing ≥10% baseline weight (%)	7	20[c]	25[c]	5.7	—	28.3[e]	20.2	—	41.5[e]	5.7	18.5[e]

[a] The trial included an approximate 3-week dose escalation period.
[b] Not included in these trials.
[c] $P < 0.0001$ vs placebo.
[d] $P < 0.0099$ for nal/bup SR 32/360 vs nal/bup SR 16/360.
[e] $P < 0.001$ vs placebo.

[1] Greenway FL, et al; COR-I Study Group. *Lancet*. 2010;376(9741):595-605.
[2] Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring)*. 2013;21(5):935-943.
[3] Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120.
[4] Hollander P, et al; COR-Diabetes Study Group. *Diabetes Care*. 2013;36(12):4022-4029.

FIGURE 9.9 — COR-I Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] $P<0.0001$ vs placebo.
[b] $P<0.0099$ for nal/bup SR 32/360 vs nal/bup SR 16/360.

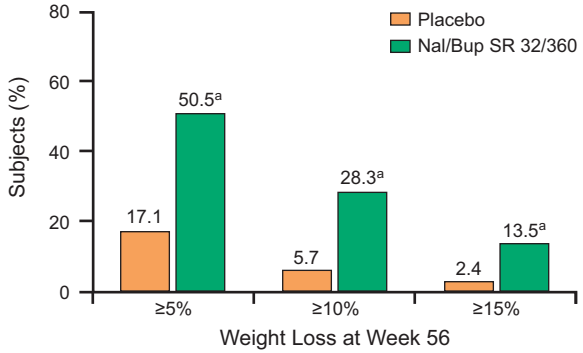
Modified from Greenway FL, et al; COR-I Study Group. *Lancet.* 2010;376(9741): 595-605.

double-blind treatment through week 56 (6.4% vs 1.2; $P<0.001$). In addition, nal/bup 32/360 was associated with significantly larger proportion of participants achieving ≥5%, ≥10%, and ≥15% weight loss both in the mITT-LOCF and "completer" populations vs placebo at weeks 28 and 56 (**Figure 9.10**).

COR-BMOD

Given that intensive behavioral modification programs (BMOD) have been shown to significantly increase weight loss compared with treatment by weight loss medication,[21,22] the COR-BMOD trial was designed to assess the efficacy of nal/bup 32/360 added to a BMOD program compared with BMOD alone.[20] A total of 793 obese participants (BMI = 36.5 ± 4.2) were randomly assigned in a 1:3 ratio to placebo + BMOD ($n=202$); or nal/bup 32/360 + BMOD ($n=591$). All participants also were prescribed an energy-reduced diet.

FIGURE 9.10 — COR-II Trial: Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] $P<0.001$ vs placebo.

Modified from Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring).* 2013;21(5):935-943.

Throughout the study, decreases in body weight in the mITT-LOCF population were significantly (P <0.001) greater with nal/bup 32/360 + BMOD compared with placebo + BMOD (**Figure 9.11**). At week 56, the mean changes in body weight were significantly greater with nal/bup + BMOD than with BMOD alone (-11.5 % and -7.3%, respectively; P <0.001) (**Table 9.9**). Similarly, significantly greater (P <0.001) proportions of patients in the nal/bup + BMOD group had a decrease in body weight of ≥5% and ≥10% compared with those who received placebo + BMOD (**Figure 9.11**).

COR-Diabetes

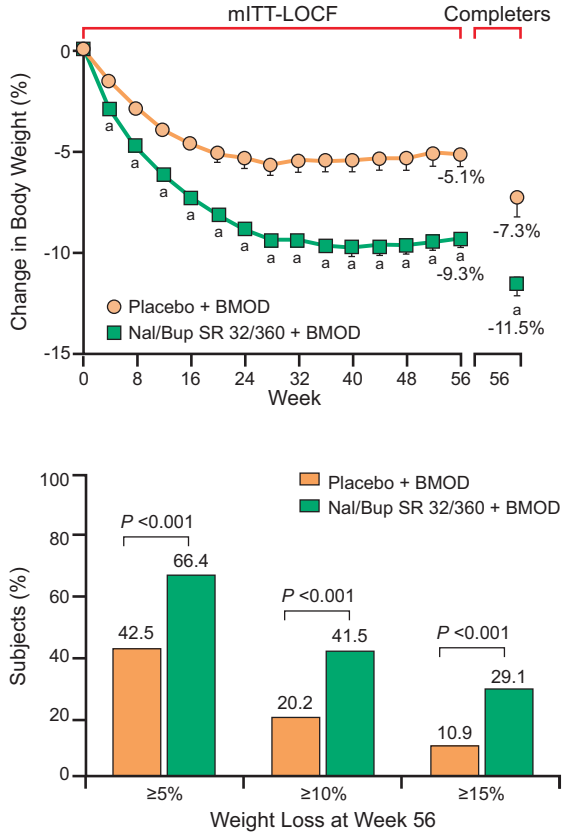
The efficacy and safety of nal/bup in overweight patients with diabetes was assessed in the COR-Diabetes trial.[23] 505 overweight/obese individuals with T2D with or without background oral antidiabetes drugs were randomized 2:1 to 32 mg/360 mg nal/bup or placebo. In the modified ITT population, nal/bup resulted in significantly greater weight reduction (-5.0% vs -1.8%; P <0.001) and proportion of patients achieving ≥5% weight loss (44.5% vs 18.9%, P <0.001) compared with placebo (**Figure 9.12**).

Secondary Efficacy Endpoints

In addition to the primary efficacy endpoints, the COR-I, COR-II, COR-BMOD, and COR-Diabetes studies also assessed several secondary efficacy endpoints, including changes from baseline in CV, metabolic, and anthropometric risk factors associated with obesity. The results are summarized in **Table 9.10**.

In the COR-1 trial, patients who received either nal/bup 16/360 or nal/bup 32/360 had significantly greater changes compared with placebo in lipid parameters (HDL-cholesterol, and triglycerides), SBP and DPB, HOMA-IR, and waist circumference. In addition, changes with nal/bup 32/360 were significantly greater for fasting glucose and fasting insulin.

FIGURE 9.11 — COR-BMOD Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5%, ≥10%, or ≥15% Loss of Body Weight During 56 Weeks of Treatment



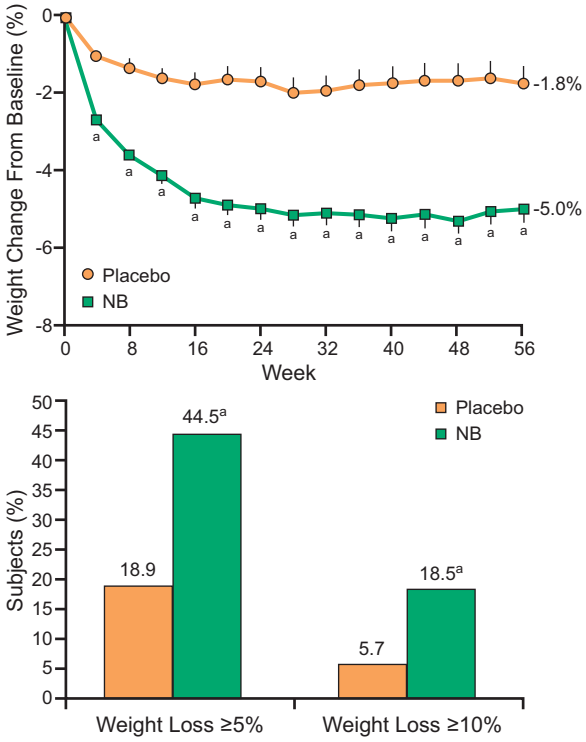
Data from mITT-LOCF population.

This trial included an approximate 3-week dose escalation period.

[a] P <0.001 vs placebo.

Modified from Wadden TA, et al. *Obesity (Silver Spring)*. 2011; 19(1):110-120.

FIGURE 9.12 — COR-Diabetes Trial: Change From Baseline in Body Weight and Proportion of Patients Achieving ≥5% or ≥10% Loss of Body Weight During 56 Weeks of Treatment



Data from mITT-LOCF population. This trial included an approximate 3-week dose escalation period.

[a] $P<0.001$.

Adapted from Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

In the COR-II study, changes from baseline in all but DBP and fasting glucose were significantly different from the results with placebo.

In the COR-BMOD trial, there were significant changes with nal/bup + BMOD compared with placebo + BMOD in HDL cholesterol, triglycerides, fasting insulin, HOMA-IR, and waist circumference. Changes in BP were not assessed.

In COR-Diabetes, nal/bup treatment was associated with improvements in glycemic control and select CVD risk factors, as shown by significantly greater HbA1c reduction, percent of patients achieving HbA1c <7% (53 mmol/mol), and improvement in triglycerides and HDL cholesterol compared with placebo. Nal/bup was associated with higher incidence of nausea, constipation, and vomiting. No difference was observed between groups in the incidence of depression, suicidal ideation, or hypoglycemia.

■ Safety

Nal/bup was generally well-tolerated in the four 56-week, randomized, placebo-controlled trials. Nausea, generally mild to moderate and transient, typically occurring during the dose-escalation period, was the most frequent adverse event (29.8%, 29.2%, 34.1%, and 32.5% in COR-I, COR-II, COR-BMOD, and COR-Diabetes respectively). Other adverse events reported noticeably more frequently by patients treated with nal/bup included headache, constipation, dizziness, vomiting, and dry mouth (**Table 9.11**). Treatment with nal/bup was not associated with increased reports of depressive or suicidal events compared with placebo.

■ Prescribing and Administration

Nal/bup is available as film-coated, extended-release tablets containing 8 mg naltrexone HCl and 90 mg bupropion HCl, and should be taken in the morning and evening. Nal/bup dosing should initially be escalated during the first 4 weeks, arriving at a total daily dosage of two tablets twice daily from week 4 onwards (**Table 9.2**).

TABLE 9.10 — Summary of Mean Changes From Baseline in Metabolic and Cardiovascular Risk Factors and Waist Circumference in 56-Week Randomized, Placebo-Controlled Trials With Fixed-Dose Combination Treatment With Naltrexone SR/Bupropion SR

	COR-I[1]			COR-II[2]			COR-BMOD[3]			COR-Diabetes[4]	
		Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)			Nal/Bup SR (mg/mg)
Change From Baseline	**Placebo (*n* = 511)**	**16/360 (*n* = 471)**	**32/360 (*n* = 471)**	**Placebo (*n* = 456)**	**16/360[a] —**	**32/360 (*n* = 702)**	**Placebo (*n* = 193)**	**16/360[a] —**	**32/360 (*n* = 482)**	**Placebo (*n* = 159)**	**32/360 (*n* = 265)**
LDL cholesterol (%)	-0.5	-1.5	-2.0	-2.1	—	-6.2	+10.0	—	+7.1	0.0	-1.4
HDL cholesterol (%)	+0.8	+7.6	+8.0	-0.9	—	+3.6	+2.8	—	+9.4	-0.3	+3.0
Triglycerides (%)	-3.1	-8.0	-12.7	-0.5	—	-9.8	-8.5	—	-16.6	-0.8	-11.2
SBP (mm Hg)	-1.9	+0.3	-0.1	-0.5	—	+0.6	NA	—	NA	-1.1	0.0
DBP (mm Hg)	-0.9	+0.1	0.0	+0.3	—	+0.4	NA	—	NA	-1.5	-1.1
Fasting glucose (mg/dL)	-0.7	-1.9	-2.6	-1.3	—	-2.8	0.0	—	-1.5	-4.0	-11.9
Fasting insulin (mU/mL)	-4.6	-11.8	-17.1	+3.5	—	-11.4	-15.5	—	-28.0	-10.4	-13.5
HOMA-IR (%)	-5.9	-14.3	-20.2	+1.2	—	-13.8	-16.6	—	-29.9	-14.7	-20.6
Waist circumference (cm)	-2.5	-5.0	-6.2	-2.1	—	-6.7	-6.1	—	-9.1	-2.9	-5.0

Highlighted results indicate significant difference with naltrexone SR/bupropion SR (Nal/Bup) compared with placebo.

[a] Not included in these trials.

[1] Greenway FL, et al; COR-I Study Group. *Lancet*. 2010;376(9741):595-605.
[2] Apovian CM, et al; COR-II Study Group. *Obesity (Silver Spring)*. 2013;21(5):935-943.
3 Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120.
[4] Hollander P, et al; COR-Diabetes Study Group. *Diabetes Care*. 2013;36(12):4022-4029.

TABLE 9.11 — Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Naltrexone SR/Bupropion SR and More Commonly Than Placebo

Adverse Reaction	Naltrexone SR/Bupropion SR 32 mg/360 mg *N* = 2545 (%)	Placebo *N* = 1515 (%)
Nausea	32.5	6.7
Constipation	19.2	7.2
Headache	17.6	10.4
Vomiting	10.7	2.9
Dizziness	9.9	3.4
Insomnia	9.2	5.9
Dry mouth	8.1	2.3
Diarrhea	7.1	5.2
Anxiety	4.2	2.8
Hot flush	4.2	1.2
Fatigue	4.0	3.4
Tremor	4.0	0.7
Upper abdominal pain	3.5	1.3
Viral gastroenteritis	3.5	2.6
Influenza	3.4	3.2
Tinnitus	3.3	0.6
Urinary tract infection	3.3	2.8
Hypertension	3.2	2.2
Abdominal pain	2.8	1.4
Hyperhidrosis	2.6	0.6
Irritability	2.6	1.8
Blood pressure increased	2.4	1.5
Dysgeusia	2.4	0.7
Rash	2.4	2.0
Muscle strain	2.2	1.7
Palpitations	2.1	0.9

Contrave [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2014.

Total daily doses greater than two tablets twice daily (32 mg/360 mg per day) are not recommended. Nal/bup should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure. Nal/bup should be discontinued if ≥5% weight loss is not achieved by week 12.[24]

Liraglutide (Saxenda)

Liraglutide is a glucagon-like peptide-1 (GLP-1) that is a GLP-11 analogue of human GLP-1, a gut-derived incretin hormone. Native GLP-1 has a short elimination half-life of 1 to 2 minutes, whereas liraglutide has a half-life of about 13 hours and therefore can be administered once a day by subcutaneous injection. Since many patients on liraglutide experienced a dose-dependent weight loss, it appeared to be an attractive treatment option for obesity. Liraglutide has been approved for the treatment of T2D, having a significant effect on improving A1C, weight, blood pressure, and lipids. Liraglutide is currently available under the brand name Saxenda for chronic weight management in obese patients. It is also available in the United States and other countries at lower doses under the brand name Victoza for treatment of patients with T2D.

■ Efficacy

In dose-ranging studies, liraglutide 3 mg was found to result in greater weight loss compared to placebo or orlistat. Liraglutide reduced blood pressure and reduced the prevalence of prediabetes. An 84-week, open-label extension following this study switched liraglutide/placebo recipients to liraglutide 2.4 mg after 1 year, then to 3 mg. In the ITT-LOCF population, the mean weight loss from randomization to year 1 was significantly greater with all liraglutide doses compared with placebo and was dose-dependent. Weight loss for those on liraglutide 3 mg for 2 years was also significantly greater than with orlistat. In addition to weight loss, mean change in waist circumference was significantly greater with liraglutide 3 mg vs placebo. With liraglutide 3 mg, the 2-year prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, with improvements in BP and lipids.[25]

SCALE Obesity and Pre-diabetes

The efficacy of liraglutide 3 mg as an adjunct to diet and exercise on weight loss was examined in a 56-week trial. 3731 participants (non-diabetic obese [BMI ≥30] and non-diabetic overweight [BMI ≥27] with ≥1 comorbidity) were randomized to once-daily subcutaneous treatment with liraglutide 3 mg or placebo in combination with a 500 kcal/day deficit diet and exercise. Randomization was stratified by pre-diabetes status (according to ADA 2010 criteria) and BMI. After 56 weeks of treatment, patients receiving liraglutide 3 mg showed significantly greater loss of body weight of 8% from baseline compared with those receiving placebo (2.6%) (P <0.0001). Proportions of patients losing ≥5% and >10% of body weight with liraglutide 3 mg was 64% and 33%, respectively, compared with those receiving placebo (27% and 10%, respectively). In conjunction with weight loss, treatment with liraglutide 3 mg significantly reduced waist circumference by -8.19 cm compared with -3.94 cm with placebo (P <0.0001). Furthermore, treatment with liraglutide 3 mg improved blood glucose levels. In fact, in the studies, liraglutide expressed a specific effect on preventing diabetes, converting nearly 70% of the subjects with prediabetes to normoglycemia, blood pressure, and lipids levels (**Table 9.12**).[26] Loss of body weight was independent of prediabetes status at screening and baseline BMI.[27]

SCALE Diabetes

This trial was a 56-week, randomized, placebo-controlled, double-blind clinical trial that demonstrated the effect of liraglutide 3 mg on weight loss and involved 846 adults with obesity or who are overweight and have T2D. All treatment groups followed

TABLE 9.12 — Changes From Randomization to Week 56 in Measures of Glycemic Control, Lipids, and Cardiovascular Biomarkers

	SCALE Obesity and Prediabetes (Obesity or Overweight With Comorbidities Without Diabetes)		SCALE Diabetes (Patients With Type 2 Diabetes)	
	Liraglutide 3 mg ($n = 2487$)	Placebo ($n = 1244$)	Liraglutide 3 mg ($n = 423$)	Placebo ($n = 212$)
Waist circumference (cm)	-8.2	-4.0	-6.0	-2.8
Systolic blood pressure (mm Hg)	-4.3	-1.5	-3.0	-0.4
Diastolic blood pressure (mm Hg)	-2.7	-1.8	-1.0	-0.6
Heart rate (bpm)	2.6	0.1	2.0	-1.5
Total cholesterol (mg/dL)	-3.2	-0.9	-1.4	2.4
LDL cholesterol (mg/dL)	-3.1	-0.7	0.9	3.3
HDL cholesterol (mg/dL)	2.3	0.5	4.8	1.9
Triglycerides (mmol l–1)	-13.0	-4.1	-14.5	-0.7

Changes from randomization to week 56 are means (SD) and estimated treatment differences from an analysis of covariance, both using the full analysis set with the last observation carried forward. Least squares mean adjusted for treatment, country, sex, prediabetes status at screening, baseline BMI stratum.

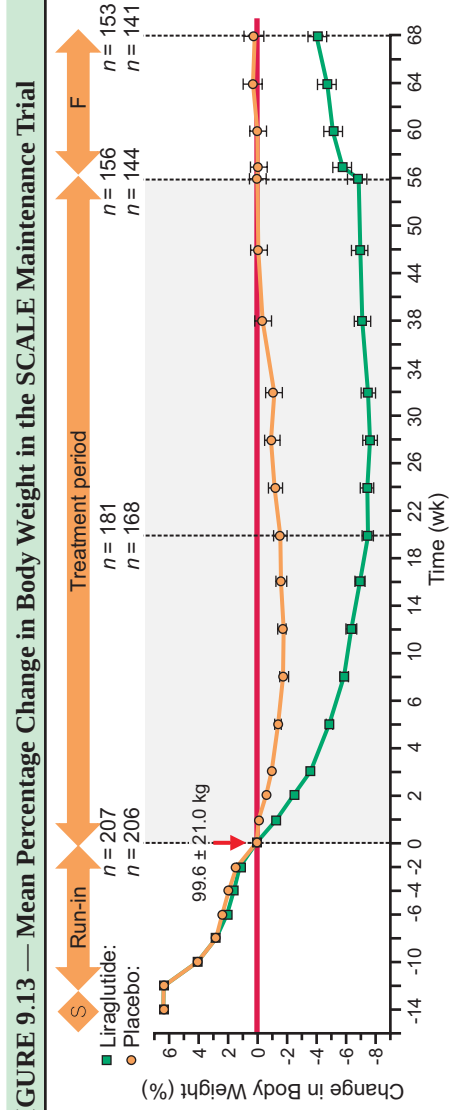
Saxenda [package insert]. Liraglutide (rDNA) injection. Plainsboro, NJ: Novo Nordisk; 2014.

a reduced-calorie diet and increased physical activity program. At 56 weeks, adults treated with liraglutide 3 mg achieved significantly greater mean weight loss of 5.9% compared with 2.0% with placebo (P <0.0001). Waist circumference was also significantly reduced with liraglutide 3 mg (-6 cm) compared with placebo (-2.8 cm, $P \leq 0.0004$). Liraglutide 3 mg significantly reduced systolic blood pressure by 3.0 mm Hg compared with 0.4 mm Hg with placebo (P <0.05), although no significant difference was observed in diastolic blood pressure. Compared with baseline, liraglutide 3 mg significantly improved total cholesterol (-4%) and fasting lipid levels, including vLDL, HDL, and triglycerides (-13%, +3% and -14%, respectively). Liraglutide 3 mg also significantly improved levels of CRP by -27% compared with placebo ($P \leq 0.0002$). In addition, treatment with liraglutide 3 mg provided statistically significantly greater improvements in CV disease risk factors, such as blood pressure and cholesterol, compared with placebo in combination with diet and physical activity (**Table 9.12**).[28]

SCALE Maintenance

The efficacy of liraglutide in maintaining weight loss achieved with a low calorie diet was examined in the SCALE maintenance study. Four hundred twenty-two obese/overweight adult patients who lost ≥5% of their initial weight during a caloric restriction period were randomly assigned to receive subcutaneous liraglutide 3 mg/day or placebo for 56 weeks. Diet and exercise counseling were provided throughout the trial. Participants lost a mean 6% of screening weight during the caloric restriction period. From randomization to week 56, weight decreased an additional mean 6.2% with liraglutide and 0.2% with placebo (P <0.0001) (**Figure 9.13**). Significantly more participants receiving liraglutide (81.4%) maintained the ≥5% run-in weight loss compared with those receiving placebo (48.9%) (P <0.0001). Similarly, more patients in the liraglutide

FIGURE 9.13 — Mean Percentage Change in Body Weight in the SCALE Maintenance Trial



Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg.

Wadden TA, et al. *Int J Obes (Lond)*. 2013;37(11):1443-1451.

group lost ≥5% of their randomization weight than in the placebo group (50.5 vs 21.8%; P <0.0001). These results suggest that liraglutide, in conjunction with diet and exercise, maintained weight loss achieved by caloric restriction and induced further weight loss over 56 weeks. Improvements in some CV disease risk factors, such as BMI, waist circumference, and glycemic parameters, were also observed compared to placebo.[29]

Safety

Liraglutide was well-tolerated in clinical studies (**Table 9.13**). In the SCALE Obesity and Prediabetes trial, the most common adverse events with liraglutide 3 mg were nausea and diarrhea, with most events being mild/moderate and transient in intensity. In the SCALE diabetes trial, the most frequently reported side effects were gastrointestinal disorders, and occurred in 65% of people treated with liraglutide 3 mg compared with 39% with placebo. In the SCALE maintenance trial, GI disorders were also reported more frequently with liraglutide (74%) than placebo (45%), but most events were transient, and mild or moderate in severity. Discontinuations due to adverse events occurred in 9.9% of liraglutide-treated patients and 3.8% of placebo-treated patients, and were mostly due to GI events.

Emerging Antiobesity Agents

Recent research has identified many potential therapeutic targets for antiobesity drugs (**Figure 9.14**). There are numerous antiobesity agents under development, which are currently undergoing various stages of clinical trials.

Summary

Successful treatment of obesity requires a multidisciplinary approach and multimodal therapy including dietary and behavioral strategies. Since not

TABLE 9.13 — Adverse Reactions With an Incidence of at Least 2% Among Patients Treated With Liraglutide and More Commonly Than Placebo

Adverse Reaction	Liraglutide 3 mg *N* = 3384 (%)	Placebo *N* = 1941 (%)
Gastrointestinal		
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal pain	5.4	3.1
Upper abdominal pain	5.1	2.7
GERD	4.7	1.7
Abdominal distension	4.5	3.0
Eructation	4.5	0.2
Flatulence	4.0	2.5
Dry mouth	2.3	1.0
Metabolism and Nutrition		
Hypoglycemia in T2D	23.0	12.7
Decreased appetite	10.0	2.3
Nervous System		
Headache	13.6	12.6
Dizziness	6.9	5.0
General Disorders and Administration Site Conditions		
Fatigue	7.5	4.6
Injection site erythema	2.5	0.2
Injection site reaction	2.5	0.6
Asthenia	2.1	0.8
Infections and Infestations		
Gastroenteritis	4.7	3.2
Urinary tract infection	4.3	3.1
Viral gastroenteritis	2.8	1.6
Investigations		
Increased lipase	5.3	2.2
Psychiatric Disorders		
Insomnia	2.4	1.7
Anxiety	2.0	1.6

Continued

TABLE 9.13 — *Continued*

Saxenda [package insert]. Liraglutide (rDNA) injection. Plainsboro, NJ: Novo Nordisk; 2014.

all patients respond to lifestyle modification alone, pharmacologic treatment options can be pursued. There are several FDA-approved agents currently available in the United States. Effective pharmacotherapy may require either single or multiple agents, and attention to patient medical history is critical to determining the appropriate choice of agent or agents.

The original model of obesity management used medications as a short-term treatment. However, since obesity is now considered to be a chronic disease, newer agents have been approved for long-term therapy. The future of obesity treatment will likely consist of multiple combinations of agents in conjunction with behavioral approaches in order to achieve clinically significant weight loss. Weight maintenance and relapse prevention justifies a long-term approach requiring chronic treatment and follow-up.

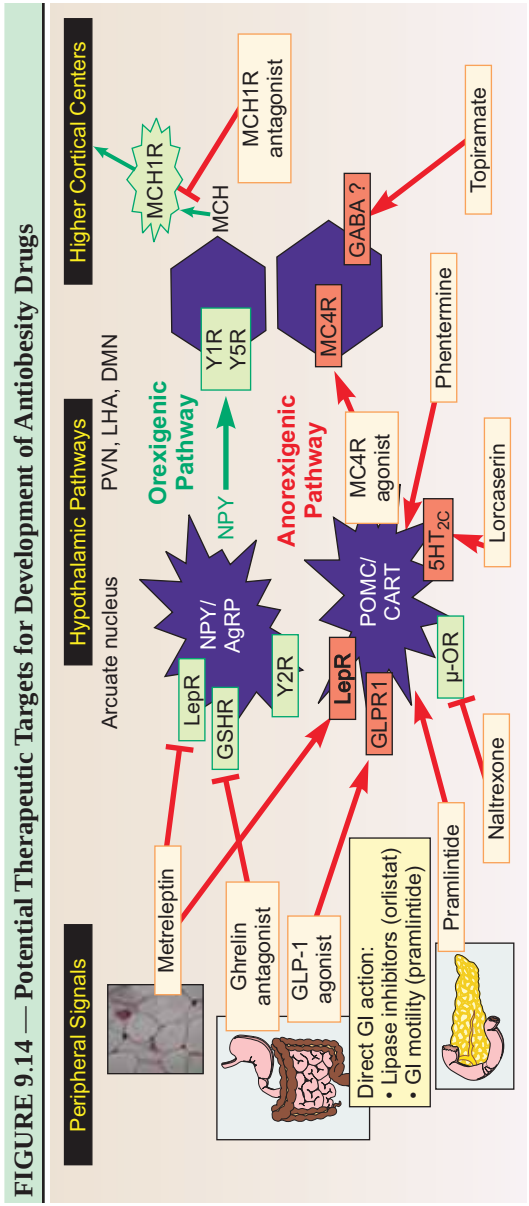


FIGURE 9.14 — Potential Therapeutic Targets for Development of Antiobesity Drugs

For illustrative purposes. Based on recommended dosage recommendations for Qsymia and for phentermine and topiramate ER used in other indications.

REFERENCES

1. Valentino MA, Colon-Gonzalez F, Lin JE, Waldman SA. Current trends in targeting the hormonal regulation of appetite and energy balance to treat obesity. *Expert Rev Endocrinol Metab*. 2010;5(5):765-783.
2. Rodgers RJ, Tschöp MH, Wilding JP. Anti-obesity drugs: past, present and future. *Dis Model Mech*. 2012;5:621-626.
3. Powell AG, Apovian CM, Aronne LJ. New drug targets for the treatment of obesity. *Clin Pharmacol Ther*. 2011;90(1):40-51.
4. Munro JF, MacCuish AC, Wilson EM, Duncan LJP. Comparison of continuous and intermittent anorectic therapy in obesity. *Brit Med J*. 1968;1:352-354.
5. Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA*. 2014;311(1):74-86.
6. Aronne LJ, Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)*. 2013;21(11):2163-2171.
7. Xenical (orlistat) [package insert]. South San Francisco, CA: Genentech USA, Inc.
8. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENICAL in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155-161.
9. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)*. 2012;20:330-342.
10. Qsymia (phentermine and topiramate extended-release) [package insert]. Mountain View, CA: Vivus, Inc. 2012-2013.
11. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:1341-1352.
12. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012;95:297-308.

13. Belviq (lorcaserin HCl) [package insert]. Zofingen, Switzerland: Arena Pharmaceuticals. 2012.

14. Smith SR, Weissman NJ, Anderson CM, et al; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med*. 2010;363(3):245-256.

15. Fidler MC, Sanchez M, Raether B, et al; BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab*. 2011;96:3067-3077.

16. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)*. 2012;20:1426-1436.

17. Greenway FL, Dunayevich E, Tollefson G, et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab*. 2009;94(12):4898-4906.

18. Greenway FL, Fujioka K, Plodkowski RA, et al; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010;376(9741):595-605.

19. Apovian CM, Aronne L, Rubino D, et al; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)*. 2013;21:935-943.

20. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity*. 2011;19:110-120.

21. Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med*. 2005;353:2111-2120.

22. Digenio AG, Mancuso JP, Gerber RA, Dvorak RV. Comparison of methods for delivering a lifestyle modification program for obese patients: a randomized trial. *Ann Intern Med*. 2009;150:255-262.

23. Hollander P, Gupta AK, Plodkowski R, et al; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight adn glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care*. 2013;36(12):4022-4029.

24. Contrave [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. 2014.

25. Astrup A, Carraro R, Finer N, et al; on behalf of the NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obesity*. 2012;36:843-854.

26. Pi-Sunyer X, Astrup A, Fujioka K, et al. Liraglutide 3.0 mg reduces the prevalence of prediabetes and delays onset of type 2 diabetes in overweight and obese adults: results from Scale Obesity and Prediabetes, a randomized, double-blind and placebo-controlled 56-week trial. ICE/ENDO 2014; Chicago, IL. June 21-24, 2014. Poster Board SAT-0925.

27. Pi-Sunyer X, Astrup A, Fujioka K, et al. Efficacy and safety of liraglutide 3.0 mg for weight management in overweight and obese adults: the SCALE obesity and prediabetes, a randomized, double blind and placebo-controlled trial. Paper presented at American Association of Clinical Endocrinologists 23rd Annual Scientific and Clinical Congress. Las Vegas, NV: May 13-18, 2014; 137. Abstract #700. Obesity.

28. Saxenda [Package Insert]. Liraglutide (rDNA) injection. Plainsboro, NJ; Novo Nordisk. December 2014.

29. Wadden TA, Hollander P, Klein S, et al; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)*. 2013;37(11):1443-1451.

10 Bariatric Surgery

Introduction

Bariatric surgery has evolved rapidly since its introduction in the 1950s. Bariatric surgical procedures have increased exponentially in the United States until the number of procedures reached a peak in 2008 (**Figure 10.1**). However, there was no increase in 2009 and the rate likely has remained stable (numbers for subsequent years are not available).[1-5] One reason may have been the impact of the major recession from 2007 to 2009 during which many patients may have deferred or delayed elective procedures (including bariatric surgery) that generally were not covered by most insurance companies. Another reason may have been that as bariatric surgery became more common, the general perception of this procedure may have changed from being a "cure" to being the first step that requires continuing commitment to major changes in lifestyle in order to maintain a healthy weight.

The most plausible explanation however is that bariatric surgery has gone through a period of slow acceptance by the medical and lay community and is now an established option for weight loss in patients who are willing to undergo surgery. Newer procedures such as the sleeve gastrectomy have been introduced recently such that those who may have opted for the laparoscopic adjustable band or the Roux-en-Y Gastric bypass might have chosen the sleeve instead, but the total number of procedures in the United States has remained unchanged.

Candidates and Qualifications

The basic qualifications for bariatric surgery include[1,3,6,7]:

FIGURE 10.1 — Number of Bariatric Procedures Performed in the United States From 1992 to 2009

The fast growth in weight-loss surgeries has ended. Though numbers are not available beyond 2009, most in the field believe the number of procedures is going down.

Elliott VS. Bariatric surgery maintains, doesn't gain. American Medical News Web site. http://www.amednews.com/article/20120423/business/304239976/4/. Accessed June 10, 2014.

- BMI ≥40 (or more than 100 pounds overweight)
- BMI ≥35 and at least one obesity-related comorbidity such as T2D, hypertension, OSA and other respiratory disorders, NAFLD, OA, lipid abnormalities, GI disorders, or heart disease
- Inability to achieve a healthy weight loss sustained for a period of time with prior weight loss efforts.

Patients considering bariatric surgery need to understand the procedure and its potential benefits and risks, and be willing to accept the responsibility of long-term compliance to lifestyle changes, and medical follow-up. Answers to the following questions may help patients decide whether weight-loss surgery is right for them.[1,5-7]

Is the patient[5,6]:

- Unlikely to lose weight or keep it off over the long term using other methods?
- Well informed about the surgery and treatment effects?
- Aware of the risks and benefits of surgery?
- Ready to lose weight and improve his or her health?
- Aware of how life may change after the surgery? (For example, patients need to adjust to side effects, such as the need to chew food well and the loss of ability to eat large meals.)
- Aware of the limits on food choices, and occasional failures?
- Committed to lifelong healthy eating and physical activity, medical follow-up, and the need to take extra vitamins and minerals?

Procedures

Currently, the following four bariatric procedures are the most commonly used in the United States[2,3,5,6]:

- Roux-en-Y gastric bypass (RYGB)
- Adjustable gastric banding (AGB)

- Biliopancreatic diversion with or without duodenal switch (BPD or BPD/DS)
- Vertical sleeve gastrectomy (VSG).

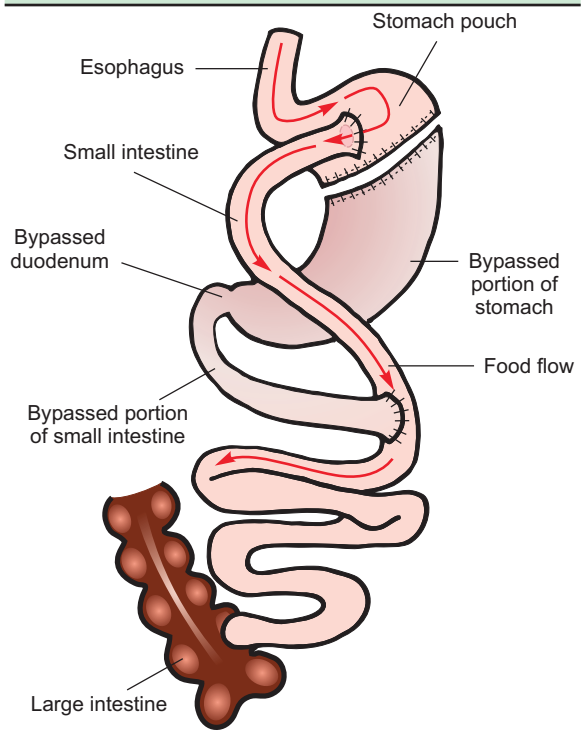
Although the RYGB is currently the most commonly performed procedure in the United States, the use of AGB had been increasing at least up until recently. VSG gastrectomy has become very popular due to the simplicity of the procedure, the durability of weight loss, and the potential that side effects such as vitamin and mineral deficiencies are less common than the RYGB. Initially, these procedures were performed using open surgical techniques; however, there has been an overwhelming trend toward the use of laparoscopic technologies. For example, the proportion of laparoscopic bariatric operations increased from 20.1% in 2003 to 90.2% in 2008.[2]

Although the mechanisms by which bariatric surgery cause weight loss have not been completely elucidated, it is generally accepted that some procedures can have a restrictive effect on the amount of food (thus the total number of calories consumed). Other procedures most likely cause weight loss from a combination of restriction plus the bypass of portions of the stomach and small intestine resulting in changes in the gut biome and hormone milieu that alter appetite, satiety, and possibly even metabolism.

■ Roux-En-Y Gastric Bypass (RYGB)

The RYGB (often simply called "gastric bypass") is generally considered the gold standard of weight loss surgery and is the most commonly performed bariatric procedure worldwide. There are two major steps in this procedure (**Figure 10.2**).[1,5-7] In the first step, the top of the stomach is divided from the rest of the stomach to create a small stomach pouch (~30 mL in volume). Next, the proximal portion of the small intestine is divided (30-40 cm from the junction between the duodenum and jejunum), and the distal end is brought up and connected to the newly created small stomach pouch. The procedure is completed by

FIGURE 10.2 — Roux-en-Y Gastric Bypass



The RYGB surgery restricts food intake and also decreases how food is absorbed. A new stomach pouch is created from which food flows directly into the small intestine *(red arrows)*, bypassing the stomach, duodenum, and the upper intestine.

connecting the top portion of the small intestine to the rest of the small intestine (100-150 cm further down) so that the stomach acids and digestive enzymes from the bypassed stomach and first portion of small intestine will eventually mix with the food.[8] The RYGB is generally considered a nonreversible procedure but can reversed in "emergency" situations.

The RYGB works by several mechanisms. First, the newly created stomach pouch is considerably smaller and facilitates significantly smaller meals, which translates into fewer calories consumed. Most importantly, the rerouting of the food stream produces changes in gut hormones that promote satiety and suppress hunger. The concept that RYGB is a strictly malabsorptive procedure has been controversial due to the discovery that there are changes in the the gut microbiome and hormone milieu that occur after RYGB.

The potential advantages and disadvantages of RYGB according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.1**.

TABLE 10.1 —RYGB: Potential Advantages and Disadvantages

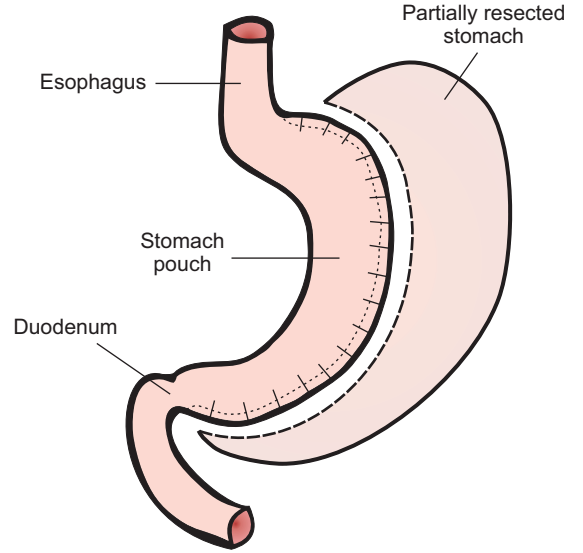
Advantages
• 60% to 80% long-term excess weight loss
• Restricts amount of food that can be consumed
• May lead to conditions that increase energy expenditure
• Produces favorable changes in gut hormones that reduce appetite and enhance satiety
• Associated with maintenance of >50% excess weight loss
• Greater incidence of diabetes remission compared with other bariatric procedures
Disadvantages
• Long-term vitamin/mineral deficiencies, particularly in vitamin B12, iron, calcium, and folate
• Requires adherence to dietary recommendations, lifelong vitamin/mineral supplementation, and follow-up compliance

■ Vertical Sleeve Gastrectomy (VSG)

The VSG (often simply called the "sleeve") is a procedure that permanently removes ~80% of the stomach. (**Figure 10.3**) The remaining stomach is a tubular pouch that resembles a banana. The VSG was originally performed as a modification to another bariatric procedure (BPD/DS), and then later as the first part of a two-stage gastric bypass operation on extremely obese patients for which the risk of performing gastric bypass surgery was deemed too great. The initial weight loss in these patients was so successful that it began to be investigated as a stand-alone procedure.

Since the new stomach pouch holds a considerably smaller volume than the normal stomach, there is a significantly reduced amount of food (and thus calories) that can be consumed. In addition, surgery can also alter the gut microbiome and the gut hormone milieux, which, in turn, impacts the metabolic factors that influence hunger, satiety, and blood sugar control.

FIGURE 10.3 — Vertical Sleeve Gastrectomy



The VSG procedure removes most of the stomach, restricting food intake by decreasing the amount of food that can be ingested.

The potential advantages and disadvantages of VSG according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.2**.

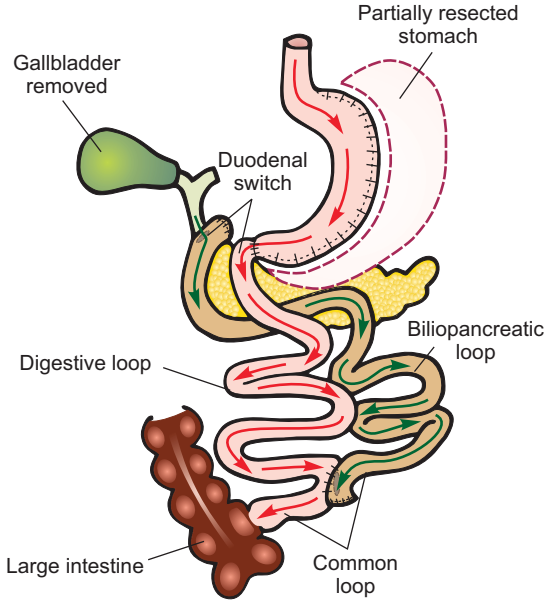
TABLE 10.2 — VSG: Potential Advantages and Disadvantages

Advantages
• Restricts the amount of food passing into the stomach
• Induces rapid and significant weight loss similar to that with RYGB (>50% during 3-5+ year maintenance)
• Requires no foreign objects (as in AGB) and no bypass or re-routing of the food stream (as in RYGB)
• Requires a relatively short hospital stay (~2 days)
• Causes changes in gut hormones that suppress hunger, reduce appetite, and improve satiety
Disadvantages
• A nonreversible procedure
• The potential for long-term vitamin deficiencies—less than RYGB but greater than AGB
• A higher early complication rate than the AGB

■ Biliopancreatic Diversion With Duodenal Switch (BPD/DS)

The BPD/DS is a two-step procedure. First, a smaller, tubular stomach pouch is created by removing a portion of the stomach, very similar to the sleeve gastrectomy (**Figure 10.4**). Next, a large portion of the small intestine is bypassed. The duodenum is divided just past the outlet of the stomach. A segment of the distal small intestine is then brought up and connected to the outlet of the newly created stomach. Therefore, when the person eats, the food goes through a newly created tubular stomach pouch and empties directly into the last segment of the small intestine. Roughly three fourths of the small intestine is bypassed by the food stream. The bypassed small intestine, which carries the bile and pancreatic enzymes that are necessary for the breakdown and absorption of protein and fat, is reconnected to the last portion of the small intestine so that they can eventually mix with the food stream.

FIGURE 10.4 — Biliopancreatic Diversion With Duodenal Switch



This surgery involves three features: removal of a large part of the stomach *(see VSG)*, a duodenal switch that re-routes food away from much of the small intestine *(red arrows)*, and the final feature changes how bile and other digestive juices affect how the body digests food and absorbs calories *(green arrows)*.

Currently, the BPD/DS is not used very frequently in the United States, although there are a few states in which it is currently performed.

Unlike the other procedures, there is a significant amount of small bowel that is bypassed. Additionally, the food does not mix with the bile and pancreatic enzymes until very far down (100 cm from the end of the small intestine).[8] This results in a significant decrease in the absorption of calories and nutrients

(particularly protein and fat) as well as nutrients and vitamins dependent on fat for absorption (fat soluble vitamins and nutrients). Lastly, the BPD/DS, similar to the gastric bypass and sleeve gastrectomy, affects gut hormones in a manner that impacts hunger and satiety as well as blood sugar control.

The potential advantages and disadvantages of BPD/DS according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.3**.

TABLE 10.3 — BPD/DS: Potential Advantages and Disadvantages

Advantages

- Greater weight loss than RYGB, VSG, or AGB (60% to 70% excess weight loss or greater, at 5-year follow-up)
- ≥70% reduction of fat absorption
- Favorable changes in gut hormones to reduce appetite and improve satiety
- Most effective against diabetes compared with RYGB, LSG, and AGB
- Allows patients to eventually eat near "normal" meals

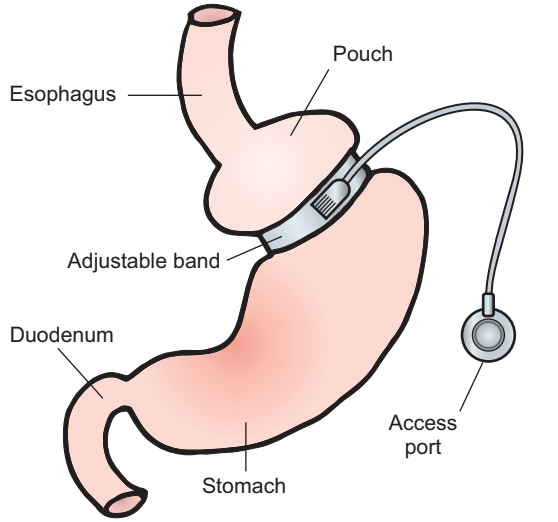
Disadvantages

- Higher complication rates and risk for mortality than AGB, LSG, and RYGB
- Longer hospital stay than the AGB or LSG
- Greater potential for protein deficiencies and long-term deficiencies in vitamins and minerals (iron, calcium, zinc, fat-soluble vitamins such as vitamin D)
- Requires compliance with follow-up care and strict adherence to dietary and vitamin supplementation guidelines

■ Adjustable Gastric Band (AGB)

The AGB (often simply called the "band") is a laparoscopic procedure in which an inflatable band is placed around the upper portion of the stomach, creating a small pouch above the band, and the rest of the stomach below the band (**Figure 10.5**).

FIGURE 10.5 — Adjustable Gastric Band



The AGB surgery restricts food intake by placing a small band around the top of the stomach, enabling restriction of the size of the opening from the throat to the stomach. This opening can be adjusted by the surgeon utilizing a circular balloon inside the band. The balloon can be deflated or inflated using saline solution as needed to accommodate the patient's needs via an access port.

The common explanation of how this device works is that with the smaller stomach pouch, eating just a small amount of food will satisfy hunger and promote the feeling of fullness. The size of the stomach opening can be adjusted by filling the band with sterile saline, which is injected through a subcutaneous port. The size of the opening is gradually reduced over time with repeated adjustments or "fill" until a so-called "sweet spot" is achieved where restriction of the size causes decreased food intake but no regurgitation or obstruction.

The notion that the band is a restrictive procedure (works by restricting how much food can be consumed

per meal and by restricting the emptying of the food through the band) has been challenged by studies that show the food passes rather quickly through the band, and that absence of hunger or feeling of being satisfied was not related to food remaining in the pouch above the band. What is known is that there is no malabsorption; the food is digested and absorbed as it would be normally. The clinical impact of the band seems to be that it reduces hunger, which helps the patients to decrease the amount of calories that are consumed.

The potential advantages and disadvantages of AGB according to the American Society for Metabolic and Bariatric Surgery are listed in **Table 10.4**.

Clinical Experience

While there are considerable and increasing clinical trial data on the clinical efficacy and safety of bariatric surgery, the quality of the studies varies considerably due to the difficulties implicit in performing high quality, randomized, controlled trials of surgeries. As a result, most of the data come from studies with less rigorous designs. Nevertheless, the efficacy of the various bariatric procedures is supported by systematic reviews and meta-analyses, as well as the results of recent individual studies.

■ Systematic Reviews and Meta-analyses

One early analysis of 147 studies concluded that surgery resulted in a weight loss of 20 to 30 kg, which was maintained for up to 10 years and was accompanied by improvements in some comorbid conditions.[9] One large, matched cohort analysis reported greater weight loss with surgery than with medical treatment in individuals with an average BMI ≥40. For BMIs of 35 to 39, data from case series strongly supported superiority of surgery but was not considered to be conclusive.

Bariatric procedures have been performed with an overall mortality rate of <1%. Overall, AEs occurred in

TABLE 10.4 — AGB: Potential Advantages and Disadvantages

Advantages

- Induces excess weight loss of approximately 40% to 50%
- No cutting of the stomach or rerouting of the intestines
- Requires a shorter hospital stay, usually <24 hours, with some centers discharging the patient the same day as surgery
- Reversible and adjustable
- The lowest rate of early postoperative complications and mortality among the approved bariatric procedures
- Lowest risk for vitamin/mineral deficiencies

Disadvantages

- Slower and less early weight loss than other surgical procedures
- Greater percentage of patients failing to lose at least 50% of excess body weight compared with the other surgeries commonly performed
- Requires a foreign device to remain in the body
- Possible band slippage or band erosion into the stomach in a small percentage of patients
- Can have mechanical problems with the band, tube, or port in a small percentage of patients
- Can result in dilation of the esophagus if the patient overeats
- Requires strict adherence to the postoperative diet and to postoperative follow-up visits
- Highest rate of re-operation

about 20% of cases. Laparoscopic approaches resulted in fewer wound complications than open procedures.[9]

A subsequent systematic review included three randomized controlled trials (RCTs) and three cohort studies that compared surgery with nonsurgical interventions, and 20 RCTs that compared different surgical procedures.[1] Overall, bariatric surgery was a more effective intervention for weight loss than nonsurgical options. RYGB was more effective for weight loss than VSG and AGB. All comparisons of open vs laparoscopic surgeries found similar weight losses in

each group. Comorbidities after surgery improved in all groups, but with no significant differences between different surgical interventions.

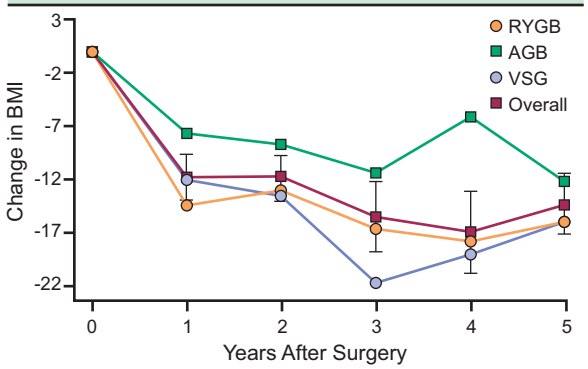
Another systematic review analyzed the results of 14 trials (one randomized trial) of at least 1 year of follow-up that compared RYGB and AGB.[10] Excess body weight loss at 1 year was consistently greater for RYGB than with AGB (median difference, 26%; P <0.001). Resolution of comorbidities also was greater after RYGB. In the highest-quality study, excess body weight loss was 76% with RYGB vs 48% with AGB. Both operating room time and length of hospitalization were shorter for those undergoing AGB and perioperative complications were more common with RYGB (9% vs 5%). However, long-term reoperation rates were lower after RYGB (16% vs 24%).

In the most recent systematic review and meta-analysis, Chang and associates analyzed data from 37 randomized clinical trials and 127 observational studies published from 2003 to 2012. A total of 161,756 patients with a mean age of 44.5 years and mean BMI of 45.6 were included.[11] As shown in **Figure 10.6**, RYGB was more effective for weight loss than AGB. Although data were limited for VSG, it appeared to be more effective for weight loss than AGB and comparable to RYGB.

■ Recent Individual Studies

O'Brien and colleagues reported the 15-year follow-up data from their prospective longitudinal cohort study of AGB that enrolled 3227 patients with a mean BMI of 43.8.[12] Seven hundred fourteen patients completed ≥10 years of follow-up. Among patients who were at ≥10 years post procedure, the mean excess weight loss was 47.0%. This weight loss occurred regardless of whether any revisional procedures were needed. These results were compared with a systematic review of the literature that reported weight loss at ≥10 years after other bariatric procedures. In this review, there was ≥50% excess weight loss with all current procedures (**Table 10.5**).

FIGURE 10.6 — Meta-analysis of Postoperative Change in BMI Over 5 Years[a]



[a] Based on 37 studies published between 2003 and 2012.

Chang SH, et al. *JAMA Surg*. 2014;149(3):275-287.

The weighted mean excess weight loss with AGB was 54.2% and 54.0% with RYGB. Revisional procedures were performed for proximal enlargement (26%), erosion (3.4%), and port and tubing problems (21%). The band was explanted in 5.6%. Although this was a single-center study, the results support the long-term durability of weight loss with bariatric surgery, specifically laparoscopic ABG.

The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium recently reported the 3-year follow-up results of a multicenter observational cohort study in 2458 adults who underwent first-time bariatric surgical procedures between 2006 and 2009 and then followed up until September 2012.[13] At baseline, 79% were women, median BMI was 45.9, and median weight was 129 kg. RYGB was the initial procedure in 1738 participants; AGB was the initial procedure in 610 participants, while 110 underwent other procedures. At baseline, 774 (33%) participants had T2D, 1252 (63%) had dyslipidemia, and 1601 (68%) had hypertension. Three years after surgery, median

TABLE 10.5 — Pooled Data From Systematic Review

Procedure	No. Reports	Mean % EWL	Range % EWL	Revision Range
RYGB	9	54.0	28-68	8-39
AGB	7	54.2	33-64	8-60
Gastroplasty	5	52.9	-10 to 62	10-40
BPD/DS	3	73.3	70-75	—

NOTE: In this analysis, the primary efficacy endpoint was change in % EWL. Percent total weight losses (%TWL) were not reported. However, %TWL can be estimated from %EWL by assuming that %TWL is numerically about one-half the numerical value of the %EWL. Thus, if the %EWL is 50% then the %TWL would be ~25%.

O'Brien PE, et al. *Ann Surg*. 2013;257:87-94.

actual weight loss was 41 kg in RYGB recipients, corresponding to a percentage of baseline weight loss of 31.5%. In AGB recipients, actual weight loss was 20 kg corresponding to 15.9% baseline weight loss. The majority of weight loss was evident 1 year after surgery for both procedures. Among participants who had T2D at baseline, 216 (67.5%) RYGB recipients and 28 (28.6%) LAGB recipients experienced partial remission at 3 years. The incidence of T2D was 0.9% after RYGB and 3.2% after LAGB. Dyslipidemia resolved in 237 (61.9%) RYGB recipients and 39 (27.1%) in AGB recipients; remission of hypertension occurred in 269 (38.2%) of RYGB recipients and in 43 (17.4%) of AGB recipients.

Although many studies of short-term to mid-term outcomes of LAGB have been published, long-term outcomes reports with a follow-up of ≥10 years are still scarce. A recent study assessed the long-term results of AGB in 60 consecutive patients (44 women, 16 men) who were treated for morbid obesity by AGB between 1996 and 1999.[14] The median age of the patients at the time of operation was 45 years and their median preoperative BMI was 45. All patients were instructed to adhere to a strict follow-up program. Complete data on all 60 patients could be assessed; thus, the overall rate of follow-up was 100%. After a median follow-up of 14.1 years, the mean BMI decreased from 45 to 36, with a mean 49% excess weight loss (EWL). At 15 years of follow-up, 48% of bands had been removed. In those patients with the band still in place at 14 years, 40% had >50% EWL while 20% had <25% EWL.

The efficacy and complications of VSG were assessed in a prospective cohort of 68 patients who underwent VSG either as primary bariatric procedure ($n = 41$) or as a redo operation after failed AGB ($n = 27$) between August 2004 and December 2007.[15] At the time of VSG, the mean BMI was 43, the mean age was 43.1 years, and 78% were female. The follow-up rate was 100% at 1 year postoperatively, 97% after 2 years, and 91% after 5 years; the mean follow-up

time was 5.9 years. The average EWL was 61.5% after 1 year, 61.1% after 2 years, and 57.4% after 5 years. Comorbidities improved considerably. For example, remission of T2D was achieved in 85% of cases. Complications included: one leak (1.5%), two incisional hernias (2.9%), and new-onset gastroesophageal reflux in 11 patients (16.2%). Reoperation due to insufficient weight loss was necessary in eight patients (11.8%).

A retrospective cohort analysis compared clinical outcomes in 190 consecutive patients who underwent primary BPD/DS between 2005 and 2010, of whom 178 (93.7%) were available for follow-up. These patients were matched with 139 patients who underwent primary RYGB in the same medical center during the same period.[16] While percentage changes from baseline in each group were significant, there was no significant difference in percent total weight loss between groups. T2D, hypertension, and hyperlipidemia all improved significantly within each group, although the improvements were significantly higher in the BPD/DS group. Loose stools and bloating symptoms were more frequently reported among BPD/DS patients. With the exception of increased emergency department visits among BPD/DS patients ($P<0.01$), overall complication rates were not significantly different between BPD/DS and RYGB. There was no difference in mortality rates between the groups.

■ Safety

Operative (30-day) mortality for bariatric surgery has been reported to range from 0.1% to 2%.[3,6,10] These rates depend on several factors: complexity of the operation, patient comorbidities, and experience of the surgeon and the center. AGB typically has the lowest mortality rate of 0.1%, whereas the rate with RYGB or VSB is ~0.5%. Higher mortality rates have been correlated with visceral obesity, sex, BMI ≥50, diabetes mellitus, sleep apnea, and older age.

Early general complications include thromboembolism (1%), pulmonary or respiratory insufficiency

(<%), hemorrhage (1%), peritonitis (1%), and wound infection (2%). The increased use of laparoscopy has been instrumental in decreasing these rates. GI obstructions are of most concern among long-term complications. The cause of the obstruction typically depends on the type of bariatric procedure. For example, gastric obstruction associated with AGB may be due to food entrapment at the narrowed banded area, from overinflation of the band, or from band "slippage," which causes pouching over the band. Symptoms can be resolved by loosening the band but in certain circumstances, surgical repositioning of the band is necessary. Gastric obstruction associated with RYGB or VSG may be caused by stenosis of the gastric outlet secondary to scar tissue and may be treated with endoscopic dilation.[10] Intestinal obstruction can occur after gastric bypass or other malabsorptive procedures and typically requires urgent surgical intervention.

Topart and colleagues retrospectively reviewed their recent 2-year, single institution bariatric surgery experience to compare the 30-day morbidity and 90-day mortality rates with VSG ($n=88$), RYGB ($n=360$), and BPD-DS ($n=59$).[17] Thirty day morbidities were significantly more frequent with VSG and BPD-DS than with RYGB. The global complication rate was significantly higher after BPD-DS ($P=0.0017$) compared with RYGB, however, there was no difference between RYGB and VSG. Compared with RYGB, bleeding was more frequent, after comparison with BPD-DS and VSG.

In the most recent meta-analysis by Chang and colleagues (discussed above), the overall complication rate was 17% in RCTs (**Table 10.6**).[11] This pattern persisted across all of the surgical procedures. In RCTs, complications rates were relatively lowfor VSG (13%) and AGB (13%) compared with VGB (21%). Reoperation rates were not as high as complication rates. In RCTs, RYGB appeared to have the lowest reoperation rate (3%) followed by VSG (9%)

TABLE 10.6 — Estimated Rates (%) of Surgical Risks and Complications[a]

	RYGB	AGB	VSG	Overall
Mortality ≤30 days	0.08	0.11	0.50	0.08
Mortality >30 days	0.39	0.14	0.60	0.31
Complication rates	21.00	13.00	13.00	17.00
Reoperation rates	2.56	12.23	9.05	6.95

[a] Based on meta-analysis of 64 studies published between 2003 and 2012.

Chang SH, et al. *JAMA Surg*. 2014;149*3):275-287.

Surgery as Diabetes Treatment

Weight loss has long been regarded as the first approach to prevent T2D in high-risk subjects and to manage the metabolic derangements of established T2D. The attractiveness of weight control as a therapeutic intervention and the limited efficacy of producing medically induced weight loss has led to increased interest in the effect of surgically produced weight loss to correct the metabolic abnormalities in patients with established T2D and to prevent or remit T2D in high-risk individuals.[3,18-20]

Although the results of clinical trials so far have been promising, there still is a lack of consensus regarding the minimum BMI requirement and uncertainties regarding the comparative effectiveness of different bariatric procedures, especially in the long term. For example, in one literature review, bariatric surgery in T2D patients with a BMI of ≥35 resulted in a 56% EWL and remission of T2D in 57% to 95% of patients, depending on the type of surgery and the definition of diabetes resolution.[19] Four other reviews reported similar benefits of surgery in adults with T2D or other metabolic conditions and a BMI of 30.0 to 34.9.[18,20,21,22] In many trials, there also were significant benefits in other comorbidities.

Several recent trials also reported beneficial effects of bariatric surgery in patients with T2D. However, it is difficult to compare the studies due to the difference in type of procedures used as well as different definitions of remission of diabetes. A randomized, non-blinded, single-center trial evaluated the efficacy of intensive medical therapy alone vs medical therapy plus RYGB or VSG in 150 obese patients with uncontrolled T2D.[23] The mean age of the patients was 49 years, and 66% were women. The average baseline HbA1C was 9.2%. The primary end point was the proportion of patients with an HbA1C level of 6% or less 12 months after treatment. Of the 150 patients, 93% completed 12 months of follow-up. The proportion of patients with

the primary end point was 12% in the medical-therapy group vs 42% in the RYGB group ($P = 0.002$) and 37% in the VSG group ($P = 0.008$).

Glycemic control improved in all three groups, with a mean HbA1C level of 7.5% in the medical-therapy group, 6.4% in the RYGB group ($P < 0.001$), and 6.6% in the VSG group ($P = 0.003$). The index for homeostasis model assessment of insulin resistance (HOMA-IR) improved significantly after both bariatric procedures. Weight loss was greater in the RYGB and VSG groups (-29.4 kg and -25.1 kg, respectively; $P < 0.001$ for both comparisons) than in the medical-therapy group (-5.4 kg; $P < 0.001$ for both comparisons). In addition, use of drugs to lower glucose, lipid, and BP levels decreased significantly after both surgical procedures but increased in patients receiving medical therapy only. Four patients underwent reoperation. There were no deaths or life-threatening complications.

Another single-center, non-blinded, randomized, controlled trial in 60 adult patients compared the effects of bariatric surgery vs conventional medical therapy for T2D in morbidly obese patients (BMI ≥35) and a history of T2D for at least 5 years and a baseline HbA1C level of ≥7.0%.[24] Patients were randomly assigned to receive conventional medical therapy or undergo either RYGB or BPD. The primary end point was the rate of T2D remission at 2 years (defined as a fasting glucose level of <100 mg per deciliter [5.6 mmol/l per liter] and an HbA1C level of <6.5% in the absence of pharmacologic therapy). At 2 years, no patients in the medical-therapy group experienced T2D remission compared with 75% of those in the RYGB group and 95% of those in the BPD group ($P < 0.001$ for both comparisons).

Age, sex, baseline BMI, duration of T2D, and weight changes were not significant predictors of T2D remission at 2 years or of improvement in glycemia at 1 and 3 months. At 2 years, the average baseline HbA1C level (8.65%) had decreased in all groups, but patients in the two surgical groups had the greatest degree of

improvement in average HbA1C levels, 7.69% in the medical-therapy group, 6.35% in the RYGB group, and 4.95% in the BPD group.

An analysis of clinical outcomes in 217 patients with T2D who underwent bariatric surgery (RYGB [$n = 162$]; AGB [$n = 32$]; VSG [$n = 23$]) between 2004 and 2007 and had at least 5-year follow-up assessed the effects of bariatric surgery on long-term T2D remission rates.[25] Overall, RYGB resulted in the greatest short-term and long-term reductions in total and EWL weight loss (**Table 10.7**). Complete remission was defined as HbA1C <6% and FBG <100 mg/dL off diabetic medications. At a median follow-up of 6 years after surgery a mean EWL of 55% was associated with mean reductions in HbA1C from 7.5% to 6.5% ($P = 0.001$) and FBG from 155.9 to 114.8 ($P < 0.001$). Long-term complete and partial remission rates were 24% and 26%, respectively, whereas 34% of patients improved (>1% decrease in HbA1C without remission) from baseline and 16% remained unchanged. Shorter duration of T2D ($P < 0.001$) and higher long-term EWL ($P = 0.006$) predicted long-term remission. Recurrence of T2D after initial remission occurred in 19% of patients and was associated with longer T2D duration ($P = 0.03$), less EWL ($P = 0.02$), and weight regain ($P = 0.015$).

On the basis of evidence available, the IDF issued a position statement stating that bariatric surgery can be considered an appropriate treatment for obese individuals (BMI 35 or greater) with T2D who have not achieved recommended treatment targets with medical therapies, especially in the presence of other major comorbidities.[26]

Bariatric Surgery in Adolescents

As noted in *Chapter 1*, the most recent (2009-2010) national data on obesity prevalence indicate that about 12.5 million US children and adolescents (5 million girls and approximately 7 million boys) were

TABLE 10.7 — Short-Term and Long-Term Weight Loss With RYGB, AGB, or VSG

	Whole Cohort	RYGB	VSG	*P1* Value (RYGB vs VSG)	AGB	*P2* Value (VSG vs AGB)
Total Weight Loss (%)						
Short-term	27.6	30.9	21.2	<0.001	16.5	0.068
Long-term	25.4	28.1	22.2	0.015	13.2	0.002
EWL (%)						
Short-term	60.3	66.8	49.7	0.029	37.0	0.112
Long-term	54.9	6.5	49.5	0.47	29.5	0.004

Short-term: 1 to 2 years after surgery.
Long-term: ≥5 years after surgery.
P1: gastric bypass vs sleeve gastrectomy.
P2: sleeve gastrectomy vs gastric banding.

Brethauer SA, et al. *Ann Surg.* 2013;258:628-636.

obese, thereby presenting a major health problem now and in the future as many of these individuals age and become obese individuals with longstanding comorbidities.[27] Therefore, obesity in childhood and adolescence presents a major current (and future) health problem with few effective treatments. Nevertheless, weight-loss surgery is beginning to be used to treat selected obese adolescents, although with very limited data regarding the safety of currently used, minimally invasive procedures.

A recent ongoing prospective, multisite observational study assessed the preoperative clinical characteristics and perioperative safety outcomes in 242 severely obese adolescent patients aged 19 years or younger who underwent weight-loss surgery from February 28, 2007 through December 30, 2011. The mean age of participants was 17.1 years and the median BMI was 50.5. At baseline, 51% demonstrated four or more major comorbid conditions.[28] The procedures included RYGP, VSG, and AGB in 66%, 28%, and 6% of patients, respectively. There were no deaths during the initial hospitalization or within 30 days of operation. Major complications (eg, reoperation) occurred in 19 patients (8%). Minor complications (eg, readmission for dehydration) were noted in 36 patients (15%). All reoperations and 85% of readmissions were related the surgery itself. At this time, this study reported a favorable short-term complication profile, supporting the early postoperative safety of weight-loss surgery in selected obese adolescents. This cohort is being followed in order to provide longer-term data.

Bariatric Surgery and Obstructive Sleep Apnea

Obesity, older age, male sex, and heredity are well-established risk factors for OSA, with obesity being the single most important modifiable risk factor.[29] If untreated, OSA is associated with increased risk of diabetes, CV disease, driving accidents, and all-cause

mortality.[30] However, few studies have compared the effect of surgical and conservative weight loss strategies on OSA in obese patients.

A recent one-year study in a total of 133 morbidly obese subjects (70% females) were treated with either a 1-year ILI program ($n = 59$) or bariatric surgery (RYGB) ($n = 74$) and underwent repeated sleep recordings with a portable somnograph.[31] At baseline, participants had a mean age of 44.7 years, a mean BMI of 45.1, and an AHI of 17.1 events/hour. Eighty-four patients (63%) had a diagnosis of OSA. The average weight loss was 8% in the ILI-group and 30% in the RYGB-group ($P < 0.001$). The mean AHI decreased in both treatment groups, although significantly more in the RYGB group (group difference 7.2; $P = 0.017$) and 66% of RYGB-treated patients experienced remission of OSA compared with 40% of the ILI-patients ($P = 0.028$).

At follow-up, after adjusting for age, gender, and baseline AHI, the RYGB-patients had significantly lower adjusted odds for OSA than the ILI-patients (OR 0.33; $P = 0.0150$). However, after further adjustment for BMI change, the treatment group difference was no longer statistically significant (OR 1.31; $P = 0.709$). The authors concluded this study demonstrates that RYGB was more effective than ILI at reducing the prevalence and severity of OSA. However, further analysis also suggests that weight loss, rather than the surgical procedure per se, explains the beneficial effects bariatric surgery in obese individuals.

Many studies have reported significant improvement of OSA in obese patients after bariatric surgery. It also has been noted that weight loss following surgery often is rapid in the first few months but often can take at least 1 year to reach the maximum effect. In order to assess the time course of the benefits of bariatric surgery, a recent study compared the effects of bariatric surgery on its effects at two postoperative intervals.[32]

Patients who had been diagnosed with OSA preoperatively were invited to undergo PSG at least 6 months postoperatively and again at least 12 months postoperatively if OSA persisted. At a mean of 7.7 months after surgery, 110 patients completed a first postoperative PSG. At that time, the mean AHI had decreased significantly from 39.5/hr to 15.6/hr. In 26% of patients, the AHI was reduced to <5/hr. Fifty patients underwent a first PSG at a mean of 7.1 months and a second PSG at a mean 16.9 months after surgery. The mean AHI decreased significantly from a baseline of 49.1/hr to 2.7/hr and 17.4/h following bariatric surgery. Thus, while the beneficial effects of bariatric surgery occur early in the postoperative period, they continue at a slower rate. Therefore, the authors suggest that follow-up PSG after surgery should be considered to check for residual disease and possible retitration of continuous positive airway pressure.

Postsurgical Care

There is a large population of patients who are receiving, or should be receiving, continuing postsurgical monitoring and care. Many of these patients have been, or may ultimately be, lost to the original surgeon and will now be in the care of the other physicians.

Follow-up of the obese patients who have had bariatric surgery can be divided into three periods: the issues of surgical complications and weight loss during the first year, the nutritional and metabolic issues that typically arise after the first postoperative year, and the problem of weight maintenance over the longer term.[33-35]

Female patients should be advised that pregnancy is contraindicated for at least 18 months after surgery because of the rapid weight loss and nutritional requirements. In addition, all patients should be encouraged to stop both smoking and the use of alcohol.

Short-term complications of bariatric surgery include vomiting, wound infections, stomal stenosis (ie, narrowing of the gastrojejunostomy), marginal ulceration, and constipation.

Common long-term complications of bariatric surgery include cholelithiasis, dumping syndrome, persistent vomiting, and nutritional deficiencies.

Table 10.8 provides a list and suggested schedule of laboratory tests useful for long-term follow-up of patients who have had bariatric surgery.

The Swedish Obese Subjects Study

The Swedish Obese Subjects (SOS) study is an ongoing, nonrandomized, prospective, controlled study conducted at 25 public surgical departments and 480 primary health care centers in Sweden that included 2010 obese participants who underwent bariatric surgery and 2037 contemporaneously matched obese controls who received usual care. Participants were followed up for a median of 14.7 years. The objectives of the SOS study were to determine the long-term effects of weight-loss surgery on "hard" clinical endpoints, including overall mortality, CV events, incidence of diabetes, and stroke.[36] Of the patients who had surgery, 13% underwent a bypass procedure, 19% underwent a banding procedure, while 68% had vertical banded gastroplasty.

In the surgery group, the mean changes in body weight after 2, 10, 15, and 20 years were -23%, -17%, -16% and -18% while the mean changes in the usual care group were 0%, 1%, -1%, and -1%. Compared with usual care, bariatric surgery was associated with a long-term reduction in overall mortality (adjusted HR = 0.71, $P = 0.01$).[36] Bariatric surgery also was associated with a reduced number of CV deaths (28 events among 2010 patients in the surgery group vs 49 events among 2037 patients in the control group (HR,= 0.47; $P = 0.002$). The number of total first time (fatal or nonfatal) CV events (myocardial infarction or stroke, whichever came first) was also lower in the surgery group (199 events among 2010 patients) than in the control group (234 events among 2037 patients; HR = 0.67; $P < 0.001$).[37] Perhaps the most striking find-

TABLE 10.8 — Routine Postsurgical Laboratory Follow-Up of Individuals After Bariatric Surgery

Follow-up Period	Laboratory Tests
1 month	CBC, SMA-21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine
3 months	CBC, SMA-21 , B12 (MMA and HCy optional), folic acid, iron studies, 25-Vitamin D, iPTH, thiamine (copper, zinc, and selenium if clinically indicated)
6 months	CBC, SMA-21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, lipids, 24-hr urinary calcium (at 6 months, then annually) (copper, zinc, and selenium if clinically indicated)
12 months	CBC, SMA-21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, lipids (copper, zinc, and selenium if clinically indicated)
24 months	CBC, SMA-21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine, bone density (copper, zinc, and selenium if clinically indicated)
Annually	CBC, SMA-21 , B12, folic acid, iron studies, 25-Vitamin D, iPTH, thiamine (copper, zinc, and selenium if clinically indicated)

Mechanick JI, et al. *Surg Obes Relat Dis*. 2013;9:159-191.

ing was that during the follow-up period, the incidence of T2D was substantially lower than in the usual care group (6.8 cases per 1000 person-years vs 28.4 cases per 1000 person-years, respectively (HR = 0.17; $P = 0.54$).[38]

Future Development and Devices

There is an extensive research focused on innovative strategies to manage obesity. Implantable devices which reduce the need for invasive bariatric surgery are attractive therapeutic alternatives. Modifying stomach contractions through gastric electrical stimulation (GES) has potential for treating not only gastric motor disorders but also morbid obesity. Depending on device settings, GES may enhance or inhibit stomach muscle contractions or pressure, and therefore may alter how quickly the stomach empties. GES can be administered by an implantable pulse generator connected to gastric electrodes, which synchronizes pulses with ingestion of food. Short-term therapy with the GES has been shown to improve glucose control, induce weight loss, and improve blood pressure and lipids in obese patients with T2D.[39]

Another implantable device shown to be effective at reducing excess weight and minimizing CVD risk factors is the duodenal-jejunal bypass sleeve (EndoBarrier). It is a fluoropolymer sleeve that is reversibly fixated to the duodenal bulb and extends 80 cm into the small bowel, terminating in the proximal jejunum. This endoscopically inserted device aids weight loss through induction of malabsorption and activating hormonal triggers. Studies using the EndoBarrier found that patients were able to achieve between 11.9% to 23.6% excess weight loss within 12 weeks. A longer trial found that patients were able to achieve 47% mean excess weight loss in 52-weeks.[40] In addition to weight loss, one study found that this procedure resulted in statistically significant reductions in fasting blood glucose (-30.3 ± 10.2 mg/dL), fasting insulin (-7.3 ± 2.6 μU/mL), and HbA1c (-2.1 ± 0.3%) compared with baseline.[41] The EndoBarrier may also have a positive impact on CVD risk factors, including a reduction in lipid levels and blood pressure.

Summary

Bariatric surgery has evolved since the 1950s with the emergence of the jejunoileal bypass and now includes the RYGB, VSG, AGB, and the BPD/DS. These procedures have been shown to produce significant and durable weight loss as well as reduction or resolution of the serious comorbidities associated with obesity. Comparative studies on surgical procedures vs control groups have suffered from the inability to conduct randomized controlled clinical trials; however, long-term studies have recently been published which clearly show benefit. The exact mechanism of action of the durable weight loss in especially the combination procedures are still being researched but a combination of restriction and change in gut hormone milieu seems to be partly if not completely responsible for the reduction in appetite and increase in satiety, and hence, weight loss.

REFERENCES

1. Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess*. 2009;13:1-190, 215-357.
2. Nguyen NT, Nguyen XT, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: Findings from the National Health and Nutrition Examination Survey, 1999–2006. *Obes Surg*. 2011;21:351-355.
3. Poirier P, Cornier MA, Mazzone T, et al. Bariatric surgery and cardiovascular risk factors: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1683-1701.
4. Van Gaal LF, De Block CE. Bariatric surgery to treat type 2 diabetes: what is the recent evidence? *Curr Opin Endocrinol Diabetes Obes*. 2012;19:352-358.
5. American Society for Metabolic and Bariatric Surgery Web site. For professionals/How can I help my patients?/Procedures. www .asmbs.org. Accessed June 10, 2014.
6. Bariatric Surgery for Severe Obesity. The Weight-control Information Network (WIN) Web site. http://win.niddk.nih.gov/publications/gastric.htm. NIH Publication No. 08–4006. Published March 2009. Updated June 2011. Accessed June 10, 2014.
7. Baptista V, Wassef W. Bariatric procedures: an update on techniques, outcomes and complications. *Curr Opin Gastroenterol*. 2013;29:684-693.
8. Noria SF, Grantcharov T. Biological effects of bariatric surgery on obesity-related comorbidities. *Can J Surg*. 2013;56(1):47-57.
9. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med*. 2005;142:547-559.
10. Tice JA, Karliner L, Walsh J, et al. Gastric banding or bypass? A systematic review comparing the two most popular bariatric procedures. *Am J Med*. 2008;121:885-893.
11. Chang SH, Stoll CR, Song J, et al. The effectiveness and risks of bariatric surgery: An updated systematic review and meta-analysis, 2003-2012. *JAMA Surg*. 2014;149(3):275-287.
12. O'Brien PE, MacDonald L, Anderson M, et al. Long-term outcomes after bariatric surgery: fifteen-year follow-up of adjustable gastric banding and a systematic review of the bariatric surgical literature. *Ann Surg*. 2013;257:87-94.

13. Courcoulas AP, Christian NJ, Belle SH, et al; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. *JAMA*. 2013;310:2416-2425.
14. Victorzon M, Tolonen P. Mean fourteen-year, 100% follow-up of laparoscopic adjustable gastric banding for morbid obesity. *Surg Obes Relat Dis*. 2013;9:753-757.
15. Sieber P, Gass M, Kern B, Peters T, Slawik M, Peterli R. Five-year results of laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis*. 2014;10(2):243-249.
16. Dorman RB, Rasmus NF, al-Haddad BJ, et al. Benefits and complications of the duodenal switch/biliopancreatic diversion compared to the Roux-en-Y gastric bypass. *Surgery*. 2012; 152(4):758-765; discussion 765-767.
17. Topart P, Becouarn G, Ritz P. Comparative early outcomes of three laparoscopic bariatric procedures: sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion with duodenal switch. *Surg Obes Relat Dis*. 2012;8(3):250-254.
18. Bariatric Surgery and Nonsurgical Therapy in Adults With Metabolic Conditions and a Body Mass Index of 30.0 to 34.9 kg/m². Rockville, MD: Agency for Healthcare Research and Quality. AHRQ Publication No. 12(13)-EHC139-EF. June 2013.
19. Van Gaal LF, De Block CE. Bariatric surgery to treat type 2 diabetes: what is the recent evidence? *Curr Opin Endocrinol Diabetes Obes*. 2012;19:352-358.
20. Maggard-Gibbons M, Maglione M, Livhits M, et al. Bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults with diabetes: a systematic review. *JAMA*. 2013; 309:2250-2261.
21. Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934.
22. Kalyvas AV, Vlachos K, Abu-Amara M, et al. Bariatric surgery as metabolic surgery for diabetic patients [published online ahead of print September 12, 2013]. *Curr Pharm Des*. doi: 10.2174/13816128113196660672.
23. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med*. 2012;366:1567-1576.

24. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med*. 2012;366:1577-1585.

25. Brethauer SA, Aminian A, Romero-Talamás H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Ann Surg*. 2013;258:628-636.

26. Dixon JB, Zimmet P, Alberti KG, Rubino F; International Diabetes Federation Taskforce on Epidemiology and Prevention. Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med*. 2011;28:628-642.

27. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief*. 2012;(82):1-8.

28. Inge TH, Zeller MH, Jenkins TM; for the Teen-LABS Consortium. Perioperative Outcomes of Adolescents Undergoing Bariatric Surgery: The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study. *JAMA Pediatr*. 2014;168(1):47-53.

29. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Prog Cardiovasc Dis*. 2009;51:285-293.

30. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*. 2008;31:1071-1078.

31. Fredheim JM, Rollheim J, Sandbu R, et al. Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention. *J Clin Sleep Med*. 2013;9:427-432.

32. Ravesloot MJ, Hilgevoord AA, van Wagensveld BA, de Vries N. Assessment of the effect of bariatric surgery on obstructive sleep apnea at two postoperative intervals. *Obes Surg*. 2014;24(1):22-31.

33. Elliott VS. Bariatric surgery patients need care for a lifetime. American Med News Web site. www.ama-assn.org/amednews/2004/06/28/hlsa0628.htm. June 28, 2004. Accessed June 10, 2014.

34. Virji A, Murr MM. Caring for patients after bariatric surgery. *Am Fam Physician*. 2006;73:1403-1408.

35. Fujioka K. Follow-up of nutritional and metabolic problems after bariatric surgery. *Diabetes Care*. 2005;28:481-484.

36. Virji A, Murr MM. Caring for patients after bariatric surgery. *Am Fam Physician*. 2006;73:1403-1408.

37. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273:219-234.

38. Fujioka K. Follow-up of nutritional and metabolic problems after bariatric surgery. *Diabetes Care*. 2005;28:481-484.

39. Sanmiguel CP, Conklin JL, Cunneen SA, et al. Gastric electrical stimulation with the TANTALUS System in obese type 2 diabetes patients: effect on weight and glycemic control. *J Diabetes Sci Technol*. 20091;3(4):964-970.

40. Patel SR, Hakim D, Mason J, Hakim N. The duodenal-jejunal bypass sleeve (EndoBarrier Gastrointestinal Liner) for weight loss and treatment of type 2 diabetes. *Surg Obes Relat Dis*. 2013;9(3):482-484.

41. de Moura EG, Martins BC, Lopes GS, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. *Diabetes Technol Ther*. 2012;14(2):183-189.

11 Abbreviations/Acronyms

5-HT	serotonin
A1C	glycosylated hemoglobin
AACE	American Association of Clinical Endocrinologists
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADAPT	Arthritis, Diet, and Activity Promotion Trial
ADMA	asymmetric dimethylarginine
AE	adverse event
AED	anti-epileptic drug
AGB	adjustable gastric banding
AgRP	agouti-related peptide
AHA	American Heart Association
AHEAD	[Look] Action for Health in Diabetes [study]
AHI	apnea-hypopnea index
AIDS	acquired immunodeficiency syndrome
αMSH	alpha melanocyte-stimulating hormone
AMA	American Medical Association
AP	acute pancreatitis
ARB	angiotensin receptor blocker
ARC	arcuate nucleus
ASP	acylation-stimulating protein
ATP	Adult Treatment Panel
BDI	Beck Depression Inventory
BIA	bioelectrical impedance analysis
BID	twice daily
BMI	body mass index
BMOD	behavior modification
BP	blood pressure
BPD	biliopancreatic diversion
BPD/DS	biliopancreatic diversion without duodenal switch
bpm	beats per minute
BUN	blood urea nitrogen

CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults [study]
CART	cocaine- and amphetamine-regulated transcript
CCB	calcium channel blocker
CCK	cholecystokinin
CGS	Clinical Guidelines Subcommittee
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CMDS	cardiometabolic disease staging system
CNS	central nervous system
COR	Contrave Obesity Research [study]
COR-BMOD	Contrave Obesity Research with Behavior Modification
COR-II	Contrave Obesity Research-II [study]
CRF	chronic renal failure
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
CVD	cardiovascular disease
DA	dopamine
DBP	diastolic blood pressure
DMPA	depot medroxyprogesterone acetate
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DSE	diabetes support and education
EGF	epidermal growth factor
EOSS	Edmonton Obesity Staging System
EPIC	European Prospective Investigation into Cancer and Nutrition [study]
ER	extended-release
EWL	excessive weight loss
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGP	food guide pyramid
GABA	gamma aminobutyric acid
GES	gastric electrical stimulation
GI	gastrointestinal
GLP-1	glucagon-like peptide 1

h	hour(s)
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HO	hypothalamic obesity
HOMA-IR	homeostasis model assessment of insulin resistance
HR	hazard ratio
HRT	hormone replacement therapy
IDF	International Diabetes Foundation
IFG	impaired fasting glucose
IGF-1	insulin-like growth factor-1
IGFBP	insulin-like growth factor-binding protein
IGT	impaired glucose tolerance
IL	interleukin
ILI	intensive lifestyle intervention
LABS	Longitudinal Assessment of Bariatric Surgery
lb	pound(s)
LCD	low calorie diet
LOCF	last observation carried forward
LSG	laparoscopic sleeve gastrectomy
MAOI	monoamine oxidase inhibitor
MC4R	melanocortin 4 receptor
MDD	major depressive disorder
MHO	metabolically healthy obese
MI	myocardial infarction
mITT	modified intent-to-treat
mo	month(s)
MRI	magnetic resonance imaging
NAc	nucleus accumbens
NAFLD	nonalcoholic fatty liver disease
nal/bup SR	naltrexone SR/bupropion SR [Contrave]
NASH	nonalcoholic steatohepatitis
NE	norepinephrine
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NMS	neuroleptic malignant syndrome
NSAID	nonsteroidal anti-inflammatory drug
NYP	neuropeptide Y
OA	osteoarthritis

OR	odds ratio
OSA	obstructive sleep apnea
OTC	over-the-counter [drug]
OXM	oxyntomodulin
PAI-1	plasminogen activator inhibitor-1
PCOS	polycystic ovarian syndrome
PCP	primary care physician
PfC	prefrontal cortex
phen/top ER	phentermine/topiramate ER [Qsymia]
PMR	partial meal replacement
POMC	proopiomelanocortin [neuron]
PSG	polysomnography
PSMF	protein-sparing modified fast
PVN	paraventricular
PYY	peptide YY
QD	once daily
RCT	randomized controlled trial
REE	resting energy expenditure
RR	relative risk
RYGB	Rou-en-Y gastric bypass
SBP	systolic blood pressure
SGLT2	sodium glucose cotransporter 2
SHBG	sex hormone-binding globulin
SOS	Swedish Obese Subjects [study]
SSRI	selective serotonin reuptake inhibitor
T1D	type 1 diabetes
T2D	type 2 diabetes
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse events
TEE	total energy expenditure
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha
TOS	The Obesity Society
TSH	thyroid-stimulating hormone
TZD	thiazolidinediones
VLCD	very low calorie diet
VSG	vertical sleep gastrectomy
VTA	ventral tegmental area
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
y	year(s)

INDEX

Note: Page numbers in *italics* indicate figures.
Page numbers followed by a "t" indicate tables.
Clinical trials and studies are indexed
under the acronym of the name.

AACE algorithm/guidelines for treatment, 75, *76*, 78, 87, *93*
Abbreviations and acronyms, 287-290
ACE inhibitors, 152
Acute pancreatitis (AP), 63-64
ADAPT (Arthritis Diet, and Activity Promotion Trial), 121-122
Adipokines, 30, 56
Adiponectin, *29*
Adipose signals, *29*, 30
Adipose tissue, factors secreted by, 26, *29*, 30, 47, *49*
Adjustable gastric banding (AGB), 253, 260-262, *261*
  complications and mortality, 269, 270t
  diabetes and, 273, 274t
  efficacy, 263-264, 265-267, *265*, 266t
  mechanisms of action, 261-262
  potential advantages and disadvantages, 263t
Adolescents
  bariatric surgery in, 273-275
  prevalence of obesity in, 14-15, 273-275
Agouti-related peptide. See *AgRP.*
AgRP (agouti-related peptide), 24-26, *25*, *34*, *35*
  lowered satiety and overeating with, *25*, 26
  neurons, 24-26, *25*, *27*, *34*, *35*
  stimulation of, 24-26, *25*
Algorithm for treatment, 75, *76*, 78, 87, *93*, 141, *142-143*
α-Adrenergic blockers, 130t
Amphetamine derivatives, 183, 184t
Amylin, AgRP production and, 26
Anorexigenic substances/pathway, 26, 30, 43, 210, *246*
Anti-epileptic drugs, 149t, 152-153
Antibiotics, 39
Anticonvulsant medications, 130t, 149t, 152-153
Antidepressants, 130t, 148t, 154-156
Antidiabetic medications, 130t, 146-151, 149t

Antihistamines, 131t, 150t, 156
Antihypertensive medications, 148t-149t, 151-152
Antimanic agent, 130t
Antineoplastics, 131t
Antipsychotics, 130t, 150t, 154-156
Antiretroviral medications, 156
Apnea. See *Obstructive sleep apnea.*
Appetite. See also *Satiety.*
  hypothalamic regulation of, 24-26, *32*
  satiety and, 26, 28
  suppression, by obesity treatments, 33, *34*, *35*
ARBs, 152
Arcuate nucleus (ARC), 24, *25*, 26, *27*
Arthritis
  ADAPT trial, 121-122
  osteoarthritis (OA), 59
  weight loss benefit for, 121-122
Autonomic nervous system, 28

Babinski-Frohlich syndrome, 42
Bacteria, 39
Bardet-Biedl syndrome, 33, 36
Bariatric surgery, 251-285
  in adolescents, 273-275
  BMI categories, and treatment choices, 92t, 253
  candidates and qualifications, 251-253
  clinical experience/efficacy, 262-269, 281
    AGB, 263-264, 265-267, *265*, 266t, 269, 270t
    BPD/DS, 266t, 268, 269
    gastroplasty, 266t
    laparoscopic procedures, 263-264, 269
    recent individual studies, 264-268, 266t
    RYGB, 263-264, 265-267, *265*, 266t, 269, 270t
    safety, 268-269, 270t
      complications, 268-269, 277-278
      operative (30-day) mortality, 268, 269, 270t
      reoperation rates, 269, 270t
    systematic reviews and meta-analyses, 262-264, *265*
    VSG, 263, 264, *265*, 267-268, 269, 270t
  contraindication for pregnancy, 277
  as diabetes treatment, 271-273
Bariatric surgery *(continued)*
  future development and devices, 280-281
    duodenal-jejunal bypass sleeve (EndoBarrier), 280-281
    gastric electrical stimulation (GES), 280
    implantable devices, 280
  intensification of therapies to achieve weight loss goals, *93*
  mechanisms of action for weight loss, 254, 256, 281
  number of procedures performed, 251, *252*
  obstructive sleep apnea (OSA) and, 275-277
  postsurgical care, 277-278
    laboratory follow-up, 279t
  procedures, 253-262
    adjustable gastric banding (AGB), 253, 260-262, *261*
      complications and mortality, 269, 270t
      diabetes and, 273, 274t
      efficacy, 263-264, 265-267, *265*, 266t
      mechanisms of action, 261-262
      potential advantages and disadvantages, 263t
    biliopancreatic diversion with or without duodenal switch (BPD or BPD/DS), 254, 258-260, *259*
      complications and mortality, 269, 270t
      diabetes and, 272-273
      efficacy, 266t, 268
      mechanisms of action, 258, 259-260
      potential advantages and disadvantages, 260t
    laparoscopic approaches, 254, 263-264
    Roux-en-Y gastric bypass (RYGB), 253, *255*, 264-266
      complications and mortality, 269, 270t
      diabetes and, 271-273, 274t
      efficacy, 263-264, 265-267, *265*, 266t
      mechanisms of action, 256
      as nonreversible, 255
      potential advantages and disadvantages, 256t
      sleep improvement with, 119-121
    vertical sleeve gastrectomy (VSG), 254, 256-257, *257*
      complications and mortality, 269, 270t
      diabetes and, 271-272, 274t
      efficacy, 263, 264, *265*, 267-268
      mechanisms of action, 257
      potential advantages and disadvantages, 258t
  questions for patients, 253
  safety, 268-269, 270t
  Swedish Obese Subjects (SOS) study, 278-280

Basal metabolic rate, 23
Behavioral modification, 171-172, 179, 243
  Contrave Obesity Research Behavioral Modification (COR-BMOD) trial, 224-225, 226t-227t, 229-230, *231*, 233
Behavioral Risk Factor Surveillance System, 50
Belviq. See *Lorcaserin (Belviq).*
Benzphetamine, 184t
β-Blockers, 131t, 148t, 151
Biliopancreatic diversion with or without duodenal switch (BPD or BPD/DS), 254, 258-260, *259*
  complications and mortality, 269, 270t
  diabetes and, 272-273
  efficacy, 266t, 268
  mechanisms of action, 258, 259-260
  potential advantages and disadvantages, 260t
Binge-eating disorder, 41
Bioelectrical impedence analysis (BIA), 135
Bisphenol A, 37
Blood pressure (BP)
  high, 53. See also *Hypertension.*
    improvement values with lorcaserin, 220t
    improvement with phen/top ER (Qsymia), 203-205, *206*
    improvement with weight loss, 98-100, *103*, 106, 107t, *109*, *117*
  in metabolic syndrome, 85t, 104t
BLOOM trial, 211, 213, 214t-215t, *216*, 218, 220t-223t
BLOOM-DM trial, 211, 213-217, 214t-215t, *217*, 218, 219, 220t-221t
BLOSSOM trial, 211-212, *212*, 214t-215t, 219, 220t-221t
  secondary endpoints in, 218, 220t-221t
BMI (body mass index), 129-131
  BMI-centric model for treatment, 77-78, 87, 92t
  comorbidities and, 55t, 56, 57t
  genetics and, 38
  hypertension and, 51t
  mortality statistics and, 15-19, *16*, 18t, *20-21*
  obesity classification/categories, 13, 49t, 57t, 77, *82-83*, 129-131, 132t
  in overweight, 13
  in severe obesity, 13

BMI (body mass index) *(continued)*
  sleep deprivation and, 41
  in treatment algorithm, *142-143*
BMIQ Professionals Program, 177-178
Body fat, percentage of, 133-135, 134t
Body mass index. See *BMI (body mass index).*
Bupropion
  action mechanism, 33, *34*, 224
  POMC and appetite suppression, 33, *34*
Bupropion SR plus naltrexone SR. See *Contrave (naltrexone SR/bupropion SR).*

C-reactive protein (CRP), 47-50, 49t, 51t
Calcium channel blockers, 152
Cancer
  comorbid with obesity, 59-61
  EPIC study, 60-61
  mortality statistics, 18-19, *20-21*
  obesity and, 18-19, *20-21*
Carbamazepine, 149t, 152
Carbohydrates
  content of diet, 165-167
  low carbohydrate diets, 163, 166-167
CARDIA study, 86, *90*
Cardiac valvulopathy, 184, 219
Cardiometabolic Disease Staging System (CMDS), 84-87, 88t-89t, *91*
Cardiovascular disease
  mortality statistics, 18, 18t
  obesity and, *48*, 53-54, 67
Cardiovascular risk factors
  lorcaserin and, 220t-221t
  reduction by weight loss (DPP/DPPOS), 78-79, 98-100, *102-103*
  reduction by weight loss (Look AHEAD), 105-114, 107t, *108-111*, *116-117*
  topiramate and, 206-207t
CART (cocaine- and amphetamine-regulated transcript), 26
  neurons, *25*, 26, *27*, *246*
Carvedilol, 148t, 151-152
CCK (cholecystokinin), 26, 28, *29*, 43
Central adiposity, 132

Central nervous system (CNS). See also *Hypothalamus.*
regulation and satiety signals, *32*
Children, prevalence of obesity in, 14-15, 273-275
Cholecystokinin (CCK), 26, 28, *29*, 43
Chronic renal failure (CRF), 66
Clinical trials, 211-212, *212*, 214-215t
Cocaine- and amphetamine-regulated transcript (CART), *25*, 26, *27*, *246*
Cognitive restructuring, 172
Comorbidities, 47-74, *48*
acute pancreatitis, 63-64
cancer, 59-61
chronic renal failure, 66
coronary heart disease, *48*, 53-54
depression, 61-62
diabetes, 50-53
dyslipidemia, 53-54, 55t, 80, 85t
evaluation of, 137-139, *138*
gallbladder disease, 62-63
hypertension, 53, 55t
inflammation, 47-50
multiple concurrent, 56-66, 57t
nonalcoholic fatty liver disease, 64
obstructive sleep apnea (OSA), 56-58
osteoarthritis (OA), 59
polycystic ovary syndrome (PCOS), 65-66
prevalence of major, 50-55, 55t
reduction with weight loss, 78-79
Complications-centric approach to treatment of obesity, 75-94
evaluation, risk assessment, and disease staging, 79-87
focus on risk reduction, 77-78
intensification of therapies, *93*
medical model, 87-91
obesity as a disease, 75-77
weight loss reduction of comorbidity and mortality risk, 78-79
CONQUER trial, 198-199, 201t, *203*, 205, 206t-207t, 208
Constipation
lorcaserin and, 218, 222t
naltrexone SR/bupropion SR and, 233, 236t
phentermine/topiramate ER (phen/top), 208

Contraceptives, hormones, and steroids, 150t, 153-154
Contrave (naltrexone SR plus bupropion SR), 33, 186t-192t, 224-238
action mechanisms, 224
adverse events, 189t, 233, 236t-237t
contraindications, 188t-189t
dosage/administration, 191t-192t, 233-238
efficacy, 224-234, 226t-227t
COR-I trial, 224-225, 226t-227t, *228*, 230
COR-II trial, 224-229, 226t-227t, *229*, 233
COR-BMOD trial, 224-225, 226t-227t, 229-230, *231*, 233
COR-Diabetes trial, 224-225, 226t-227t, 230, *232*, 233
primary endpoints (weight loss), 225-229, 226t-227t, *228-229*, *231-232*
secondary endpoints (metabolic and cardiovascular risk), 230-233, 234t-235t
indications for, 186t
limitations of, 187t
prescribing information, 186t-192t, 233-238
safety, 233, 236t-237t
warnings and precautions, 190t
Contrave Obesity Research I (COR-I) trial, 224-225, 226t-227t, *228*, 230
Contrave Obesity Research II (COR-II) trial, 224-229, 226t-227t, *229*, 233
Contrave Obesity Research Behavioral Modification (COR-BMOD) trial, 224-225, 226t-227t, 229-230, 233
Contrave Obesity Research-Diabetes (COR-Diabetes) trial, 224-225, 226t-227t, 230, *232*, 233
Coronary heart disease (CHD), *48*, 53-54
Corticosteroids, 150t, 154
Cushing's Syndrome, 40

Depression, 61-62
comorbid with obesity, 61-62
major depressive disorder (MDD), 61
weight loss, benefit of, 114-115, *118*
Dexfenfluramine, 183-184, 184t
Diabetes, 50-53
AACE algorithm for treatment of, 75
antidiabetic medications, 146-151, 149t
antidiabetics medications, weight gain and, 130t

Diabetes *(continued)*
bariatric surgery and, 271-273, 274t, 280
CARDIA study, 86, *90*
comorbid with obesity, 50-53, 51t, *52*, 55t
COR-Diabetes trial (Contrave), 224-225, 226t-227t, 230, *232*, 233
CRP and fibrinogen in, 47, 51t
depression and (Look AHEAD trial), 114-115, *118*
DPP (Diabetes Prevention Program) Study, 95-103, 172-173, 174t
DPPOS (Diabetes Prevention Program Outcomes Study), 95-103
DPP and DPPOS, 95-103
metabolic syndrome in, 101-103, 104t
objectives and design, 95-97
prevention/delay of diabetes, 97-98, *97*, *99*, 99t
reduction in CV risk factors, 98-100, *102-103*
weight loss in severely obese patients, 100-101
Look AHEAD trial, 78-79, 105-122, 173, 174t
objectives and design, 105
reduction in CV events and risk factors, 105-114, 107t, *108-111*, *116-117*
reduction of depression, 114-115, *118*
remission of diabetes, 112, *113*
prediction of, 86, 88t-89t, *90*
SCALE Diabetes trial (liraglutide), 239-241, 240t
type 2, 50, *52*, 271-273
Diarrhea, liraglutide and, 243, 244t
Diet, 161-169, 179, 243
behavioral modification and, 171-172
BMI categories, and treatment choices, 92t
cognitive restructuring and, 172
composition relative to cardiometabolic parameters, 166-168
low calories diets (LCDs), 163, 163t
low carbohydrate diets, 163, 166-167
low energy density diets, 164
low fat diets, 166-167
macronutrient content, comparison of, 165-166
magnitude of weight loss, 161
meal replacements, 164-165
new options in, 91

Diet *(continued)*
portion size and, *169*
problem-solving techniques and, 171-172
protein-sparing modified fast (PSMF), 162-163
relapse prevention, 172
sample dietary compositions, 163t
self-monitoring of intake, 171
tips for counseling patients on, 168, *168*, *169*
trigger or stimulus control, 171
very low calories diets (VLCDs), 161-162, 163
Diethylpropion, 184t
Disease staging. See *Staging of obesity.*
Dizziness
naltrexone SR/bupropion SR and, 233, 236t
phentermine and, 193-194
phentermine/topiramate ER (phen/top) and, 208
Dopamine, *34*
reward pathway, 31
DPP-4 inhibitors, 147, 149t
DPP (Diabetes Prevention Program) study, 95-103, 172-173, 174t
metabolic syndrome in, 101-103, 104t
objectives and design, 95-97
prevention/delay of diabetes, 97-98, *97*, *99*, 99t
reduction in CV risk factors, 98-100, *102-103*
weight loss in severely obese patients, 100-101
DPPOS (Diabetes Prevention Program Outcomes Study), 95-103. See also *DPP (Diabetes Prevention Program) study.*
Drug-induced weight gain, 145-160. See also *Medications*; *Weight gain.*
Dry mouth
lorcaserin and, 218, 222t
naltrexone SR/bupropion SR and, 233, 236t
phentermine and, 193-194
phentermine/topiramate ER (phen/top) and, 208
Duodenal-jejunal bypass sleeve (EndoBarrier), 280-281
DXA (formerly DEXA), 133-135
Dyslipidemia, 53-54, 55t, 80, 85t
improvement with weight loss, 98-100, *102*, 106-112, 107t, *110-111*, *116-117*
in metabolic syndrome, 104t

Edmonton Obesity Staging System (EOSS), 79-80, 81t, *82-83*
EndoBarrier (duodenal-jejunal bypass sleeve), 280-281
Endocrine disruptors, 37
Energy balance (homeostasis), 23-26, *32*, 43
 basal metabolic rate, 23
 basic mechanisms of, 23-24
 changes in, associated with weight loss, 42-43
 hypothalamus and, 23-26, *25*, *27*, *29*
 peptide modulators of, *27*
 positive energy balance, *32*
 regulation of, 23-43
 resting energy expenditure (REE), 42
 total energy expenditure (TEE), 23, 42-43
Environmental chemicals, 37
Environmental factors, 37-38
 vs genetics, 38
EPIC (European Prospective Investigation into Cancer and Nutrition), 60-61
Epigenetics, 37
EQUIP trial, 197-198, 200t-201t, *202*, 206t-207t
Etiology. See *Pathophysiology of obesity.*
European Prospective Investigation into Cancer and Nutrition (EPIC), 60-61
Evaluation
 examination of patient, 129-136
 risk assessment, and disease staging, 79-87
 of weight-related comorbidities, 137-139
 weight-specific history, 127-129
Examination of patient, 129-136
Exercise. See *Physical activity.*

Fasting glucose, *82*, 85t, 104t
 improved values with lorcaserin, 220t
 improved values with phen/top ER (Qsymia), 203-205, 205, *207*
Fat
 amount in diet, 166
 low fat diets, 166-167
 storage, 24
Fenfluramine, 183-184, 184t
Fetus, obese mothers and, 37

Fibrinogen, 47-50, 49t
Food, rewarding effect of, 31, *32*
Food intake, 23-26, 43. See also *Diet*; *Energy balance.*
 homeostatic control of, 23-24
 hypothalamus and, 23-26, *25*, *27*, *29*
 peptide modulators of, *27*
 regulation of, 23-26, *25*, *27*, *29*, *32*
 reward circuitry and, 31, *32*
FTO gene (fat mass and obesity associated gene), 33, 36

Gallbladder disease, 62-63
Gastrectomy. See *Vertical sleeve gastrectomy (VSG).*
Gastric banding. See *Adjustable gastric banding (AGB).*
Gastric bypass. See *Roux-en-Y gastric bypass (RYGB).*
Gastric distention, 28
Gastric electrical stimulation (GES), 280
Gastric emptying, delayed, 28
Gastrointestinal signaling, 28-30, *29*
Gender
 mortality rates and, *16*, 18-19, *20-21*
 prevalence of obesity and, 13-15, *14*
Genetic factors, 33-38
 epigenetics, 37
 gene mutations, 33-36
 obesity genes, 33-36
 twin studies, 38
 vs environment, 38
Ghrelin, 26, *27*, *29*
 actions of, 28-30
 AgRP production and, 24
 antagonist (in development), *246*
 increased with weight loss, 43
GLP-1. See *Glucagon-like peptide.*
Glucagon-like peptide (GLP-1), 28, *29*, 147, 149t
 liraglutide, 238-243
 potential new therapeutic targets, *246*
Growth hormone deficiency, 40
Gut hormones, 26, 28-30, *29*
Gut microbes, 38-39
Gynecological abnormalities, *48*

Hazard ratios (HR), 15-18, *16*
Headaches, naltrexone SR/bupropion SR and, 233, 236t
Hedonic pathway, 31, *32*, 43
High blood pressure (BP), 53
History, weight-specific, 127-129
HIV, medications for, 156
Homeostasis, 23-24. See also *Energy balance.*
Hormone replacement therapy (HRT), 154
Hormones, 26-30, *29*
Humoral signaling, 28-30, *29*
  humoral factors, 26-28
Hyperphagia
  leptin deficiency and, 30
  POMC deficiency and, 36
Hypertension, 53, 55t
  antihypertensive medications, 148t-149t, 151-152
  CRP and fibrinogen in, 47, 51t
  improvement with weight loss, 98-100, *103*, 106, 107t, *109*, *117*
Hypothalamic obesity (HO), 41-42
Hypothalamus, 24-26
  damage to and syndromes of, 41-42
  genetic defects, 33
  potential new therapeutic targets, *246*
  as regulator of energy balance and food intake, 23-26, *25*, *27*, *29*, *32*
Hypothyroidism, 40
Hypoventilation syndromes, 137

Inflammation, 47-50
Insomnia, phentermine/topiramate ER (phen/top), 208
Insulin, 26, *27*, *29*, 30
  AgRP production and, 26
  fasting levels of, 30
  reduced levels with weight loss, 43
  resistance, 80
  weight gain and, 146-147, 149t

Jenny Craig, 175

Kidneys, chronic renal failure (CRF), 66

Laboratory examination, 136-137
Leptin, 26, *27*, *29*, 30
  AgRP production and, 26
  deficiency/absence of, 30, 33-36
  gene mutations, 33-36
  reduced levels with weight loss, 43
Lifestyle interventions, 172-179, 174t, 243-245
  BMIQ Professionals Program, 177-178
  commercially available, 175-176
    Jenny Craig, 175
    NutriSystem, 175-176
    Weight Watchers, 175
  intensification of therapies to achieve weight loss goals, *93*
  intensive, in DPP and DPPOS, 95-103, 172-173, 174t
  key components, 179
  long-term intervention, necessity of, 179
  magnitude of weight loss, 179
  remote and mobile technologies, 176-177
Limitations of, 187t, limitations of, 187t
Lipids
  dyslipidemia, 53-54, 55t, 80, 85t
  improved values with lorcaserin, 218, 220t
  improved values with phen/top ER (Qsymia), 203-205, *206*
  improved values with weight loss, 98-100, *102*, 106-112, 107t, *110-111*, *116-117*
  in metabolic syndrome, 104t
Liraglutide (Saxenda), 184-185, 186t-192t, 238-243
  adverse effects, 189t
  adverse events, 243, 244t-245t
  approved treatments, 238
  brand names: Saxenda and Victoza, 238
  contraindications, 188t-189t
  dosage/administration, 191t
  efficacy, 238-243
    SCALE Diabetes, 239-241, 240t
    SCALE Maintenance, 241-243, *242*
    SCALE Obesity and pre-diabetes, 239, 240t
  elimination half-life, 238
  indications for, 186t
  limitations of, 187t
  safety, 243, 244t-245t

Liraglutide (Saxenda) *(continued)*
side effects, 189t
warnings and precautions, 190t
Liver, nonalcoholic fatty liver disease (NAFLD), 64
Look AHEAD trial, 78-79, 100-101, 105-122, 173, 174t
magnitude of weight loss, clinical benefits and, 112-114, *116-117*
objectives and design, 105
reduction in CV events and risk factors, 105-112, 107t, *108-111*
reduction of depression, 114-115, *118*
reduction of obstructive sleep apnea, 115-121, *120*
remission of diabetes, 112, *113*
Lorcaserin (Belviq), 184, 185, 210-233
action mechanism, 33, *35*, 210-211, *246*
adverse effects, 189t, 218-219, 222t-223t
approval of, 90, 210
cautions, 219
clinical trials, 211-217, 214t-215t
BLOOM, 211, 213, 214t-215t, *216*, 218, 219, 220t-221t
BLOOM-DM, 211, 213-217, 214t-215t, *217*, 218, 219, 220t-221t
BLOSSOM, 211-212, *212*, 214t-215t, 218, 219, 220t-221t
secondary endpoints, 218, 220t-221t
contraindications, 188t, 188t-189t
dosage/administration, 191t, 219
efficacy, 211-217
enhancement of POMC by, 33, *35*
indications for, 186t
indications for discontinuance, 219
limitations of, 187t
prescribing and administration, 219
safety, 218-219, 222t-223t
as Schedule IV controlled substance, 191t, 219
side effects, 189t, 218-219, 222t-223t
warnings and precautions, 190t
Low calories diets (LCDs), 163, 163t
Low carbohydrate diets, 163, 166-167
Low energy density diets, 164
Low fat diets, 166-167

Macronutrient content (of diet), 165-166
Management of obesity. See *Treatment of obesity.*
MCH1R antagonist, *246*
Meal replacements, 164-165
Medical conditions (linked to obesity), 39-41
binge-eating disorder, 41
Cushing's Syndrome, 40
growth hormone deficiency, 40
hypothyroidism, 40
night-eating syndrome, 41
PCOS, 40
sleep deprivation, 41
Medical model, 87-91
Medications contributing to obesity/weight gain, 39, 129, 130t-131t, 145-160
anticonvulsant medications, 149t, 152-153
antidiabetic medications, 146-151, 149t
antihistamines, 150t, 156
antihypertensive medications, 148t-149t, 151-152
antipsychotics and antidepressants, 148t, 150t, 154-156
contraceptives, hormones, and steroids, 150t, 153-154
HIV medications/antiretrovirals, 156
weight-neutral medications, 148t-150t
Medications for treatment of obesity. See *Pharmacologic treatment.*
Megestrol acetate, 150t, 153
Melanocortin receptor 4 (MC4R), 26, 33, *34*, *35*, *246*
Melanocyte-stimulating hormone (α-MSH), 26, 33
Men
mortality statistics, *16*, 18-19, *20-21*
prevalence of obesity in, 13-15, *14*
Metabolic factors, 28, *49*
Metabolic syndrome, 80-84
abnormal findings in, 84, 85t, 104t
diagnostic criteria for, 84, 85t
prevalence of, 54, 55t
weight loss, benefits of, 101-103, 104t
"Metabolically healthy obesity (MHO)," 67
Metformin, 147, 149t
Metreleptin, *246*
Monoamine oxidase inhibitors, 130t, 148t, 155

Mortality, 15-19
all-cause, 15-17, *16*
BMI and, 15-19, *16*, 18t, *20-21*, 77-78
cancer-related, 18-19, *20-21*
cardiovascular-related, 86, *91*
cause-specific, 17-19, 18t
hazard ratios, 15-18, *16*
metabolic syndrome and, 84
obesity-associated, 15-19, 67, 75-77
prediction of, with EOSS or BMI criteria, *82-83*
risk, reduction with weight loss, 78-79
Mutations, genetic, 33-36

Naltrexone, action mechanism, 33, *34*, 224, *246*
Naltrexone SR/bupropion SR (Contrave), 186t-192t, 224-238
action mechanisms, 224
adverse events, 189t, 233, 236t-237t
contraindications, 188t-189t
dosage/administration, 191t-192t, 233-238
efficacy, 224-234, 226t-227t
COR-I trial, 224-225, 226t-227t, *228*, 230
COR-II trial, 224-229, 226t-227t, *229*, 233
COR-BMOD trial, 224-225, 226t-227t, 229-230, *231*, 233
COR-Diabetes trial, 224-225, 226t-227t, 230, *232*, 233
primary endpoints (weight loss), 225-229, 226t-227t, *228-229*, *231-232*
secondary endpoints (metabolic and cardiovascular risk), 230-233, 234t-235t
FDA approval of, 90, 184, 185
indications for, 186t
limitations of, 187t
prescribing information, 186t-192t, 233-238
safety, 233, 236t-237t
warnings and precautions, 190t
National Health and Nutrition Examination Study. See *NHANES.*
Nausea
liraglutide and, 243, 244t
lorcaserin and, 218, 222t
naltrexone SR/bupropion SR and, 233, 236t
Neuropeptide Y (NPY), 24, *25*, *34*, *35*
neurons, 24-26, *25*, *27*, *34*, *35*, *246*

NHANES (National Health and Nutrition Examination Study), 47, 49t
body weight and diabetes in, 50, *52*
EOSS and, 80, *82-83*
metabolic syndrome, 54, 55t
mortality statistics, 86, *91*
Night-eating syndrome, 41
Nonalcoholic fatty liver disease (NAFLD), *48*, 64
Nucleus accumbens (NAc), 31, *32*
Nurses' Health Study, 50
NutriSystem, 175-176

Obese patient. See *Patient (obese patient).*
Obesity. See also *Severe obesity.*
as a chronic disease, xii, 23, 75, 144, 245
classes of, 49t, 57t
comorbidities of, 47-74
defined by BMI, 13, 49t, 77, 132t
focus on risk reduction, 77-78
"metabolically healthy," 67
mortality statistics, 15-19, 67
pathophysiology of, 23-46
prevalence of, 13-15, *14*
staging systems, 79-87, 139-140
treatment of, 75-285
Obstructive sleep apnea (OSA), 56-58
bariatric surgery and, 275-277
weight loss benefit for, 115-121, *120*
Older adults, prevalence of obesity in, 13-14
Oral contraceptives, 150t, 153-154
Orexigenic substances/pathway, 24, 28, 30, 43, *246*
Orlistat (Xenical), 184t, 185, 194-196
adverse effects, 189t
contraindications, 188t
dosage/administration, 191t, 195-196
efficacy, 194-195, *195*
formulations and dosages available (Xenical and Alli), 196
indications for, 186t, 194
limitations of, 187t
prescribing information, 186t-192t, 195-196
safety/adverse events, 195
side effects, 189t

Osteoarthritis (OA), 59, 121-122
ADAPT trial, 121-122
comorbid with obesity, 59
weight loss benefit for, 121-122
Overweight
BMI in, 13, 17, 49t, 132t
mortality and, 17-18
OXM (oxyntomodulin), *29*

Pancreas, factors secreted by, 26, *27*, 30
Pancreatitis, *48*, 63-64
Paresthesia, phen/top and, 208
Pathophysiology of obesity, 23-46
adaptive responses to weight loss, 42-43
energy balance and food intake regulation, 23-26
genetic and environmental factors, 33-38
gut microbes, 38-39
humoral signaling, 26-30
hypothalamic obesity (HO), 41-42
hypothalamus, 24-26
medical conditions, 39-41
obesity pharmacotherapy and, 33
peripheral signaling, 26-28
regulation of food intake, 23-26, *25*, *27*, *29*, *32*
reward/hedonic pathway, 31, *32*
Patient (obese patient), 127-144
approach to, 127-144
body fat, percentage of, 133-135, 134t
examination, 129-136
goal setting, 140
laboratory examination, 136-137
motivation, assessment of, 140
office equipment, 140-141
physical examination, 136
review of medications, 129, 130t-131t
treatment plan, creating, 141-144, *142-143*
weight-specific history, 127-129
disease staging and risk assessment, 139-140
medical model and, 87-91
treatment plan, creating, 141-144
PCOS (polycystic ovary syndrome), 40, 65-66
comorbid with obesity, 65-66

Peptide YY (PYY), 28, *29*, 43
Peptides, *27*, *29*
AgRP (agouti-related peptide), 24-26, *25*, *34*, *35*
glucagon-like peptide (GLP-1), 28, *29*
neuropeptide Y (NPY), 24, *25*, *34*, *35*
peptide YY (PYY), 28, *29*, 43
Peripheral signaling, 26-28
potential new therapeutic targets, *246*
Pharmacologic treatment, 183-249, 186t-192t. See also *specific medications*.
adverse events. See *specific drugs.*
amphetamine derivatives, 183-184, 184t
BMI categories, and treatment choices, 92t
bupropion, 33, *34*
emerging antiobesity agents, 243, *246*
history of weight loss drugs, 183-184
intensification of therapies to achieve weight loss goals, *93*
medications available prior to 2012, 183-184, 184t
medications withdrawn, 184, 184t
medications causing weight gain, 39, 129, 130t-131t, 145-160
treatment selection to prevent weight-gain, 145-146
medications currently available, 184-185, 186t-192t. See also *specific medications.*
liraglutide (Saxenda), 185, 238-243
lorcaserin (Belviq), 33, 184, 210-223
naltrexone SR/bupropion SR (Contrave), 184, 185, 224-238
orlistat (Xenical), 185, 194-196
phentermine, 183-184, 184t, 185-194, *193*
phentermine and topiramate ER (phen/top ER; Qsymia), 184, 185, 196-210
naltrexone, 33, *34*
new drug approval process, 183
new options in, 90, 184, 243, *246*
pathways targeted, 33, *34*, *35*, *246*
bupropion, 33, *34*, 224
Contrave (naltrexone SR/bupropion SR), 33, 224
lorcaserin, 33, *35*
naltrexone, 33, *34*, 224
for treatments in development, *246*
treatment selection to prevent weight-gain, 145-146

Phen/top. See *Phentermine/topiramate ER (Qsymia).*
Phendimetrazine, 184t
Phentermine, 184t, 185-194, 186t-192t
  action mechanism, 33, 185, *246*
  adverse effects, 189t
  contraindications, 188t-189t
  dosage/administration, 191t, 194
  efficacy, 185-193, *193*
  fixed dose combination with topiramate ER, 184, 186t-192t
  indications for, 186t, 194
  limitations of, 187t
  prescribing and information, 186t-192t, 194
  safety/adverse events, 193-194
  as schedule IV controlled substance, 191t, 194
  side effects, 189t
  warnings and precautions, 190t
Phentermine/topiramate ER (Qsymia), 184, 185, 196-210
  action mechanism, 196, *246*
  adverse events, 189t, 205-210, 206t-207t, 209t
  contraindications, 188t-189t
  dosage/administration, 191t-192t, 210
  efficacy
    CONQUER, 198-199, 201t, *203*, 205, 206t-207t, 208
    EQUIP, 197-198, 200t-201t, *202*, 206t-207t
    long-term, 199-202
    secondary endpoints, 203-205, 206t-207t
    SEQUEL study, 206t-207t, 208
  indications for, 186t, 196
  limitations of, 187t
  prescribing information, 186t-192t, 210
  safety, 205-210
  as Schedule IV controlled substance, 191t, 210
  side effects, 189t
  warnings and precautions, 190t, 205
Phlebitis, *48*
Physical activity, 170-171, 179
  BMI categories, and treatment choices, 92t
  in DPP and DPPOS, 96
Physical examination, 136
Pioglitazone, 147, 149t
Polycystic ovary syndrome. See *PCOS.*

POMC (proopiomelanocortin), 26, *34*, *35*
  deficiency of, 36
  enhancement by bupropion and naltrexone, 33, *34*, 224
  enhancement by lorcaserin, 33, *35*
  enhancement by phentermine, 33
  gene, 33
  neurons, *25*, 26, *27*, *34*, *35*
    potential new therapies targeting, *246*
Portion size, *169*
Prader- Willi syndrome, 33, 36
Pramlintide, *246*
Prescription medications. See *Pharmacologic treatment.*
Prevalence
  of comorbidities with obesity, 50-55
  of obesity, 13-15, *14*
Primary care physicians, 127
Problem-solving techniques, 171-172
Progestins, 150t, 153
Proopiomelanocortin. See *POMC.*
Protease inhibitors, 156
Protein
  content of diet, 165-166
  protein-sparing modified fast, 162-163
Protein-sparing modified fast (PSMF), 162-163
Psychiatric conditions (linked to obesity), 39, 139
Pulmonary disease, *48*

Qsymia. See *Phentermine/topiramate ER (Qsymia).*

Regulation of food intake, 23-26, *25*, *27*, *29*, *32*
Resting energy expenditure (REE), 42
Reward (hedonic) pathway, 31, *32*, 43
Rimonabant, 184t
Risk
  assessment, 79-87, 90, 139-140
  reduction, focus on, 77-78
Rosiglitazone, 147, 149t
Roux-en-Y gastric bypass (RYGB), 253, *255*, 264-266
  complications and mortality, 269, 270t
  diabetes and, 271-273, 274t
  efficacy, 263-264, 265-267, *265*, 266t
  mechanisms of action, 256

Roux-en-Y gastric bypass (RYGB) *(continued)*
as nonreversible, 255
potential advantages and disadvantages, 256t
sleep improvement with, 119-121

Satiety
biochemical signals for, 26, 28-30, *29*, *32*
decreased, following weight loss, 43
Saxenda. See *Liraglutide.*
Selective serotonin inhibitors (SSRIs), 130t, 148t, 155
SEQUEL, 199-202, 201t, 206t-207t
Serotonin (5-HT), 28, *35*
AgRP production and, 26
receptor agonist (lorcaserin), 33, *35*, 210
releasing agents (fenfluramine and dexfenfluramine), 183-184
Severe obesity
BMI in, 13, 132t
prevalence of, 13
weight loss in (Look AHEAD trial), 100-101
SGLT2 (sodium glucose cotransporter 2), 149t, 151
Sibutramine, 184t
Signals
adipose, *29*, 30
gastrointestinal, 28-30, *29*
humoral, 28-30, *29*
pancreatic, 26, *27*, 30
peripheral, 26-28
Sinusitis, phen/top and, 208
Sleep, 41
apnea, 56-58, 115-121
STOP-BANG Questionnaire, 137, *138*
deprivation, 41
obstructive sleep apnea (OSA), 56-58
bariatric surgery and, 275-277
weight loss benefit for, 115-121, *120*
problems, with phentermine, 193-194
Sleep AHEAD study, 115-121, *120*
Social environment, 37-38
Sodium glucose cotransporter 2 (SGLT2), 149t, 151
SQUEL study, 208
SSRIs (selective serotonin inhibitors), 130t

Staging of obesity, 79-84, 139-140
BMI criteria and, *82-83*
Cardiometabolic Disease Staging System (CMDS), 84-87, 88t-89t, *91*
Edmonton Obesity Staging System (EOSS), 79-80, 81t, *82-83*
metabolic syndrome and, 80-84
Steroids, 130t, 150t, 154
Stimulus control, 171
STOP-BANG Questionnaire, 137, *138*
Sulfonylureas, 146, 149t
Surgery. See *Bariatric surgery.*
Swedish Obese Subjects (SOS) study, 278-280

Thermogenesis, 23
Thiazolidinediones (TZDs), 146-147, 149t
Thyroid, hypothyroidism, 40
TNF-α. See *Tumor necrosis factor alpha.*
Topiramate. See *Phentermine/topiramate ER.*
Total energy expenditure (TEE), 23
reduction in, with weight loss, 42-43
Treatment of obesity, 75-285. See also *specific topics.*
algorithm for treatment, 75, *76*, 78, 87, *93*, 141, *142-143*
approach to obese patient, 127-144
bariatric surgery, 251-285
behavioral modification, 171-172, 179
BMI-centric (weight loss) model, 77-78, 87, 92t
complications-centric approach, 75-94
evaluation, risk assessment, and disease staging, 79-87, 90
focus on risk reduction, 77-78
intensification of therapies, *93*
medical model, 87-91
obesity as a disease, 75-77, 87
weight loss reduction of comorbidity and mortality risk, 78-79
diet, 161-169, 179
goals for, 78, 87
intensification of therapies, *93*
lifestyle interventions, 172-179
medical model, 87-91
medications inducing weight gain, 145-160

Treatment of obesity *(continued)*
multidisciplinary/multimodal approach, 243-245
new options for, 87-91
pharmacologic treatment, 183-249. See also *Pharmacologic treatment*; *specific medications.*
medications available prior to 2012, 183-184, 184t
medications currently available, 184-185, 186t-192t
liraglutide (Saxenda), 185, 238-243
lorcaserin (Belviq), 33, 184, 210-223
naltrexone SR/bupropion SR (Contrave), 184, 185, 224-238
orlistat (Xenical), 185, 194-196
phentermine, 183-184, 184t, 185-194, *193*
phentermine and topiramate ER (phen/top ER; Qsymia), 184, 185, 196-210
new options in, 90, 184, *246*
physical activity, 170-171, 179
plan, creating, 141-144, *142-143*
risk reduction as treatment goal, 77-78, 87
team approach in, 141
treatment plan, creating, 141-144
weight gain, drug-induced, 145-160
weight loss, 78-79, 95-125
Tricyclic antidepressants, 130t, 148t, 155
Trigger control, 171
Tumor necrosis factor alpha (TNF-α), 26-28
Twin studies, 38
Type 2 diabetes, 50, *52*. See also *Diabetes.*

Underweight, BMI in, 132t

Vagal stimulation, 28
Valproic acid, 149t, 152
Valvulopathy, 184, 219
Vertical sleeve gastrectomy (VSG), 254, 256-257, *257*
complications and mortality, 269, 270t
diabetes and, 271-272, 274t
efficacy, 263, 264, *265*, 267-268
mechanisms of action, 257
potential advantages and disadvantages, 258t
Very low calories diets (VLCDs), 161-162, 163
Visceral fat, 132

Waist circumference, 131-133
Waist-hip ratio, 131-133
Weight categories, BMI and, 13, 49t
Weight gain. See also *Drug-induced weight gain.*
diabetes risk and, 50, *52*
drug-induced, 145-160
medications causing, 129, 130t-131t, 145-160, 148t-150t
anticonvulsant medications, 149t, 152-153
antidiabetic medications, 146-151, 149t
antihistamines, 150t, 156
antihypertensive medications, 148t-149t, 151-152
antipsychotics and antidepressants, 148t, 150t, 154-156
contraceptives, hormones, and steroids, 150t, 153-154
HIV medications/antiretrovirals, 156
metabolic changes after weight loss and, 43
regain after diets, 161, 162
treatment selection to prevent weight-gain, 145-146
Weight loss, 95-125
benefits of, 95-125
improvement for osteoarthritis, 121-122
metabolic syndrome, incidence and resolution of, 101-103, 104t
reduction of cardiovascular risk, 90-100, *102-103*, 105-112, 107t, *108-111*
reduction of comorbidities, 78-79
reduction of depression, 114-115, *118*
reduction of diabetes risk, 50-53
reduction of mortality risk, 78-79
reduction of obstructive sleep apnea, 115-121, *120*
remission of diabetes, 112, *113*
in severely obese patients, 100-101
commercially available programs, 175-176
Jenny Craig, 175
NutriSystem, 175-176
Weight Watchers, 175
diet and, 161-169
DPP and DPPOS studies, 95-103, 172-173, 174t
increased drive to eat associated with, 43
intensification of therapies to achieve weight loss goals, *93*
lifestyle interventions for, 172-179
Look AHEAD Study, 100-101, 105-122, 173, 174t
magnitude of, and clinical benefits, 112-114, *116-117*

Weight loss *(continued)*
medications associated with, 148t-150t
medications for, 183-249, 186t-192t
medications, reduction or substitution of, 129
reduced energy expenditure associated with, 42-43
remote and mobile technologies, 176-177
responses to, 42-43
as therapeutic intervention, 78
as treatment goal, 78
Weight-neutral medications, 148t-150t
Weight Watchers, 175
Women
mortality statistics, *16*, 18-19, *20-21*
prevalence of obesity in, 13-15, *14*

Xenical. See *Orlistat (Xenical).*